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Brain and diabetes

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Prof. P.-J. Guillausseau - Service de médecine B
Hôpital Lariboisière - 2, rue Ambroise-Paré - 75010 Paris - France - e-mail : diabetes-metabolism@wanadoo.fr

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Brain and diabetes

A symposium organized by SFD-ALFEDIAM (Société Francophone du Diabète)
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Central nervous system: a conductor orchestrating metabolic regulations harmed by both hyperglycaemia and hypoglycaemia

A. J. Scheen

Division of Diabetes, Nutrition and Metabolic Disorders, Department of Medicine, CHU Sart Tilman, University of Liège, B-4000 Liège, Belgium

Summary

Recent evidence suggests that the brain has a key role in the control of energy metabolism, body fat content and glucose metabolism. Neuronal systems, which regulate energy intake, energy expenditure, and endogenous glucose production, sense and respond to input from hormonal and nutrient-related signals that convey information regarding both body energy stores and current energy availability. In response to this input, adaptive changes occur that promote energy homeostasis and the maintenance of blood glucose levels in the normal range. Defects in this control system are implicated in the link between obesity and type 2 diabetes mellitus. The central nervous system may be considered the conductor of an orchestra involving many peripheral organs involved in these homeostatic processes. However, the brain is mainly a glucose-dependent organ, which can be damaged by both hypoglycaemia and hyperglycaemia. Hypoglycaemia unawareness is a major problem in clinical practice and is associated with an increased risk of coma. Stroke is another acute complication associated with diabetes mellitus, especially in elderly people, and the control of glucose level in this emergency situation remains challenging. The prognosis of stroke is worse in diabetic patients and both its prevention and management in at-risk patients should be improved. Finally, chronic diabetic encephalopathies, which may lead to cognitive dysfunction and even dementia, are also recognized. They may result from recurrent hypoglycaemia and/or from chronic hyperglycaemia leading to cerebral vascular damage. Functional imaging is of interest for exploring diabetes-associated cerebral abnormalities. Thus, the intimate relationship between the brain and diabetes is increasingly acknowledged in both research and clinical practice.

Keywords: Brain; Diabetes; Glucose regulation; Hyperglycaemia; Hypoglycaemia; Stroke, Dementia; Review

Résumé

Le système nerveux central, chef d'orchestre des régulations métaboliques exposé aux dommages de l'hyperglycémie et de l'hypoglycémie

Des observations récentes suggèrent que le cerveau joue un rôle essentiel dans le contrôle du métabolisme énergétique, des réserves adipeuses et du métabolisme du glucose. Les systèmes neuronaux qui règlent l'apport calorique, les dépenses énergétiques et la production endogène du glucose sont sensibles et répondent à des signaux hormonaux et nutritionnels qui donnent l'information concernant les réserves et la disponibilité énergétiques. En réponse à ces influx surviennent des changements adaptatifs qui jouent un rôle dans l'homéostasie énergétique et le maintien de la normoglycémie. Des anomalies de ce système de contrôle sont impliquées dans l'intrication entre obésité et diabète de type 2. Le système nerveux central peut être considéré comme le chef d'orchestre des nombreux organes impliqués dans ces processus d'homéostasie. Cependant, le cerveau est essentiellement un organe glucodépendant, qui peut être lésé à la fois par l'hypoglycémie et par l'hyperglycémie. Le défaut de perception de l'hypoglycémie ("hypoglycaemia unawareness") est un problème majeur en pratique clinique et est associé à un risque accru de coma. La thrombose cérébrale est une autre complication aiguë associée au diabète, généralement chez le sujet plus âgé, et le contrôle de la glycémie dans cette situation d'urgence reste un défi. Le pronostic des accidents vasculaires cérébraux est moins bon chez les patients diabétiques et tant leur prévention spécifique que leur prise en charge spécialisée doivent être améliorées. Enfin, les encéphalopathies diabétiques sont de plus en plus reconnues et peuvent conduire à des troubles cognitifs, voire à la démence. Ces anomalies cérébrales peuvent résulter d'hypoglycémies récurrentes et/ou d'une hyperglycémie chronique responsable d'une angiopathie cérébrale. L'imagerie fonctionnelle est intéressante pour explorer les anomalies du système nerveux central associées au diabète. Ainsi, les relations intimes entre cerveau et diabète sont de plus en plus reconnues, à la fois en recherche et en pratique clinique.

Mots-clés: Cerveau; Diabète; Glucose; Hyperglycémie; Hypoglycémie; Thrombose cérébrale; Démence; Revue générale

* Corresponding author.
E-mail address: Andre.Scheen@chu.ulg.ac.be (A. J. Scheen).

1. Introduction

Diabetes mellitus (DM) is a complex disease involving multiple organs, which are implicated in a wide variety of cross-communication. Besides the endocrine pancreas, many organ systems play a role in glucose metabolism and metabolic dysregulation including the liver, muscles, adipose tissue, gut and kidney [1]. Furthermore, diabetic complications resulting from chronic hyperglycaemia also concern many tissues, especially the arteries, nerves, heart, kidneys, eyes and feet. Numerous papers have been published describing the respective roles of the most important organs in the pathophysiology of type 2 DM [1] and the complications associated with DM that may occur in the various peripheral organs [2]. However, the brain [central nervous system (CNS)] is often forgotten in this literature. Yet, the brain may be considered the conductor of the orchestra of all players involved in the regulation of glucose and energy metabolism (Fig. 1) [1].

The brain is a glucose-dependent organ, which may be dramatically affected by both hyperglycaemia and hypoglycaemia [3] (Fig. 2). The high prevalence of CNS complications resulting from DM is a problem that is gaining more acceptance and attention. Not only well known acute complications (e.g., coma, stroke) but also chronic disorders (e.g., encephalopathies, dementia) have been recently described in detail [4, 5]. Recent evidence suggests morphological, electrophysiological and cognitive changes associated with chronic hyperglycaemia. Many of the CNS changes observed in diabetic patients and animal models of diabetes are reminiscent of the changes seen in normal aging. The central commonalities between diabetes-induced and age-related CNS changes have led to the theory of advanced brain aging in diabetic patients [6]. Furthermore, the patterns of volumetric and neurocognitive deficits in diabetic populations have been shown to be rather similar to those reported in populations of individuals with major depressive disorders [7]. It is not known, however, whether these observations may partly explain the known connection between DM and increased risk of depression [8]. Finally, patients with schizophrenia and schizoaffective disorders also have a higher incidence of glucose disorders compared to age-matched control subjects. Several underlying mechanisms have been proposed to explain this intimate connection between psychiatric disorders and metabolic disturbances, including DM [9].

Besides glucose used as a preferential energy substrate by neurons, insulin also plays important and multifaceted roles in the brain. Circulating insulin crosses the blood-brain barrier into the CNS. There are many insulin receptors in various areas of the brain, which are expressed by both astrocytes and neurons. The two main insulin actions in the brain are the control of food intake and the effect on cognitive functions. Brain insulin decreases with aging and may be related to the decrease in cognitive functions, as has also been reported in Alzheimer's disease [10]. Dysregulation of insulin signalling has been linked to aging and metabolic and neurodegenerative disorders [11]. Insulin receptor signalling, which has been

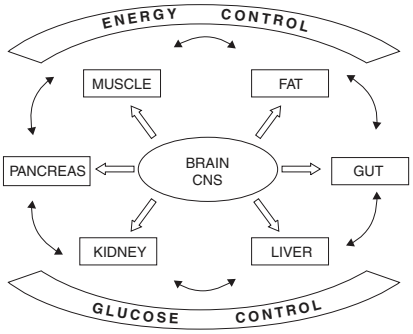

Figure 1. Central nervous system (CNS) as conductor of the orchestra of all peripheral organs implicated in energy and glucose metabolism.

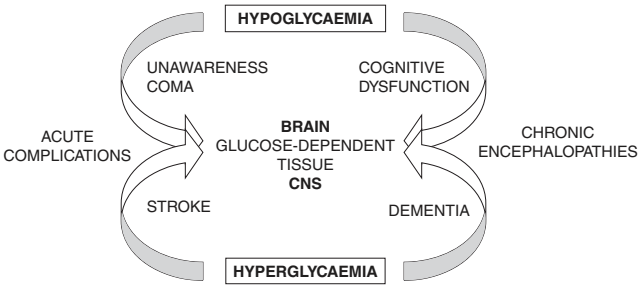

Figure 2. Brain, a glucose-dependent organ exposed to acute and chronic adverse events associated with either hypoglycaemia or hyperglycaemia.

extensively studied in peripheral organ systems such as the liver, muscles and adipocytes, has recently been implicated in various mechanisms that regulate structural and functional aspects of circuit development, including synaptic function and the development of dendritic arbor morphology. Therefore, one might speculate about a potential link between insulin receptor signalling malfunction and neurological disorders, including in patients with DM [12].

The symposium organized by the "Société Francophone du Diabète" entitled "Brain and Diabetes" (December 3, 2010) is ambitious in covering many important aspects of the intimate relationship between the CNS and integrated energy and glucose regulation on one hand, and acute and chronic glucose-related cerebral complications on the other. We thank all the distinguished contributors who accepted our invitation and have submitted excellent manuscripts that are assembled in this special issue of Diabetes & Metabolism.

2. The CNS orchestrates energy and glucose homeostasis

Growing evidence suggests that nutrient and hormonal signals converge and act directly on brain centres, leading to changes in fuel metabolism and, thus, stable body weight over time. Furthermore, these same signals act on the CNS to regulate glucose metabolism independently [13]. It has been proposed that this is not coincidental and that the CNS responds to peripheral signals for orchestrating changes in both energy

and glucose homeostasis. In this way the CNS ensures that the nutrient demands of peripheral tissues (and likely of the brain itself) are being met. Consequently, dysfunction of the ability of the CNS to integrate fuel-sensing signals may underlie the aetiology of metabolic diseases such as obesity and DM whose incidences are rising at epidemic proportions [14].

Energy homeostasis is kept through a complex interplay of nutritional, neuronal and hormonal inputs that are integrated at the level of the CNS [15]. The hypothalamus is a key integrator of nutrient-induced signals of hunger and satiety, crucial for processing information regarding energy stores and food availability. Furthermore, there are increasing data supporting the importance of nervous regulation of both white and brown adipose tissue mass. Overall, available results show the presence of a neural feedback loop between adipose tissue and the brain, which plays a major role in the regulation of energy homeostasis and has been shown to be altered in some physiological conditions, as well as in metabolic pathologies. Different physiological parameters are regulated such as metabolism (lipolysis and thermogenesis), secretory activity (leptin and other adipokines) but also plasticity of adipose tissues (proliferation, differentiation and apoptosis) [16].

The CNS control of body weight [15], but also of blood glucose concentrations [17], depends on the exquisite coordination of the function of several organs and tissues, in particular the pancreas, liver, muscle, fat, gut and kidneys (Fig. 1) [1]. These organs and tissues have major roles in the use and storage of nutrients in the form of glycogen or triglycerides and in the release of glucose or free fatty acids into the blood during periods of metabolic needs [18]. These mechanisms are tightly regulated by hormonal and nervous signals, which are generated by specialized cells that detect variations in blood glucose or lipid concentrations. The hormones insulin and glucagon regulate glycaemic levels through their action on these organs, especially the liver. Furthermore, the sympathetic and parasympathetic branches of the autonomic nervous system, which are activated by glucose or lipid sensors, also modulate pancreatic hormone secretion, as well as liver, muscle and fat glucose and lipid metabolism. Other signalling molecules, such as the adipocyte hormones'leptin and adiponectin, have circulating plasma concentrations that reflect the level of fat stored in adipocytes. These signals are integrated at the hypothalamus through the melanocortin pathway, which produces orexigenic and anorexigenic neuropeptides to control feeding behaviour, energy expenditure and glucose homeostasis. Studies from several laboratories have explored the physiological role of glucose as a signal that regulates these homeostatic processes and has tested the hypothesis that the mechanism of glucose sensing that controls insulin secretion by the pancreatic B cells is also used by other cell types. These mechanisms integrate signals from other nutrients such as lipids and their deregulation may initiate metabolic diseases [18].

The liver plays a pivotal role in the regulation of glucose metabolism because it is the key organ that maintains glucose levels during fasting via increased glycogenolysis and gluconeogenesis, two important biochemical pathways that increase hepatic glucose production (HGP). Furthermore, following the ingestion of a meal, insufficient reduction in HGP enhances postprandial hyperglycaemia in patients with type 2 DM [1]. An emerging body of literature has demonstrated the important role of the hypothalamus in controlling HGP. The hypothalamus senses circulating nutrients and hormones, conveying the energy status to the CNS, which, in turn, controls HGP in part by way of the autonomic nervous system. Animal experiments suggest that overfeeding results in the failure of the hypothalamus to sense circulating nutrients and hormones, and in a loss of the central control of HGP [19]. Interestingly, connected to the hypothalamus via the peripheral nervous system, a system of plasma glucose sensing in the portal vein allows the body to adapt its response to any variation of portal glycaemia. Intestinal gluconeogenesis, via the release of glucose into the portal vein, plays a key role in the control of hunger and satiety and of HGP through the modulation of liver insulin sensitivity [20]. These data emphasize the importance of the liver-brain and gut-brain axes in the understanding of obesity and type 2 DM, which may lead to promising therapeutic implications.

Food intake and energy expenditure are tightly regulated by the brain in a homeostatic process that integrates diverse hormonal, neuronal and metabolic signals [21]. The gastrointestinal tract is an important source of such signals, which include several hormones released by specialized enteroendocrine cells. These hormones exert powerful effects on appetite and energy expenditure. Almost all of them, i.e. peptide YY, pancreatic polypeptide, islet amyloid polypeptide, glucagon-like peptide 1 (GLP-1), glucagon, oxyntomodulin, cholecystokinin and ghrelin, are potential targets for the development of novel treatments for obesity and/or type 2 DM [21]. Over the past years tremendous amounts of clinical and fundamental data have been generated about GLP-1 and related therapeutic strategies for the treatment of type 2 DM. However, the cellular and physiological mechanisms through which GLP-1 is secreted, controls glycaemia, and behaves as a therapeutic agent are still unclear. Besides being a gut-derived hormone, GLP-1 is also a neurotransmitter synthesized in the brain. Early reports suggested that GLP-1 acts in the periphery to promote insulin secretion and affect glucose homeostasis, whereas central GLP-1 reduces food intake and body weight. However, current research indicates that in fact, GLP-1 in each location plays a role in these functions [22]. There is growing evidence showing that the enteric and CNS systems are the main players in the control of GLP-1 action. This involves the triggering of the gut-to-brain and – to-periphery axis where nutrients regulate the release of GLP-1 and activate the tightly regulated enteric and cerebral neuronal circuits. These integrate and redistribute the GLP-1-dependent signals toward numerous targeted tissues, including the brain [23].

In his Banting Lecture, De Fronzo recognizes that the brain plays an important role in the pathogenesis of type 2 DM, which together with its seven companions (muscle, liver, adipose tissue, β-cell, α-cell, gut, kidney) forms the so-called

"ominous octet" (Fig. 1) [1]. It is abundantly clear that the current epidemic of DM is being driven by the epidemic of obesity. Obese individuals, both diabetic and non-diabetic, are characterized by insulin resistance and compensatory hyperinsulinemia. Food intake is increased in obese subjects despite the presence of hyperinsulinaemia and the fact that insulin is known to be a potent appetite suppressant [10]. Thus, one could postulate that the insulin resistance in peripheral tissues also extends to the brain. The issue of impaired appetite regulation by insulin in obese subjects was confirmed using functional magnetic resonance imaging (MRI) to examine the cerebral response to an ingested glucose load. Whether the impaired functional MRI hypothalamic response in obese subjects contributes to or is a consequence of the insulin resistance and weight gain remains to be determined. Nonetheless, these results suggest that the brain, like other organs in the body (liver, muscle, and fat), may be resistant to insulin [1].

3. The brain, a glucose-dependent organ exposed to hypoglycaemia

Under most physiological conditions, glucose is the primary fuel for the brain. The brain accounts for more than half the body's glucose use, and because fuel stores such as glycogen are limited, it is very dependent on a continuous supply of glucose from the circulation. This probably explains why the glucose sensors thought to be dominant during hypoglycaemia are found in a number of brain area regions where the blood-brain barrier is leaky or absent, i.e. adjacent to the III or IV ventricles or to the circumventricular organs. This potentially allows glucose-sensing neurons direct monitoring of glucose levels in the blood, brain and cerebrospinal fluid. This is important because the presence of the blood-brain barrier ensures that brain glucose levels are only ~10–30% of the levels seen in the blood [24].

The defining feature of a glucose-sensing neuron is that it can use glucose not simply as a fuel but as a signalling molecule that regulates its activity. Such specialized neurons are glucose-sensing in so far as glucose is the major metabolic substrate for the brain. However, the fact that these neurons can use other fuels such as lactate produced either by astrocytes or delivered locally to alter their function suggests that it is more likely glucose oxidation-derived intracellular ATP that determines the activity of these neurons. Glucose-sensing neurons, by virtue of specific sensing systems, directly or indirectly translate the rate or quantity of glucose oxidation into a neural signal that alters neuronal firing rates. Interestingly, these neurons appear to use signalling mechanisms that parallel those used by pancreatic β- and α-cells [24].

Two predominant subtypes of glucose-sensing neurons have been identified: namely, glucose-excited (GE) neurons and glucose-inhibited (GI) neurons whose activity, respectively, increases and decreases as glucose levels rise. Potentially, the counterbalance between GI and GE neuronal activity forms the most sensitive means of regulating and maintaining blood glucose within a narrow physiological range, as well as ensuring an adequate supply of glucose to the brain. Recurrent exposure to hypoglycaemia disturbs this relationship in a number of ways. These may include an increased capacity for glucose-sensing regions of the brain to use glucose and/or alternate fuels, as well as changes in both the mechanisms that sense glucose and those that fine-tune the hypoglycaemic stress response, the net effect being to reduce the glucose level at which counterregulation is initiated (see below) [24].

Brain nutrient sensing permits fine regulation of physiological functions such as food intake and blood glucose regulation related to energy homeostasis. In some cases detection is probably not ensured by neurons themselves but by astrocytes, indicating that the two cell types are coupled in some way. Glucose sensing can be modulated by other nutrients (particularly fatty acids) and also by hormones (insulin, leptin and ghrelin) and peptides (NPY). The subtle cellular and molecular mechanisms involved in glucose sensing probably explain reported discrepancies in the expression of glucose transporters, hexokinases and channels [25]. Astrocytes might also be involved in one type of response, thus adding a new level of complexity.

The astrocyte-neuron lactate shuttle hypothesis occupies centre stage in the research on brain energetics [26]. The description of cell-specific metabolic characteristics have reinforced the view that a prominent conversion of glucose into lactate takes place in astrocytes, whereas neurons preferentially take up and oxidize lactate over glucose-derived pyruvate. Indeed, specific mechanisms are activated by glutamatergic activity to favour such a net lactate transfer between the two cell types. Moreover, *in vivo* demonstrations of the existence and implication of the astrocyte-neuron lactate shuttle hypothesis for particular neurophysiological processes are beginning to appear. A new concept of brain energetics based on metabolic compartmentalization between astrocytes and neurons is establishing itself as the leading paradigm that opens new perspectives in areas such as functional brain imaging and regulation of energy homeostasis [26].

In healthy volunteers, hypoglycaemia is classically associated with symptomatic responses (resulting from sympathoadrenergic stimulation and cerebral neuroglucopenia), hierarchised counterregulatory neuroendocrine responses and a sequential pattern of brain regional engagement. The analysis of changes in relative cerebral perfusion using [(15)O] – H(2)O water positron emission tomography [27] demonstrates complex dynamic responses to the stressor of hypoglycaemia that would be expected to drive physiological and behavioural changes to remedy the state. Furthermore, distinct sets of brain regions are engaged in the process, providing a neural substrate for adaptive responses to stressors such acute hypoglycaemia.

While the clinical presentation is often characteristic, particularly for the experienced individual with diabetes, the neurogenic and neuroglycopenic symptoms of hypoglycaemia are nonspecific and relatively insensitive; therefore, many episodes are not recognized. Iatrogenic hypoglycaemia is typically the result of the interplay of absolute or relative

insulin excess and compromised glucose counterregulation in type 1 and advanced type 2 DM. Decrements in insulin, increments in glucagon, and, in the absence of the latter, increments in epinephrine stand high in the hierarchy of redundant glucose counterregulatory factors that normally prevent or rapidly correct hypoglycaemia. In insulin-deficient DM (exogenous), insulin levels do not decrease as glucose levels fall, and the combination of deficient glucagon and epinephrine responses causes defective glucose counterregulation. Reduced sympathoadrenal responses cause hypoglycaemia unawareness. The concept of hypoglycaemia-associated autonomic failure in DM posits that recent antecedent hypoglycaemia causes both defective glucose counterregulation and hypoglycaemia unawareness [28, 29]. By shifting glycaemic thresholds for the sympathoadrenal (including epinephrine) and the resulting neurogenic responses to lower plasma glucose concentrations, antecedent hypoglycaemia leads to a vicious cycle of recurrent hypoglycaemia and further impairment of glucose counterregulation. Thus, short-term avoidance of hypoglycaemia reverses hypoglycaemia unawareness in most affected patients, an important observation for all diabetes care providers. The clinical approach to minimizing hypoglycaemia while improving glycaemic control includes multiple strategies that are beyond the scope of this review [29,30].

Hypoglycaemia is a frequent side effect of treatment with insulin and sulfonylureas for people with DM, threatening potentially serious morbidity and preventing optimal glycaemic control [28,30]. Indeed, fear of hypoglycaemia and the development of syndromes such as impaired awareness and counterregulatory deficiency provide additional hazards for intensification of treatment. Hypoglycaemia can disrupt many everyday activities such as driving, work performance and recreational pursuits. Hypoglycaemic coma is a major adverse event in the daily lives of diabetic patients, which may have a negative social impact but also may be hazardous on an everyday basis. Fortunately, severe brain damage following acute hypoglycaemic coma is rather rare. However, because of the associated sympathoadrenergic drive, profound hypoglycaemia may be deleterious for the heart, potentially leading to myocardial infarction and severe arrhythmias (which may explain the so-called “dead in bed” syndrome) [31,32]. Recent data from the ACCORD (“Action to Control Cardiovascular Risk in Diabetes”) trial emphasizes the increased risk of cardiovascular mortality associated with severe hypoglycaemia in patients with type 2 DM, whether treated intensively or not [33].

Thus, iatrogenic hypoglycaemia causes recurrent morbidity in most people with type 1 DM and many with type 2 DM, and it is sometimes fatal. The barrier of hypoglycaemia generally precludes maintenance of euglycaemia over a lifetime of DM and thus precludes full realization of euglycaemia's long-term benefits. Measures to reduce the risk of hypoglycaemia are labour-intensive and require substantial resources [29,30].

4. Diabetes, stroke, and control of glycaemia

Prospective observational data and results of clinical trials showed clear association between DM and vascular disease, which extends to cerebrovascular disease [34]. Recent meta-analyses included data for 698,782 people (52,765 non-fatal or fatal vascular outcomes; 8.49 million person-years at risk) from 102 prospective studies. The adjusted hazard ratios (HRs) with DM were 2.27 (95% CI 1.95-2.65) for ischaemic stroke; 1.56 (1.19-2.05) for haemorrhagic stroke; and 1.84 (1.59-2.13) for unclassified stroke compared to non-diabetic individuals [34]. The Dijon Stroke Registry is the only population-based registry in France that has collected neurological data without interruption for more than 20 years. This registry has produced reliable epidemiological data from a large non-selected population. Comparison of the descriptive epidemiology data from 1985 to 1989 and the 2000-2004 periods showed that the proportion of subjects with DM increased significantly [35].

In DM, glycaemic control should be part of a comprehensive approach to vascular risk. The benefits of interventions to lower blood glucose in terms of microvascular health are well established, but benefits for macrovascular, especially cerebrovascular, health have been less apparent. Recent large-scale trials and meta-analyses have helped us to better define the role of glycaemic control in macrovascular disease. Although few studies of glycaemic therapy have used cerebrovascular disease as a primary endpoint, stroke-specific data can be derived from several large intervention studies [36]. Five trials provided information on 1,127 episodes of stroke during about 163,000 person-years of follow-up. The mean HbA1c concentration was 0.9% lower for participants given intensive treatment than for those given standard treatment. However, intensive glycaemic control had no significant effect on stroke events (HR: 0.93, 95% CI 0.81-1.06), contrasting with a highly significant reduction in coronary events (-15%).

DM and hyperglycaemia per se are associated with poor cerebrovascular health, both in terms of stroke risk and outcomes thereafter. A period of hyperglycaemia is common, with elevated blood glucose in the peri-infarct period consistently linked with poor outcome in patients with and without DM. The mechanisms that underlie this deleterious effect of dysglycaemia on ischaemic neuronal tissue remain to be established, although *in vitro* research, functional imaging and animal work have provided some clues. However, the interaction between glycaemic control and critical neurological illness and injury is complex [37]. Hyperglycaemia can be either the cause or the result of severe brain injury. Interventions to control blood glucose are available but evidence of cerebrovascular efficacy is lacking.

The association between poor glycaemic control and an unfavourable prognosis for patients with acute ischaemic stroke is particularly evident in individuals with persistent hyperglycaemia, patients without a known history of DM, and subjects with cortical infarction. While prompt correction of hyperglycaemia can be achieved, trials of acute insulin

administration in stroke, as in other critical care populations, have been equivocal. In acute stroke, theoretical data suggest that intervention to lower markedly elevated blood glucose may be of benefit, especially if thrombolysis is administered. However, trials have been underpowered to demonstrate treatment effect or have had several limitations, and any intervention must be balanced against risk of hypoglycaemia [38]. Despite a lack of clinical evidence supporting the use of glycaemic control in the treatment of patients with stroke, international guidelines recommend treating this subset of critically ill patients for hyperglycaemia in the hospital setting. This treatment regime is, however, particularly challenging in patients with stroke, and is associated with an increased risk of the patient developing hypoglycaemia, which may also be deleterious for the brain [39]. The add-on value of using a continuous glucose monitoring system to avoid both hyperglycaemia and hypoglycaemia in DM patients with acute stroke deserves further evaluation.

Reducing the excess cerebrovascular burden in patients with type 2 DM remains a major therapeutic challenge, especially with respect to the high risk of recurrent events. Targeting the traditional metabolic risk factors of hypertension, dyslipidaemia and hyperglycaemia has failed to remove this excess risk, and agents targeting thrombotic risk (i.e., antiplatelet and anticoagulant drugs) remain poorly studied in the context of stroke in DM. This may relate to the accumulation of risk factors in type 2 DM, as well as to diabetes-specific pathophysiological factors. There is a lack of prospective evidence to support the efficacy of interventions in the secondary prevention of cerebrovascular events in type 2 DM, particularly recurrent stroke events. Overall, there is a need for rigorous evaluations of new therapeutic approaches in both primary and secondary prevention of stroke, as well as management of acute stroke in patients with type 2 DM [40].

5. Diabetes and cognitive dysfunction

Reviews on the epidemiological studies of cognitive impairment in patients with DM found evidence of cross-sectional and prospective associations between type 2 DM and moderate cognitive impairment, memory and executive functions [41]. Neuropsychology contributes greatly to the diagnosis of dementia in the general population, and validated methods for the detection of cognitive disorders may also be applied to patients with DM [42]. Cognitive deficits can be detected several years before the clinical diagnosis of dementia. Neuropsychological assessment at an early stage of dementia has two goals: (a) to determine a memory disorder, not always associated with a memory complaint, and (b) to characterize the memory disorder in light of the cognitive neuropsychology and to assess other cognitive (and non-cognitive) functions in order to integrate the memory disorder in a syndrome. Considering the high prevalence of cognitive dysfunction among diabetic patients [41,43], diabetologists should be aware of the global tools and memory tests that describe the memory profile and indicate the underlying pathology. The results must be interpreted in the light of the history, rate of progression, imaging data and nature of existing behavioural disturbances. Careful follow-up of patients is necessary to improve diagnostic accuracy [42].

Acute hypoglycaemia impairs cerebral function, and available data indicate that cognitive performance becomes impaired at a blood glucose level of 2.6-3.0 mmol/L in healthy subjects [44]. The onset of hypoglycaemic cognitive dysfunction is immediate, but recovery may be considerably delayed. There is persuasive evidence of adaptation to hypoglycaemia, partly due to increased brain glucose uptake capacity, although other mechanisms may exist. Patients who are exposed to chronic or recurrent hypoglycaemia become remarkably tolerant to the state, but this is insufficient to prevent severe hypoglycaemia with neuroglycopenic decompensation, probably because symptomatic and counterregulatory responses adapt even more. The chronic effects of recurrent hypoglycaemia remain contentious. Several case reports of hypoglycaemic brain damage and of cognitive deterioration attributed to repeated severe hypoglycaemic episodes have been published [44]. Children may be more prone to acute metabolic insults, and there is evidence of developmental disadvantage associated with hypoglycaemic events [45]. It is well established that recurrent hypoglycaemia diminishes counterregulatory responses to further hypoglycaemia, as already mentioned [28, 29]. However, despite significant patient concern, the impact of recurrent hypoglycaemia on cognitive and neural function remains controversial. Overall, recurrent hypoglycaemia appears to cause brain adaptations that may enhance cognitive performance and fuel supply when euglycaemic but which pose significant threats during future hypoglycaemic episodes [44].

With the aging of the population, the prevalence of two common disorders is expected to rise: DM and dementia. It has been shown that people with DM are approximately 1.5-fold more likely to experience cognitive decline and 1.6-fold more likely to develop frank dementia than individuals without diabetes. This is likely due to a higher prevalence of both vascular dementia and Alzheimer's disease [46]. Alzheimer's disease has characteristic histopathological, molecular, and biochemical abnormalities. Currently, there is a rapid growth in the literature pointing toward insulin deficiency and insulin resistance as mediators of Alzheimer's disease-type neurodegeneration, but this surge of new information is riddled with conflicting and unresolved concepts regarding the potential contributions of type 2 DM, metabolic syndrome, and obesity to Alzheimer's pathogenesis. The term "type 3 diabetes" reflects the fact that Alzheimer's disease is a form of DM that selectively involves the brain and has molecular and biochemical features that overlap with other types of DM [47].

Diabetic encephalopathies are now accepted complications of DM [4]. They appear to differ in type 1 and type 2 DM as to the underlying mechanisms and the nature of resulting cognitive deficits. According to epidemiological data, the

increased incidence of Alzheimer's disease in type 2 DM is associated with insulin resistance, hyperinsulinaemia, hyperglycaemia and commonly accompanying attributes such as hypercholesterolaemia, hypertension and (abdominal) obesity. The pathobiology of beta-amyloid and tau protein accumulation, the hallmarks of Alzheimer's disease, has been demonstrated in experimental data. Type 1 diabetic encephalopathy is likely to increase as a result of the increased global incidence of type 1 DM, and its occurrence in increasingly younger patients is particularly worrisome. Alzheimer-like changes and dementia are not prominently increased in type 1 DM. Instead, the type 1 diabetic encephalopathy involves impairments in learning abilities, intelligence development and memory retrieval, resulting in poor school and professional performances. The major underlying component here appears to be insulin deficiency with subsequent effects on the expression of neurotrophic factors, neurotransmitters, and oxidative and apoptotic stressors resulting in defects in neuronal integrity, connectivity and loss commonly occurring in the still developing brain [10,11]. Recent experimental data emphasize the role of impaired central insulin action and provide information as to potential therapies [4]. Therefore, the underlying mechanisms resulting in diabetic encephalopathies are complex and appear to differ between type 1 and type 2 DM. Major advances have been made in our understanding of their pathobiology. However, many questions remain to be clarified and we have to expand our understanding of these complications in order to find therapeutic means to prevent and modify these disastrous consequences in patients with DM [4].

People with DM, especially type 2 DM, are at increased risk of cognitive dysfunction and dementia [41,43]. Possible risk factors such as hypo- and hyperglycaemia, vascular risk factors, micro- and macrovascular complications, depression and genetic factors may play a role. Those who have the metabolic syndrome with or without diabetes suffer more often from dysexecutive problems and slower psychomotor speed than do other patients. In epidemiological studies, DM has appeared to be a risk factor for all types of dementia, including vascular dementia, although the role of the metabolic syndrome in the risk of Alzheimer's disease is still a matter of debate. Drug interventional trials addressing the prevention of cognitive decline through action on features of the metabolic syndrome are disappointing, albeit scarce at this time [48].

Type 2 DM is associated with modest cognitive decrements in non-demented patients that evolve only slowly over time, but also with an increased risk of more severe cognitive deficits and dementia. There seems to be a dissociation between these two “types” of cognitive dysfunction with regard to affected age groups and course of development. Therefore, it has been hypothesized that the mild and severe cognitive deficits observed in patients with type 2 DM reflect separate processes, possibly with different risk factors and aetiologies [43]. In any case, cognitive decline and dementia both place a heavy burden on patients and their relatives, and any means of preventing such age-related changes are worthy of consideration.

Most studies on cognitive dysfunction in type 2 DM have been performed in adults or elderly individuals [41,43]. A recent preliminary study involving both MRI and neuropsychological evaluations documented brain abnormalities in obese adolescents with type 2 DM relative to obese adolescent controls. These abnormalities are not likely to result from education or socioeconomic bias and may result from a combination of subtle vascular changes, glucose and lipid metabolism abnormalities and subtle differences in adiposity in the absence of clinically significant vascular disease. Future efforts are needed to elucidate the underlying pathophysiological mechanisms, and it would be interesting to perform longitudinal studies to see what the late prognosis of these young patients might be [49]. This may be a major concern from a public health point of view considering the increasing epidemics of obesity and type 2 DM in young individuals in the United States and many other countries.

6. Conclusion

The physiological and pathophysiological relationships between the brain and DM are multiple. The hypothalamus may be considered as an integrator of all peripheral signals for controlling both energy and glucose metabolism. The CNS may also be exposed to acute damages in case of either severe hypoglycaemia or hyperglycaemia but may also be exposed to various chronic encephalopathies, some of them mimicking Alzheimer’s disease. Specific prevention and treatment strategies should be evaluated and implemented in patients to reduce the increasingly recognized burden associated with diabetes-related CNS disorders We hope that the current special issue of Diabetes & Metabolism summarizing the lectures presented at the symposium “Brain and Diabetes” organized by the “Société Francophone du Diabète” (December 3, 2010) will be of interest for many people involved in diabetes research and care.

7. Conflict of interest

None related to the content of this article.

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Relationships between adipose tissues and brain: what do we learn from animal studies?

L. Pénicaud

Centre des Sciences du Goût et de l'Alimentation, UMR 6265 CNRS, 1324 INRA-Université de Bourgogne, 15 rue Hugues Picardet, Dijon, France

Abstract

Over the last decades, more and more data supporting the importance of the relationships between the brain and adipose tissues (white and brown) in regards of body weight regulation and energy homeostasis have been published. Indeed the brain via the autonomic nervous system participates to the regulation of different parameters such as the metabolic (lipolysis, lipogenesis and thermogeneis), and secretory (leptin and other adipokines) activities but also plasticity (proliferation differentiation and apoptosis) of adipose tissues. In turn the various fat pads will send information via sensory innervation of white adipose tissue as well as metabolic and hormonal signals acting directly on some brain areas. Altogether these results showed the presence of a neural feedback loop between adipose tissues and the brain which plays a major role in the regulation of energy homeostasis and as been shown to vary according to physiological and pathological states.

Keywords: White adipose tissue; Brown adipose tissue; Autonomic nervous system; Sensory nerve; Metabolism; Plasticity; Metabolic diseases; Review

Résumé

Interrelation entre les tissus adipeux et le cerveau : que nous apprennent les études animales

De nombreuses données soulignent l'importance des interrelations entre le cerveau et les différents tissus adipeux (blanc et brun) en ce qui concerne la régulation du poids et, de manière générale, l'homéostasie énergétique. Le cerveau via le système nerveux autonome est impliqué dans l'activité métabolique (lipolyse, lipogénèse et thermogénèse), l'activité sécrétoire (leptine et autres adipokines) mais également dans le plasticité de ces tissus en contrôlant la prolifération, la différenciation et l'apoptose. En retour, ces tissus, en particulier le tissu adipeux blanc envoie des informations à différentes aires cérébrales via l'innervation sensorielle ainsi que par des signaux métaboliques ou hormonaux qui agissent directement sur certaines de ces zones. L'ensemble des données démontrent la présence d'une boucle neuronale entre les tissus adipeux et le cerveau qui joue un rôle crucial dans la régulation de l'homéostasie énergétique mais également dans des pathologies métaboliques telles que l'obésité et le diabète de type 2.

Mots clés : Issu adipeux blanc ; Tissu adipeux brun ; Système nerveux autonome ; Innervation sensorielle ; Métabolisme ; Plasticité ; Pathologie métabolique ; Revue générale

1. Introduction

Factors of neural origin play an important role in the control of energy homeostasis. Indeed central and autonomic nervous systems are involved in the regulation of whole body energy by regulating its different components: intake, expenditure and storage. The metabolic or secretory activity of various tissues or organ is indeed under the control of the autonomic nervous system. This is the case for the liver, the pancreas and the adrenal glands but there are data showing that this is true for muscles as well. The metabolic and secretory capacities of adipose tissues are also deeply controlled by sympathetic and parasympathetic nerves.

In most mammals, two types of adipose tissue, white and brown, are present. Both are able to store energy in the form of triacylglycerols and to hydrolyze them into free fatty acids and glycerol. Whereas white adipose tissue (WAT) provide

* Correspondence
E-mail address: Luc.Pénicaud@u-bourgogne.fr (L. Pénicaud)

lipids as substrates for other tissues such as muscles, brown adipose tissue (BAT) uses fatty acids for heat production. Over a period of time, white fat mass reflects the balance between energy expenditure and energy intake. Remarkably body fat mass remains relatively constant in adult suggesting that food intake and energy expenditure are linked. This has been supported by numerous studies that demonstrated the inter-dependency of these parameters and thus a feedback loop between the brain and adipose tissues with the involvement of the autonomic nervous system on one side and that of sensory fibers and metabolites or hormonal signals on the other (Fig. 1).

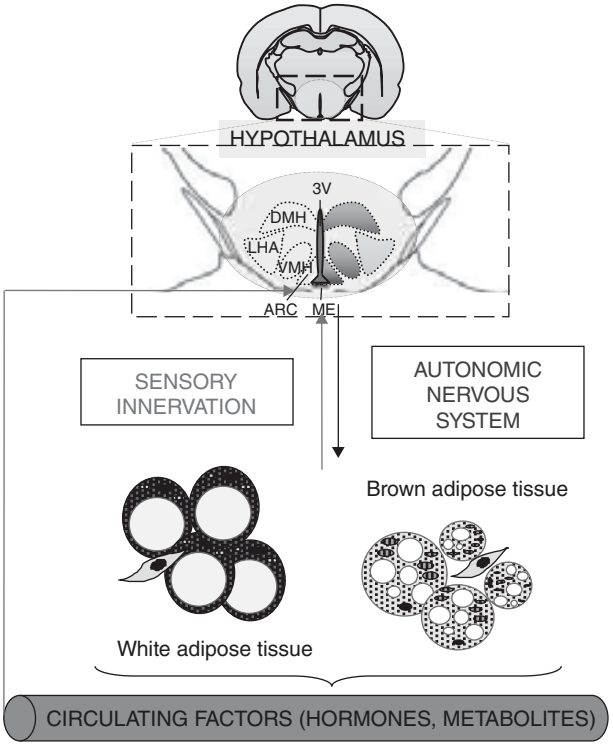

Figure 1. Schematic representation of the feedback loop between the brain and adipose tissues. Brown and white adipose tissues are innervated by the autonomic nervous system, mainly sympathetic one. This will modulate both metabolic (lipogenesis, lipolysis and thermogenesis) and secretory activity of these tissues. Changes in circulating hormones and metabolites associated to sensory nerves originating from white fat pads will in turn signal to some brain areas the energy status of the organism.

2. How the brain talks to adipose tissues? The role of the autonomic nervous system

BAT receives dense SNS innervation both at the level of blood vessels but also directly on adipocytes [1]. It is demonstrated that each brown adipocyte receives one or more nerve endings [2]. In WAT, the noradrenergic innervation fibres have initially been reported as closely associated with the blood vessels leading to its implication in WAT blood flow [3, 4]. Whereas data questioned this in the late eighties [5], it was in the nineties that Bartness and its group demonstrated, direct neuro-anatomical evidence for innervation of white adipocytes [6]. Furthermore they elegantly showed, using viral tracing methodologies that the inputs originate from CNS nuclei (paraventricular hypothalamus, noradrenergic tegmental system, caudal raphe region etc…) that are part of the SNS outflow [7,8].

The neurotransmitter involved is mainly norepinephrine although these nerves contain different neuropeptides among which neuropeptide Y or pancreatic polypeptide Y have been shown to control lipolysis [9-12]. Adipose cells express different noradrenergic receptor subtypes [13]. In BAT, ß-adrenergic receptor subtype (ß3 in rodents) is the only one present and lipolysis is always activated when the sympathetic drive increases [14]. In WAT it has been demonstrated that the lipolytic activity of adipocytes depends on a balance between lipolysis-promoting ß-adrenergic receptor and lipolysis-inhibiting α2-adrenergic receptor [15]. Depending on this balance an increased sympathetic tone can lead to an increase or a decrease in lipolysis.

Most organs or tissues are innervated by both SNS and PNS. For a long time it was thought that white adipose tissues did not received parasympathetic nerves. Recent neuro-anatomical studies in rats have reported parasympathetic innervation of WAT. A physiological role of such input was proposed since vagotomy was shown to reduce the insulin-dependent glucose and free fatty acid uptakes [16]. Such role of PNS can be also sustained by the demonstration of the presence of functional nicotinic receptor on white adipocytes as well as an increased insulin sensitivity of these cells under nicotine stimulation [17]. However the PNS innervation of WAT is highly controversial and remains a subject of debates [18-20].

Although adipose tissue is used as a general term, the fat pads are quite different in regards of their origin, anatomical characteristics and functions so that one should rather speak about white adipose tissues. Indeed both autonomic innervation and the number and affinity of the adrenoceptors of fat depots are heterogeneous. First a relatively separated sympathetic innervation of inguinal and epididymal pads exist, since there are no overlapping patterns of labelled postganglionic cells within the sympathetic chain innervating these two deposits using fluorescent tracers [6]. Viral tracers technologies suggest also differential innervation of fat pads for both sympathetic and parasympathetic nerves [7-8,16,21]. Second, taking norepinephrine turn-over as an index of SNS activity, specific pattern has been delineated which might also depend of the stimulus considered [22]. Altogether these last data indicate a higher lipolysis in intra-abdominal fat pads as compared to subcutaneous one. Third, this is reinforced by the distribution of the different subclasses of receptors that depends on species, sex, and fat depot. Thus, in women, for example, it has been demonstrated that the number of α2 and ß1, ß2-adrenoceptors varies between omental, abdominal and femoral adipose tissues and as a consequence the lipolytic response to epinephrine or norepinephrine [15, 23-25].

The two main metabolic pathways of both white and brown adipocytes are on one hand the synthesis and accumulation of triglycerides and on the other their degradation into free fatty acid and glycerol [26]. The increase in lipids store in adipocytes is performed by two ways. First by the direct uptake of triglycerides associated with lipoproteins coming from the circulation and which are hydrolized by lipoprotein lipase in non esterified free fatty acids. These fatty acids are then transported into and in the cells by a family of fatty acid binding protein (FABP, FAT, FATP, aP2…). Second by the lipogenic pathways i.e. the de novo synthesis from glucose. This last one is transported into the cell mainly via the insulin-sensitive glucose transporter isoform Glut 4. The glucose allows the synthesis of pyruvate and glycerol-3-phosphate, substrates, which will lead to the synthesis of triglycerides. Indeed, pyruvate will be utilized for the formation of acetyl-CoA and then its transformation into malonyl CoA under the control of acetyl-CoA carboxylase. The last step catalyzed by fatty acid synthase, a multienzyme complex, leads to the formation of long chain fatty acids. These anabolic pathways are mainly under the control of insulin.

It is now recognized that lipolytic pathways is mainly under the dependency of three main players: adipose triglyceride lipase, hormone sensitive lipase, and perilipin A [26]. In regards of metabolism the main differences between white and brown adipocytes is located downstream to lipolysis. Indeed in white adipocyte, both free fatty acids and glycerol are released into the adjacent blood vessels to provide fuel for other tissues. In brown adipocyte, free fatty acids will be oxidized by the cell itself. The energy produced will be then dissipated as heat, thanks to the presence of a specific mitochondrial protein: the uncoupling protein 1 [27]. UCP1 confers to the mitochondria of brown adipose tissue their capacity of becoming uncoupled. As already mentioned above catecholamines and particularly norepinephrine are the main hormones involved in the control of lipolysis in both cell types. However one has to underline that, the antilipolytic effect of insulin is predominant and thus catecholamines exert their effect when insulin level is low. From what is said above it is easy to conclude that the sympathetic nervous system is the main driver for adipose tissues lipolysis.

Apart its well-known effect on lipolysis in both adipose tissue types and its effect on thermogenesis in brown adipose tissue, sympathetic nervous system plays a role in regulating the anabolic pathways. Thus it has been shown that stimulation of sympathetic nerves induces a dramatic increase in glucose uptake, utilization and lipogenesis in BAT but not in WAT [28-30]. Whereas, as already mentioned, there are evidences that PNS innervation increases insulin sensitivity in WAT [16].

Over the last 20 years the notion has emerged that WAT is not only involved in the storage and release of energy but could also be part of other physiological functions due to its capabilities in synthesis and secretion of numerous factors such as leptin, adiponectin and many proteins involved in inflammation and immunity [31,32]. So that adipose tissue is now considered as a true endocrine organ.

The synthesis and secretion of some of these compounds are under the control of numerous factors among which the sympathetic nervous system via catecholamines plays a role. Leptin control has probably been the most studied. They are numerous evidence that stimulation of ß-adrenoceptor decreases the release of leptin. In human adipose tissue this occurs through a posttranslational mechanism, most likely secretion per se. In contrast, in rat adipose tissue, isoproterenol does not affect basal leptin secretion but has a short-term action to antagonize the insulin- stimulated leptin biosynthesis [33,34]. Although an elegant study demonstrates a decrease leptin secretion when 3T3L1 adipocytes (a well-characterized white adipose cell line) are cultured in the presence of primary sympathetic neurons [35]. It has then been proposed that catecholamines may mediate short-term decrease in plasma leptin that occur within hours of fasting and cold exposure [36].

Adiponectin is also negatively regulated by ß-adrenoceptor [37]. By contrast the secretion of cytokines such as TNFα and IL6 are increased under ß-adrenergic stimulation [38, 39]. Overall these data suggest that upregulation of proinflammatory cytokines and downregulation of adiponectin by ß-adrenoceptor activation may contribute to the pathogenesis of catecholamine-induced insulin resistance.

Fat mass is the result of two processes i.e. the regulation of the size and the number of adipocytes. We have shown that the autonomic nervous system is indeed involved in the first one by regulating both energy stores and thermogenesis in WAT and BAT respectively. There are also numerous evidence showing that the SNS is involved in the control of proliferation and differentiation and to a lesser of apoptosis of white and brown adipocytes (Fig. 2).

It is then well established than norepinephrine induces both proliferation and differentiation of brown adipocytes precursors in vivo and in vitro [40,41]. Results observed after a decreased (denervation, noradrenergic blockade, hypothalamic lesion) or increased (ß-agonist treatment, cold exposure) sympathetic activity lead to the same general conclusion.

By contrast sympathetic activation would inhibit the development of WAT [25,42]. Norepinephrine inhibits proliferation of adipocyte precursor cells in vitro and can be blocked by propranolol, a general ß-adrenoceptor antagonist [43]. In vivo surgical denervation of WAT triggers significant increases both in rats and Siberian hamsters [8,30,44]. We have been the first to demonstrate that one week after denervation of one retroperitoneal fat pad, DNA content was largely increased without change in the number of mature white adipocytes. Furthermore, the amount of A_2COL6, an early marker of white adipocyte differentiation was enhanced in the denervated pad. One month later, the number of mature adipocytes was significantly increased in the denervated pad [30]. A recent study using transgenic mice having a massive reduction of innervation due to the lack of Nscl-2, a neuronal specific transcription factor, came in support of such observation [45]. These mice present an increase preadipocytes number and a bimodal distribution of the size of adipocytes indicating an increase in the number of small adipocytes.

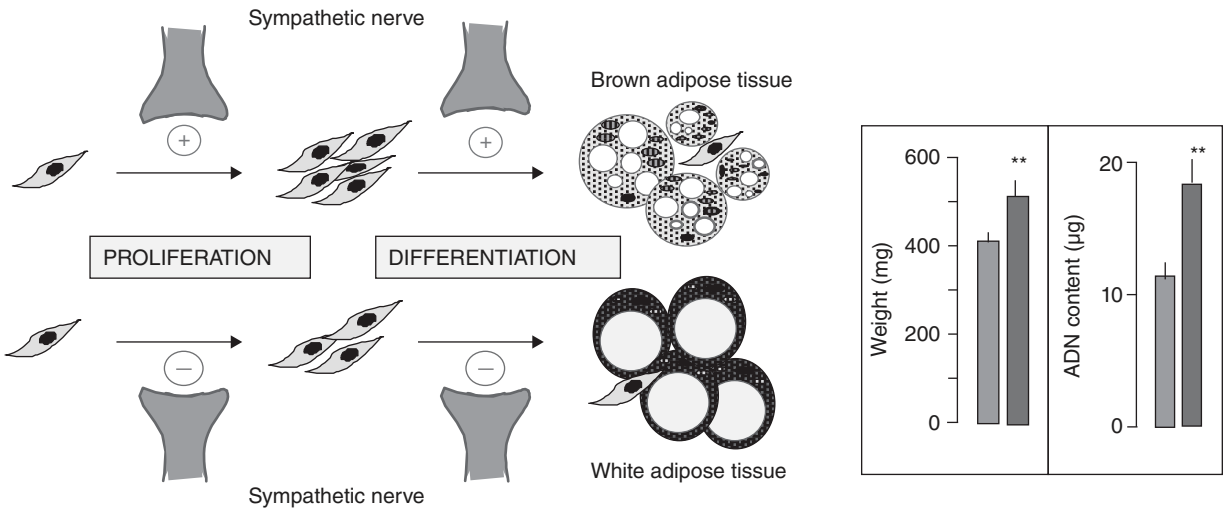

Figure 2. Schematic representation of the opposite effects of sympathetic nerve activity on proliferation and differentiation of brown and white adipose tissues. As an illustration the weight and DNA content are increased in denervated white fat pad (red column) compared to un-denervated control (blue column), demonstrating the inhibiting effect of the sympathetic tone on proliferation and differentiation of white adipose tissue (adapted from Cousin et al. 1993).

Although the importance of apoptosis in the biology of adipose tissues is still a controversial issue, there are different reports describing such process in both white and brown adipocytes. To our knowledge there is no direct demonstration of a role of the SNS in regulating the rate of apoptosis in adipose tissues, however several observations are in support of such role. It has been demonstrated that the proapoptotic effect of TNFα in brown adipocytes is abrogated by noradrenaline [46]. Furthermore noradrenaline protects these cells from apoptosis by phosphorylation and activation of MAP-kinase [47]. Leptin like insulin induces a reduction of fat pad weight. This effect is observed both under peripheral or central injection of the hormones. Furthermore it has been reported that adipocyte apoptosis occurs after intracerebroventricular administration of leptin in rats [48-50]. On the other hand it is well demonstrated that leptin induces an increased sympathetic nervous system activity [51-53]. From these data, it is believe that the signal that promotes apoptosis under insulin and leptin CNS activation is probably norepinephrine or another co-secreted neurotransmitter.

Altogether, these results demonstrate that in vivo SNS innervation of WAT and BAT acts as modulator of fat cell development.

3. How adipose tissues talk to the brain

Energy balance is the result of ingestive behavior, energy expenditure and energy storage in adipose tissue. To explain the precise overall regulation of these parameters it has been hypothetized, at first by Kennedy in the 50th, that signals generated in proportion to body fat stores will act in the brain to modulate food intake and/or energy expenditure [54]. Among these signals the first to be proposed was insulin; since it was demonstrated that the pancreatic hormone acts in the CNS to reduce food intake [55,56]. Then leptin, the product of the ob gene was discovered and shown to play a major role in this regulation process [57,58]. One has to stress also the role of nutrients of which the concentration might depend on the metabolic activity of adipose tissues such as glucose an free fatty acids. Indeed both of these metabolites have been shown to play an important role as signals, reflecting energy homeostasis, to some part of the brain [59-61]. Glucose and lipids are detected by specialized fuel-sensing neurons that are incorporated in specific hypothalamic neuronal circuits. Hence, circulating nutrients cooperate with hormones, such as insulin, leptin, and ghrelin, to regulate the activity of distinct neuron populations that control food intake, energy expenditure, and glucose homeostasis.

Apart these circulating signals acting directly in the hypothalamus and other areas, adipose tissues sensory nerves may be part of this system. Indeed sensory innervation of WAT has been demonstrated by various facts. The identification of substance P and calcitonin gene-related peptide, markers of sensory neurons was a first demonstration [10]. Then a direct neuroanatomical demonstration was given by use of anterograde tracer [62]. Finally the sensory projection to different brain areas, was extensively studied by Bartness et al. [20,63]. As stated by these authors, “labelling cells were found at all levels of the neuroaxis including both the nodose ganglia (visceral afferents) as well as the dorsal horn (spinal afferents) of the spinal cord and in almost all the autonomic outputs areas in the brainstem and midbrain”.

Although one does not know what (leptin, lipid molecules such as glycerol, free fatty acids, prostaglandins) these nerves “sense”, data are in support of their role in informing the brain on lipid stores. When selective destruction of sensory innervating epididymal fat pad was performed in hamster by injecting capsaicin in one pad, the weight of the contra-lateral non-injected pad was increased in a degree that approximated the lipid deficit if the pad had been removed by lipectomy [64,65].

4. Conclusions

This review underlines the progress made over the years in delineating the relationships between the adipose tissues and the nervous system. Indeed data have clarified the neuroanatomical innervation of the different fat pads, the central localisation of their origin and their projections, the demonstration of sensory and parasympathetic innervation. This represents however new field that merits further attention since they are, as already said, a matter of debate. The role of the autonomic nervous system in the control of adipose tissues functions has also received strong attention and led to new concept in regards not only to their metabolic and secretory activity but also to their plasticity. Considering plasticity, more data are needed to strongly sustain the influence of the SNS on apoptosis but also in the development of adipose tissue. To determine whether nervous control could play a role in the fate of the different progenitors (stem cells, multipotent cells) which have been demonstrated to be present in adipose tissues [66-69] and of which the role, the differentiation potential and their regulation is still poorly understood, appears crucial for a better understanding of adipose tissues biology and physiology.

Altogether this neural feedback-loop between adipose tissues and the brain plays a crucial role in the regulation of energy homeostasis and body fat mass. As it has been shown it could be altered in numerous metabolic pathologies such as obesity and type II diabetes, this represents an important areas of research with putative clinical implications.

5. Conflict of interest

None related to the content of this article.

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Central control of glucose homeostasis: the brain – endocrine pancreas axis

B. Thorens

Center for Integrative Genomics, University of Lausanne, Genopode Building, 1215 Lausanne, Switzerland

Abstract

A large body of data gathered over the last decades has delineated the neuronal pathways that link the central nervous system with the autonomic innervation of the endocrine pancreas, which controls alpha- and beta-cell secretion activity and mass. These are important regulatory functions that are certainly keys for preserving the capacity of the endocrine pancreas to control glucose homeostasis over a lifetime. Identifying the cells involved in controlling the autonomic innervation of the endocrine pancreas, in response to nutrient, hormonal and environmental cues and how these cues are detected to activate neuronal activity are important goals of current research. Elucidation of these questions may possibly lead to new means for preserving or restoring defects in insulin and glucagon secretion associated with type 2 diabetes.

Keywords: Hypothalamus; Brainstem; Beta-cells; Insulin; Glucagon; Review

Résumé

Contrôle central de l'homéostasie glucidique : l'axe cerveau-pancréas endocrine

Les cellules beta pancréatiques, en sécrétant l'insuline, jouent un rôle clé dans le contrôle de l'homéostasie glucidique. Cette sécrétion est régulée très finement pour que l'action hypoglycémiante de l'insuline soit précisément adaptée aux augmentations de glycémie. En plus de cette régulation aigue, la régulation du nombre total des cellules bêta, ou masse cellulaire bêta, est un aspect important du maintien de la capacité du pancréas endocrine de sécréter l'insuline au cours de modifications physiologiques, comme la grossesse ou l'obésité, associées au développement d'une insulinorésistance des tissus périphériques. Cette plasticité de la masse cellulaire bêta est maintenant considérée comme importante pour permettre le maintien de l'homéostasie glucidique au cours de la vie. En effet, on pense que l'apparition du diabète de type 2 est déterminée par une réduction de la capacité sécrétoire des cellules bêta, qui ne permet plus de compenser l'insulinorésistance du foie, des muscles et du tissu adipeux. Ceci est causé par une diminution de la capacité de chaque cellule bêta de sécréter assez d'insuline et par une réduction de la masse cellulaire bêta. En plus de ces défauts d'insulinosécrétion, une hypersécrétion relative de glucagon dans l'état de jeûne et un manque de suppression du glucagon dans la phase absorptive contribuent également à la dégradation du contrôle glycémique.

Les mécanismes de contrôle de la sécrétion d'insuline et de glucagon sont étudiés très activement. Bien que la plupart des études sont centrées sur les cellules insulaires elles-mêmes, il est maintenant établi que l'insulinosécrétion et le contrôle de la masse cellulaire bêta sont fortement influencés par des signaux hormonaux et neuronaux. Ici, je vais discuter certaines nouvelles informations concernant le contrôle du pancréas endocrine par le système nerveux autonome.

Mots clés : Hypothalamus ; Tronc cérébral ; Cellules bêta ; Insuline ; Glucagon ; Revue générale

* Correspondence
E-mail address: bernard.thorens@unil.ch (B. Thorens)

1. Introduction

Pancreatic beta-cells play a key role in the control of glucose homeostasis by secreting the hormone insulin. This process is very precisely regulated so that the hypoglycaemic effect of this hormone is proportionate to the increase in glucose appearing in the blood. In addition to this acute regulation, the control of the total number of beta-cells, or beta-cell mass, is also an important aspect for preserving the insulin secretion capacity of the endocrine pancreas in changing physiological conditions, such as pregnancy or obesity, which are associated with insulin resistance of peripheral tissues. This plasticity of the beta-cell mass is now thought to be critical for proper control of glucose homeostasis over a lifetime. Indeed, the development of type 2 diabetes occurs when beta-cells are no longer able to secrete enough insulin to counter the insulin resistance of liver, fat and muscle; this is caused by both a defect in beta-cells to respond to elevations in blood glucose concentrations by an appropriate secretion of insulin, and by a reduction in the total beta-cell number. In parallel, with these defects in insulin secretion, relative hypersecretion of glucagon in the fasting state and impaired suppression of its secretion in response to feeding contribute to the worsening of the hyperglycaemia in diabetes.

The mechanisms controlling insulin and glucagon secretion and beta-cell mass are being intensely investigated. Whereas most of the studies focus on the islet cells themselves, it is clear that the secretion response, as well as the control of the beta-cell mass, are under the influence of external hormonal and neuronal signals. Here, we will review some of the new information available in the literature concerning the control of the endocrine pancreas by the autonomic nervous system.

2. Innervation of the islet cells by the sympathetic and parasympathetic nervous system

The pancreatic beta-cells are under the control of multiple external hormonal and neuronal stimuli. This is evidenced by the expression of a large number of cell surface receptors. These receptors include those for the gluco-incretin hormones, GLP-1 and GIP, secreted by gut endocrine cells following meal absorption, and for glucagon produced by pancreatic alpha cells, which can act as a paracrine signal. The receptors for these hormones are G protein-coupled receptors (GPCR) linked to activation of the cAMP/protein kinase A intracellular signalling pathway [1], which potentiate glucose-stimulated insulin secretion (GSIS). Several GPCRs respond to parasympathetic innervation: the receptors for acetylcholine (m3AChR), VIP (vasoactive intestinal polypeptide), PACAP (pituitary adenylate cylase activating peptide), and GRP (gastrin releasing peptide). They also provide stimulatory input to increase glucose-stimulated insulin secretion, a mechanism that depends on the activation of the heterotrimeric Gq protein, which controls activation of the IP3/Ca^{++} and diacylgylcerol/protein kinase C pathways. Regulation of beta-cell activity is also negatively controlled by sympathetic innervation through noradrenaline (mostly a2-AR), galanin, and NPY (neuropeptide Y) receptors. These receptors are GPCRs coupled to the Gi protein that reduces adenylate cyclase activity, reduces cAMP production and inhibits secretion [2,3].

3. Evidence for control of insulin secretion by the ANS

Many studies have demonstrated that parasympathetic innervation of the pancreatic beta-cells plays an important role in the control of GSIS. For instance electrical activation of the vagal nerve leads to an increase in insulin secretion, an effect that is augmented by the presence of a slightly elevated glucose concentration [4-7]. Activation of the parasympathetic nerve also underlies the cephalic phase of insulin secretion, i.e., the secretion induced by glucose appearing in the oral cavity. This response can be induced for instance in sham feeding experiments and can be suppressed by vagotomy. The importance for this innervation is also evidenced when studying insulin secretion by islets transplanted in the liver of diabetic mice, which is much reduced in response to an oral glucose load. The neuronal circuit involved in this response depends on direct neuronal connections from taste buds and the brainstem, which then activates the parasympathetic nerve that stimulates beta-cells [8-11].

Other neuronal pathways that activate initial insulin secretion following food absorption are found in the gut, especially in the hepatoportal vein area [12]. When glucose enters the portal vein, glucose sensors are activated that increase the firing rate of vagal afferents [13,14]. The exact cellular nature of these sensors has not yet been firmly established. However, physiological experiments using mice with inactivation of different genes or using different pharmacological agents have demonstrated that glucose sensing by these sensors depends on the presence of the glucose transporter Glut2, of the receptor for GLP-1, and can be inhibited by somatostatin [15-17]. These features are similar to those of the pancreatic beta-cell glucose sensing system. Importantly, it has been demonstrated that activation of these sensors by glucose is involved in the control of insulin secretion, through a central nervous relay, in particular in the control of first phase insulin secretion [18,19].

Glucose can also activate neurons in the central nervous system for controlling the function of peripheral tissues, including pancreatic alpha and beta-cells. For instance, intracarotid injection of glucose, which does not change peripheral glycemic levels, induces a small, transient increase in insulin secretion, mimicking cephalic insulin secretion. As these glucose injections also lead to an increase in c-fos labelling, a marker of activation, of neurons in the arcuate and paraventricular nuclei, this suggests that these hypothalamic nuclei are involved in the control of insulin secretion [20]. Earlier studies demonstrated that lesions of the hypothalamic ventromedial nucleus induced an acute increase in insulin secretion that could be suppressed by vagotomy [21].

Although these studies did not provide a precise definition of the cells and neuronal circuits involved in this control of beta-cell function, they showed the existence of a link between hypothalamic centres and the endocrine pancreas through the vagus nerve. Retrograde transsynaptic viral labelling techniques have demonstrated that the parasympathetic nerve terminals present in the pancreas are in synaptic contact with the paraventricular nucleus and the perifornical area [22]. The arcuate nucleus is certainly also involved in this control. This nucleus contains two major types of neurons, those secreting the neuropeptides NPY and AgRP, and those secreting POMC and CART. Intracerebroventricular administration of NPY rapidly stimulates insulin secretion, an action that can be suppressed by vagotomy, suggesting that activation of NPY neurons in the arcuate nucleus may normally control beta-cell function through activation of the parasympathetic nervous system [23,24]. Activation of the parasympathetic tone to the endocrine pancreas can be increased by lesions of the ventromedial hypothalamus, and this leads to increased beta-cell proliferation and mass [25,26], indicating that not only the secretion capacity but also the total number of beta-cells can be regulated by this nervous control.

It has now been established that the parasympathetic preganglionic neurons that innervate the pancreas have their cell bodies in the brainstem, in the dorsal motor nucleus of the vagus (DMNX) [27,28]. Thus understanding the regulation of the parasympathetic innervation of the beta-cells will require understanding the mechanisms that control the activation of the neurons present in the DMNX, in particular, how their firing rate is controlled by changes in blood glucose levels. The DMNX neurons can directly sense glucose levels, but they can also be controlled by other neurons present in other nuclei, which are sensitive to either increases or falls in glycaemic levels. For instance it is known that neurons from the nucleus of the tractus solitarius (NTS) form synaptic contacts with DMNX neurons and that in the NTS there are many glucose-sensing cells [29]. Thus, one possibility is that parasympathetic control of beta-cells may be modified by glucose sensing neurons of the NTS. Glucose-dependent input can also come from the glucose modulation of arcuate nucleus neurons or other hypothalamic nuclei in synaptic contact with the DMNX [25].

4. Importance of parasympathetic innervation in the control of beta-cells

A major advance in the understanding of the physiological role of the parasympathetic control of beta-cells emerged from studies of mice with beta-cell-specific inactivation of the m3AchR, the major beta-cell receptor for acetylcholine [30-32]. Inactivation of this receptor led to glucose intolerance, which worsened when mice were fed a high fat diet. The cause of this deregulation was a defect in insulin secretion by beta-cells, with normal pancreatic insulin content, although it has not been reported whether the beta-cell mass is modified. As insulin sensitivity is normal, this suggests that only the beta-cell defect in acetylcholine receptor signalling causes the defect. As mentioned above, vagotomy may reduce beta-cell mass, whereas deletion of m3AchR in beta-cells does not appear to reduce it. This suggests that signalling by the parasympathetic neuropeptides VIP, PACAP and GRP may additively contribute with acetylcholine to the control of beta-cell mass and function.

5. Regulation of glucagon secretion by the ANS

When blood glucose concentrations fall below the euglycaemic level, rapid activation of the autonomous nervous system triggers a counterregulatory response to restore normoglycaemia. This response is mediated by an increase in glucagon secretion, the release of catecholamines from the adrenal glands, and inhibition of insulin secretion [33-35]. These responses are controlled by the autonomic nervous system and the sympathoadrenal axis. Both the sympathetic and parasympathetic nervous systems activate glucagon secretion by direct alpha-cell stimulation. The sympathetic nervous system inhibits insulin secretion through α2AR-mediated mechanisms, and activation of epinephrine release from the adrenals stimulates glucagon secretion via ß2-AR activation and inhibits insulin secretion through the beta-cell α2AR. The central sites of glucose detection that activate the autonomic nervous system are located in the hypothalamus and brainstem. Lesion, pharmacological and genetic studies have been used to identify the sites of central hypoglycaemia detection that control counterregulation. Evidence exists for a role of the ventromedial hypothalamus (VMH) [36-38] and of brainstem nuclei, in particular the nucleus of the tractus solitarius (NTS), the DMNX, and A1/C1 catecholaminergic neurons of the basolateral medulla in the control of glucagon secretion [39,40]. A major role for the brainstem nuclei in the physiological response to hypoglycaemia has been suggested by different experimental approaches. For instance, in decerebrated rats, the glucagon secretion response to an i.p. injection of the glucose anti-metabolite 2-deoxy-D-glucose is preserved [41], indicating that neuronal circuits of the brainstem are sufficient for the autonomic control of counterregulation.

6. Molecular control of central glucose sensing controlling glucagon secretion

The mechanisms by which glucose sensitive neurons detect changes in glycemia and alter their firing pattern are still being investigated. There is, however, evidence for the participation in this glucose sensing process of the same proteins that control glucose signaling in pancreatic beta-cells [42]: the glucose transporter Glut2, the enzyme glucokinase and the ATP sensitive potassium channel. Also, evidence is accumulating that the fuel sensing, AMP-activated protein kinase can participate in the physiological reponse to hypoglycaemia [43], in

particular in neurons expressed by NPY and POMC neurons of the hypothalamic arcuate nucleus [44].

Studies in mice have also provided evidence for the involvement of Glut2 in central glucose sensing, in particular in both the stimulation of glucagon secretion in response to hypoglycaemia and in its supression by hyperglycaemia [45]. Evidence has been presented that Glut2 needs to be expressed in astrocytes for control of glucagon secretion in response to hypoglycaemia, but not for the feeding response to glucoprivation [46,47]. This suggests that multiple Glut2-dependent glucose sensors do exist, which depend on expression of this transporter in astrocytes or in neurons and in cells that are activated by increases or falls in glycemic levels. Furthermore, recent studies to identify the sites of Glut2 expression in the brain using fluorescent reporter genes for labelling Glut2 expressing cells have revealed a high concentrations of Glut2-neurons in the brainstem, in particular in the NTS, the DMNX and the basolateral medulla [48]. By contrast, relatively few Glut2 positive cells were observed in the hypothalamus. Almost none were detected in the arcuate but there were more in the lateral hypothalamus, the perifornical area and the zona incerta. These studies will now allow a direct assessment of the glucose sensitivity of these neurons, as fluorescently-labelled cells can be observed under the confocal microscope in a setting that is appropriate for patch-clamp electrophysiological recordings. These studies should pave the way for the identification of the neuronal circuits controlled by glucose, which depend on Glut2 expression, and to relate them with the control of specific physiological functions, in particular the control of glucagon and insulin secretion.

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8. Conflict of interest

None related to the content of this article.

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Brain, liver, intestine: a triumvirate to coordinate insulin sensitivity of endogenous glucose production

G. Mithieux

Institut National de la Santé et de la Recherche Médicale, U855, Lyon, F-69372, France
Université de Lyon, Lyon, F-69008, France
Université Lyon I, Villeurbanne, F-69622, France

Abstract

The brain, especially the hypothalamus, can modulate hepatic glucose fluxes. The sympathetic system promotes glycogen breakdown. The parasympathetic system stimulates glycogen deposition. Central insulin signalling or hypothalamic long-chain fatty acid oxidation can both control insulin's suppression of endogenous glucose production. Intestinal gluconeogenesis initiates a portal glucose signal, transmitted to the brain via the gastrointestinal nervous system. This signal may modulate the sensation of hunger and satiety and insulin sensitivity of hepatic glucose fluxes as well, via the modulation of hypothalamic activity

Keywords: Liver; Intestine; Brain; Gluconeogenesis; Insulin sensitivity; Portal glucose signal; Gut-brain axis; Review

Résumé

Cerveau, foie, intestin : un triumvirat pour coordonner la sensibilité à l'insuline de la production endogène de glucose

Le cerveau, en particulier l'hypothalamus, peut moduler les flux hépatiques de glucose. Le système sympathique promeut la dégradation du glycogène. Le système parasympathique stimule le stockage du glycogène. La signalisation centrale de l'insuline ou l'oxydation hypothalamique des acides gras à longue chaine sont deux mécanismes capables de contrôler la suppression par l'insuline de la production endogène de glucose. La néoglucogenèse intestinale initie un signal glucose portal, transmis au cerveau par le système nerveux gastro-intestinal. A travers la modulation de l'activité hypothalamique, ce signal peut moduler aussi bien les sensations de faim et de satiété que la sensibilité à l'insuline des flux hépatiques de glucose.

Mots clés : Foie ; Intestin ; Cerveau ; Néoglucogenèse ; Sensibilité à l'insuline ; Signal glucose portal ; Axe intestin-cerveau ; Revue générale

1. Introduction

Endogenous glucose production (EGP) is a crucial function, which allows the body to maintain plasma glucose concentration around 1g/L in absence of glucose supplied by food, i.e. between the periods of assimilation of meals and during the night. Three organs only can perform this function, because they are the only organs known to express glucose-6-phosphatase (Glc6Pase), the key enzyme of EGP (see [1] for a review). All three organs express all the enzymes mandatory for glucose synthesis [2-4], and all are able to release glucose when needed, e.g. during fasting [5-7]. In line with this key role in fasting glucose homeostasis, Glc6Pase together with phosphoenolpyruvate carboxykinase (PEPCK), the other key regulatory enzyme of EGP, are regulated by nutrients and hormones (notably insulin) at the level of gene expression and enzymatic activity in the liver, kidney and small intestine [2-5, 8-12].

Among the three organs capable of performing EGP, the liver is most often regarded as the major contributor. This is essentially due to its specific capacity of glycogen storage, a store of glucose that it can mobilize via the activation of glycogenolysis. This allows it to rapidly and finely tune blood glucose concentration at the beginning of post-absorptive and fasting periods. The other two organs (kidney and intestine) do not exhibit this capacity, and it is generally observed that they increase their participation in EGP as fasting is lasting [1,6,8,13,14]. For this reason, a vast majority of previous studies about the regulation of EGP have focused on hepatic glucose fluxes.

* Correspondence
E-mail address: gilles.mithieux@inserm.fr (G. Mtithieux).

2. Central control of endogenous glucose production

In addition to the control by insulin, it is well known that the hypothalamus, via the modulation of the sympathetic-parasympathetic balance, takes part in the control of whole body glucose metabolism, notably at a liver level. Several studies demonstrated that the hypothalamus influences insulin secretion [15], glucose utilization in the skeletal muscle [16] and liver glucose storage and production [17,18]. Particularly, the nervous efferents connecting the hypothalamus to the liver tightly control EGP via the regulation of hepatic glycogen storage [17,18]. More specifically, neurons in the ventromedial hypothalamus control the stimulation of liver glycogenolysis, through the activation of the sympathetic system. Conversely, neurons in the lateral hypothalamus stimulate liver glycogenogenesis, via the activation of the parasympathetic system. Additional circuits from the paraventricular nucleus to the liver have also been involved in the control of hepatic glycogen storage, via a modulation of the sympathetic-parasympathetic balance. In addition, the paraventricular nucleus has been suggested to also serve as a relay for signals from both the ventromedial and the lateral hypothalamus to the liver (for a review, see [17]).

More recently, the role of the hypothalamus in the control of glucose production by the liver has been specified, either in rats or in mice bearing targeted gene mutations affecting insulin receptor expression and signalling. A key role for insulin signalling within the hypothalamus has been suggested. Notably, insulin's suppression of EGP is decreased in rats with decreased insulin signalling in the hypothalamus [19,20]. Moreover, insulin receptor-KO mice with partial restoration of insulin receptor in the brain, liver and pancreatic β-cells are rescued from neonatal death and diabetes ketoacidosis. However, despite a full restoration of insulin signalling in the liver, they still exhibit defects in the control of HGP by insulin, due to persisting partial deficiency of insulin signalling in the arcuate and paraventricular hypothalamic nuclei [21]. At an intracellular mechanistic level, a central sensing of long chain fatty acil-CoAs, through their oxidation, and a relay via the activation state of hypothalamic ATP-dependent potassium channels, has been suggested to be involved in the suppression of glucose production by insulin [22-24]. Moreover, the descending nerve fibres of the hepatic branch of the vagus have been shown to convey a causal efferent signal to the liver [23,24]. In addition, the efferent signal is also able to regulate both hepatic Glc6Pase and PEPCK gene expression [24].

3. Gut-brain axis control of hepatic glucose production and insulin sensitivity

Numerous studies have established that the detection of portal glucose appearance within the walls of the portal vein, a phenomenon referred to as "portal glucose signal", is able to initiate several neural-mediated mechanisms influencing either the sensation of hunger and satiety or glucose homeostasis. Among them: i) a decrease in spontaneous food intake [25-28]; ii) a rapid-phase secretion of insulin [29]; iii) the induction of glucose uptake in the liver and peripheral tissues [16,30]; and iv) the inhibition of hypoglycaemia-induced sympathoadrenal response [31-34]. These effects depend on the integrity of portal innervation as the detection of glucose decreases the electrical activity of hepatoportal vagal and spinal afferents [35]. Few studies also demonstrated that this portal glucose signal influences the impulse activity of central neurons, in areas involved in the control of food intake and of glucose metabolism, the nucleus of the solitary tract [36] and the lateral hypothalamus [37, 38].

It was, therefore, tempting to speculate that intestinal gluconeogenesis, via the release of glucose into the portal vein and activation of the portal glucose signal, could modulate in the same time food intake and glucose homeostasis. This hypothesis was first tested in the context of protein-enriched regimen, known to induce satiety in animals and humans [39-41], and to rapidly improve glucose control in obese diabetic patients [42-44]. In agreement with the hypothesis, high protein-feeding induces a strong induction of the expression of the regulatory enzymes of gluconeogenesis in the small intestine (SI): Glc6Pase, PEPCK-c and glutaminase [45] (glutamine is indeed an important intestinal gluconeogenic substrate (1)). Using arterio-venous glucose balance determinations in combination with tracer-based studies, it was possible to establish that the gut actually releases glucose in the post-absorptive situation in protein-fed rats [45]. Even if this approach is somewhat inaccurate (see the discussion of ref [46] for a comprehensive analysis of its strengths and weaknesses), the rate of glucose release by the gut could be estimated to provide about 15-20% of EGP in protein-fed rats. Interestingly, this appeared sufficient to account for the decrease in food intake observed in protein-fed rats, since an equivalent infusion of glucose into the portal vein of control chow-fed rats (not exhibiting substantial intestinal glucose release) actually decreased their food intake by a comparable value [45]. An immunohistochemical study of the expression of the transcription factor c-fos (as a marker of activation of neurons) in the hypothalamus showed that the arcuate nucleus, the dorsomedial, ventromedial and paraventricular nuclei and the lateral area are similarly activated during the post-absorptive period both in high-protein fed animals, and in chow-fed rats receiving infusions of glucose in the portal vein. It is noteworthy to point out that the appearance of glucose from intestinal gluconeogenesis does not increase EGP in protein-fed rats. The liver, indeed, adapts by decreasing its proper glucose production, through the enhancement of glycogen storage [46], in agreement with previous studies [30]. In association with this increased liver glycogen deposition, rats fed upon a protein-enriched diet exhibited an increased suppression of EGP by insulin during hyperinsulinemic euglycemic clamps [46].

A further strong argument, that intestinal gluconeogenesis can have a crucial role in the control of food intake and

hepatic insulin sensitivity, has come from a study pertaining to the surgery of obesity. Two types of techniques are mostly used, with different physiological consequences. Gastric banding (GB) only consists in the reduction of the stomach volume (aiming to decrease meal size), and an increasingly used technique, the so-called "gastric bypass" (GBP), additionally excludes the proximal gut from direct contact with nutrients. Both GB and GBP patients loose weight with time. However, only GBP patients, and not GB patients, exhibit very early metabolic improvements (e.g. decreased hunger and improvements in fasting glucose, glycosylated haemoglobin or glucose tolerance), before any weight loss has occurred [47,48]. To understand this specificity of the bypass technique, two models of GB and GBP mice were developed and their glucose metabolism studied [49]. The surgery was performed in obese insulin-resistant mice fed on a high fat-high sucrose diet for 12 weeks. Two weeks after surgery, GBP mice dramatically reduce food intake and recover a quasi-normal insulin sensitivity, while GB and sham-operated mice still exhibit marked insulin resistance, as revealed from glucose and insulin tolerance tests [49]. Hyperinsulinemic euglycemic clamp experiments have demonstrated that the improvement of insulin sensitivity takes place in the liver (EGP). This corresponds notably to a decreased activity of hepatic Glc6Pase, very similar to what was observed upon activation of a brain-liver circuit in a previous study [24]. It was further observed that a marked induction of the expression of both Glc6Pase and PECK-C enzymes occurs in the distal jejunum and ileum in EGA mice. Both enzymes are poorly expressed in these portions of the SI in the normal situation. This translated in glucose release into the portal blood during the post-obsorptive period, as was observed in protein fed rats. On the contrary, the espression of gluconeogenic enzymes remained low in the same parts of the SI in GB mice. As previously shown for the satiety effect of dietary protein on food intake [45], the improvement in insulin sensitivity initiated by GBP is strongly blunted in mice in which the portal vein afferents have been destroyed [49].

4. Conclusion

It is therefore established that the brain, especially the hypothalamus, has the capacity to modulate hepatic glucose fluxes, via the regulation of glycogen storage or mobilization by the sympathetic/parasympathetic balance. In addition, a gut to brain axis, via the activation of intestinal gluconeogenesis and its portal sensing is able to signal to the hypothalamus and to initiate major modulation of liver insulin sensitivity and hepatic glucose fluxes. The hypothesis that this gut-brain-liver circuit might be a key determinant of insulin sensitivity in health and disease deserves further consideration.

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6. Conflict of interest

None related to the content of this article.

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The gut-brain axis: a major glucoregulatory player

R. Burcelin

Institut National de la Santé et de la Recherche Médicale (INSERM), U858, Toulouse, France
Université de Toulouse, UPS, Institut de Médecine Moléculaire de Rangueil (I²MR), IFR31, F-31432 Toulouse cedex 4, France

Abstract

Glucose homeostasis corresponds to the overall physiological, cellular, and molecular mechanisms which tightly maintain the glycaemia between ~4.5 and ~6 mM. The resulting blood glucose concentration is the consequence of a balance between the mechanisms that ensure the entry and the output of glucose in the blood. A dynamic balance needs hence to be perfectly achieved in order to maintain a physiological glycaemic concentration. Specialized cells from the intestine continuously detect changes in glucose concentration and send signals to peripheral tissues and the brain through the vagus nerve. The molecular mechanisms involved in glucose detection have not been perfectly defined but could resemble those from the insulin-secreting beta cells. The brain then integrates the enteric and circulating endocrine signals to generate a new signal towards peripheral tissues such as the pancreas, liver, muscles, and blood vessels. This metabolic reflex is called anticipatory since it allows the peripheral tissues to prepare for the adequate handling of nutrients. Diabetes is associated with an impaired anticipatory reflex, which hampers the proper detection of nutrients and leads to hyperglycaemic episodes. Recently, GLP-1-based therapies have demonstrated the improvement of glucose detection and their efficacy on glycaemic control. Although not yet fully demonstrated, GLP-1-based therapies regulate glucose sensors, which leads to the glycaemic improvement. Certainly other molecular targets could be identified to further generate new therapeutic strategies.

Keywords: Diabetes; Incretins; Autonomic nervous system; Review

Résumé

L'interrelation intestin-cerveau, un axe régulateur métabolique majeur

L'homéostasie glucidique correspond à l'ensemble des mécanismes physiologiques, cellulaires, et moléculaires qui ajustent étroitement la glycémie entre 4,5 et 6 mM. Les variations de la glycémie qui résultent de l'entrée ou de la sortie du glucose de l'organisme et du sang doivent sans cesse être corrigées. Un équilibre dynamique est donc mis en place entre les mécanismes responsables de l'utilisation du glucose par les tissus et ceux qui concourent à sa production. Des cellules spécialisées de la sphère entérique détectent les variations glycémiques entre le sang artériel et la veine hépatoportale. Ces glucostats envoient des signaux nerveux via le nerf vague jusqu'au tronc cérébral qui relaie l'information vers l'hypothalamus. Ce dernier intègre également les messagers du sang circulant, comme les hormones et nutriments, puis adresse un nouveau message vers les tissus périphériques comme le foie, le pancréas, l'intestin, ou encore les vaisseaux sanguins. Ce réflexe métabolique est appelé anticipateur car il permet aux tissus d'être préparés en vue de l'utilisation des nutriments lors d'un repas. Les incrétines font partie des mécanismes importants impliqués. Ainsi, chez le sujet diabétique les thérapies fondées sur le GLP-1 sont particulièrement efficaces car elles prennent en compte de nombreuses cibles périphériques en activant cet arc réflexe métabolique. De nouvelles voies thérapeutiques sont ainsi envisageables qui permettraient une régulation fine de l'axe intestin-cerveau-tissus périphériques.

Mots clés : Diabète ; Incrétines ; Système nerveux autonome ; Revue

* Correspondence.
E-mail address: remy.burcelin@inserm.fr (R. Burcelin).

1. Introduction

During a meal, nutrients once absorbed are rapidly detected by specialized cells from the intestinal tract. Glucose is detected by glucostats, which send a neural signal towards the brain. Numerous signals are sent at once, all components of the new nutritional status [1-4]. The brain has to integrate these enteric signals and those coming from the circulating blood. Indeed, peripheral glands secrete hormones such as leptin, glucagon, insulin, and ghrelin, and changes in their concentrations are detected by the hypothalamus, mostly by the arcuate nucleus. Altogether, the brain generates new signals towards the peripheral tissues and controls hepatic glucose metabolism (storage and production), endocrine pancreatic secretions (insulin, glucagon) and intestinal hormone secretion such as incretins, in addition to food intake and arterial blood flow, to cite some of the triggered functions. This concept is called the anticipatory metabolic reflex, since it prepares the peripheral tissues to handle nutrients (Fig. 1).

During fasting, it is mainly the liver that accounts for all the glucose produced. Therefore, the glucose gradient is generated by the liver and is inverted when compared to the absorptive state. The brain and the enteric nervous system detect this negative hepatic portal glucose gradient and send signals to the peripheral tissues, thus leading to increased glycaemia or food intake [5].

In type 2 diabetes, this gut-to-brain-to-peripheral tissue metabolic axis is impaired [6]. Hence, nutritional signals are no longer properly detected. This concept could serve as the basis for new therapeutic strategies, which would aim at enhancing enteric glucose detection and the generation of a metabolic signal issued from the brain towards peripheral tissues. The advantage of such a strategy would be to regulate glucose metabolism from a very upstream target. Hence, all downstream tissues would be coordinately regulated. This could therefore reduce the number of adverse events such as hypoglycaemia. Glucagon-like peptide-one (GLP-1) based therapy contributes to the activation of the gut-brain axis. I will focus the topic of this review on the role of this hormone since most of the literature refers to it.

2. Intestinal glucose detection and enteric nervous system

Specialized cells from the intestine are able to detect the entry of glucose into the mesenteric blood. The precise location of these cells is not exactly known but could be related to the presence of glial-like structures or neurons surrounding the hepatic portal vein [7,8]. This enteric glucose sensing system regulates numerous functions. Hepatic glucose production has been mostly described [9-12]. A gut signal of neural origin increases a cholinergic dependent system, which leads to the activation of hepatic glucose storage [13,14]. Similarly, hepatic glucose production can be blocked by the glucose activation of the vagus nerve [15,16]. We previously described

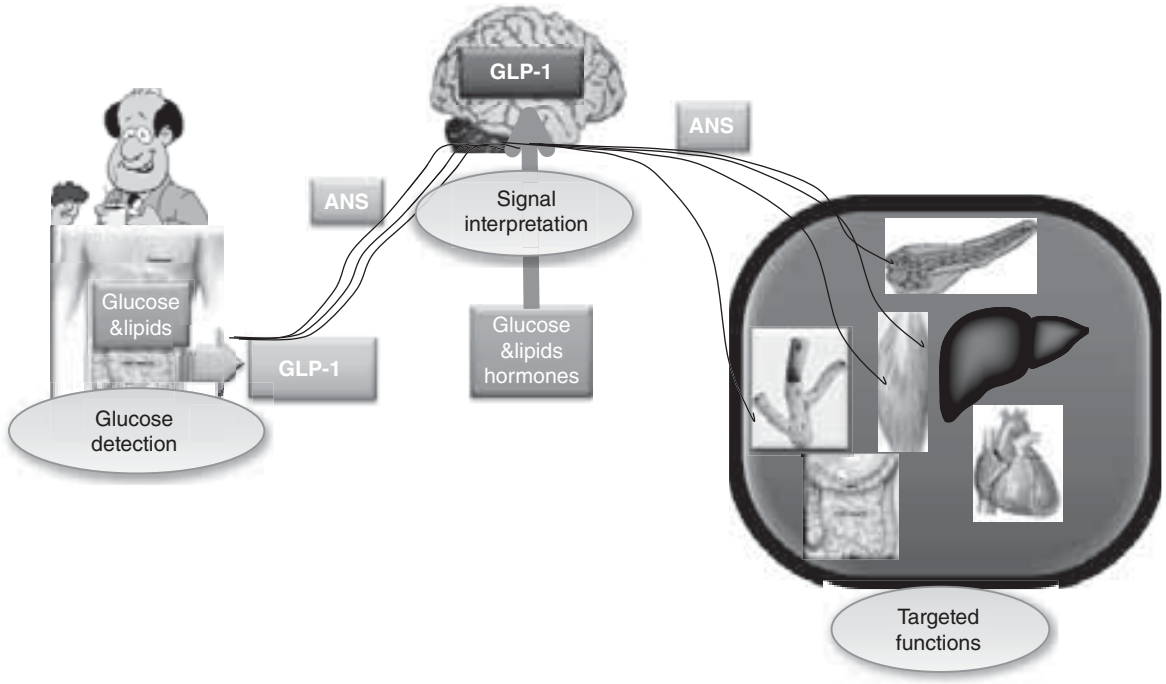

Figure 1 The anticipatory reflex prepares the peripheral tissues to handle nutrients properly when massively absorbed by the gut. First, glucose is detected by specialized cells called glucostat. A signal of neural origin is sent through the vagus nerve and the autonomic nervous system (ANS) to the brain. The nutrients and the peripheral hormones can also be detected directly by the brain, which integrates and interprets all information. A new signal is sent to the targeted tissues such as the liver, pancreas, muscles, heart, blood vessels and even the intestine. Altogether, peripheral tissues are rapidly informed that nutrients will be absorbed.

the enteric glucose sensor system as also being linked to the control of peripheral glucose utilization [4]. Muscle glucose utilization was increased in the absence of a rise in insulin secretion. The mechanisms involved the triggering of nerves surrounding the femoral artery, since their corresponding destruction prevented muscle glucose utilization. The molecular mechanisms associated with this effect were dependent on the presence of GLUT4, and of AMP-activated kinase but not insulin receptors [17]. Hence, in states of insulin resistance, this mechanism could be recruited to enhance muscle glucose utilization and better control glycaemia.

The molecular mechanisms responsible for glucose detection are poorly understood since we cannot visualize or directly address the molecular component of the system. First, glucose is detected by enterocytes and transported into these cells by glucose transporters, the SGLT1 [18] which increases the ATP/ADP ratio as observed in beta cells [19,20]. Consequently, an electrochemical gradient is generated which induces a signal for the secretion of GLP-1 into the enterocyte glucose. A role of the glucose transporter GLUT2 and the glucokinase could be also supposed but no direct demonstrations have been made. Glucose is then released into the mesenteric blood and reaches the portal vein. Other receptors seem to be involved in the firing of the vagus nerve activity. More recently, the role of carbohydrate receptors has been proposed. These are the sweet taste receptors of the T1R family expressed in the intestinal tract and enteroendocrine cells. The luminal sugar is sensed by a glucose sensor residing on the luminal membrane of the gut epithelium and linked to a G-protein-coupled receptor, cAMP/PKA (protein kinase A) pathway, resulting ultimately in modulation of intestinal monosaccharide absorption. In the small intestine and the enteroendocrine cell line, STC-1, expression has been reported, at the mRNA and protein levels, of members of the T1R sweet taste receptors and the alpha-subunit of the G-protein gustducin. In the small intestine, there is a highly coordinated expression of sweet taste receptors and gustducin, a G-protein implicated in intracellular taste signal transduction, throughout the gut. The potential involvement of these receptors in sugar sensing in the intestine has been suggested. The enteric nervous system is connected to the enteric glucostat. This neural system, also called the first brain, is composed of 200 million neurons within two plexi: the myenteric and the submucosal plexi [21]. These cellular structures secrete neuropeptides, which target smooth muscle cells, thus regulating gastric emptying, intestinal contraction, and most likely enteroendocrine cells. The neural fibres afferent to the brain are primary sensory fibres, which are connected with both plexi and make the link between the enteric brain and the central brain. Some of these fibres have prolonged dendrites within the lamina propria of the intestinal epithelium, ensuring therefore total intestinal innervation. One could easily imagine that these nerve endings are directly releasing neuromediators to enteroendocrine cells for controlling the production of the corresponding hormone, such as the incretins. Similarly, these terminal ends could sense nutrients such as glucose and lipids. The electrocapillary administration of glucose onto the vagus nerve immediately triggers its firing rate activity [22-24]. Glial-like cells have been described within the enteric nervous system. These cells are supposed to feed the neurons and produce numerous signalling molecules like neuromediators, cytokines and, metabolites, which inform the neurons of the ambient environment [25]. The hypothesis is that such cells are connected to glucose sensors and send the neural signal towards the brain stem. Therefore, the gut would be the first brain to sense glucose and to signal towards peripheral tissues that the nutrients had been absorbed. This hypothesis was demonstrated in mice and dogs when small amounts of glucose were infused into the portal vein to directly activate the sensor [4,26,27]. Muscle glucose utilization and liver production were regulated by the glucose signal to prepare these cells to handle the large amount of glucose that would be coming from the gut. This metabolic reflex was described as anticipatory.

3. GLP-1 and the gut-brain axis

More recently, the role of GLP-1 has been proposed as a major regulator of the gut-brain axis [27-30]. GLP-1 is a hormone secreted by the gut in response to a meal. It binds to its G-protein coupled receptor and increases cAMP production. It has been mostly described at the surface of the insulin secreting beta cells [31] and facilitates glucose-induced insulin secretion [32]. This is defined as the incretin concept [33,34]. GLP-1 is now the basis of numerous therapeutic strategies. However, this peptide has a major drawback. Following the incretin concept, the enzyme dipeptidylpeptidase (DPP-4), which prototypically inactivates the incretins, was discovered [35,36]. Cleavage of the N-terminus of GLP-1 by DPP-4 converts the active GLP-1-[7-37] and [7-36] – amide to the inactive GLP-1-[9-37] and [9-36] – amide, respectively. Therefore, other strategies based on the inhibition of the DPP4 are now widely used for the treatment of type 2 diabetes. Importantly, although the two strategies both consist of enhancing circulating GLP-1 concentration by means of GLP-1 analogues that cannot be degraded by the DPP4 or by using DPP4 inhibitors, both contribute to glycaemic control in different manners. The difference consists in the fact that GLP-1 analogues are provided subcutaneously and reach the systemic circulation. Therefore, the enteric to arterial gradient is not respected. One could suggest that the gut-brain axis is hence not activated. In addition, this strategy leads to a large increase in circulating GLP-1 concentration, which could reach the brain and regulate food intake as described below. Conversely, DPP4 inhibitors increase the portal vein GLP-1 concentration and activate the vagus nerve. Therefore, the gut-brain axis would be restored in type 2 diabetic patients. However, the amount of GLP-1 protected by the inhibitor strongly depends on the secretion of the peptide. Interestingly, this could be partially overcome by treating the patient with metformin [37].

This first set of analysis strongly suggests that GLP-1 analogues and DPP4 inhibitors control glycaemia by two

different mechanisms. The arguments are that the circulating concentration of GLP-1 (within the pM range) is too low to match the Km of the GLP-1 receptor, which is in the nM range. Second, the DPP4 makes sure that less that 10% of the secreted GLP-1 reaches the beta cells in an active form (GLP-1 7-36) and not in its degradation product form of GLP-1 9-36. Conversely, arguments are strongly in favour of an indirect route for the activation of insulin secretion. First, GLP-1 strongly activates the vagus nerve [38-43]. This effect leads to the control of vascular blood flow, gastric emptying, food intake and numerous other physiological functions. We initially showed that the enteric GLP-1-dependent glucose sensor system tightly regulated muscle glucose utilization [6] through a mechanism targeting vascular blood flow [44,45]. Importantly, in high-fat diet-fed diabetic mice, insulin-induced vasodilatation was blunted, testifying to a state of insulin resistance and vasoconstriction. This could be alleviated when brain GLP-1 signalling is impaired [44]. Hence, the brain to periphery axis is a strong regulator of vascular and metabolic functions.

4. Putative therapeutic outcome

From a therapeutic point of view, the enteric glucose sensor concept could certainly be considered a pharmacological target in order to control the main features of metabolic diseases, since it is involved in hepatic glucose production, peripheral glucose utilization, insulin secretion, glucagon production and GLP-1 secretion. Furthermore, the glucose sensing system seems to also be involved in the regulation of vascular and cardiac functions. As a proof of concept, numerous therapeutic strategies have emerged from the GLP-1 based concept. However, glucose sensors are not directly targeted but should be in charge of controlling many physiological functions. One advantage in targeting the enteric glucose sensing system rather than the brain glucose sensor is that the brain is downstream from the gut and therefore receives most of the nutritional information from the gut. This upstream position of the gut would allow a therapeutic strategy to efficiently regulate in a coordinated manner most of the downstream features that become dysregulated during metabolic diseases. One drawback of this concept is that the autonomic nervous system is often impaired during diabetes, which probably prevents the nutritional signals from being sent to peripheral tissues. This suggests that targeting the wires that connect tissues to each other should be done first or simultaneously. Certainly this new era of investigation should be detailed and further understood in order to accurately define a pharmacological strategy.

5. Conflict of interest

None related to the content of this article.

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Food for thought: the importance of glucose and other energy substrates for sustaining brain function under varying levels of activity

L. Pellerin

Department of Physiology, University of Lausanne, 7, rue du Bugnon, 1005 Lausanne, Switzerland

Abstract

The brain requires a constant and substantial energy supply to maintain its main functions. For decades, it was assumed that glucose was the major if not the only significant source of energy for neurons. This view was supported by the expression of specific facilitative glucose transporters on cerebral blood vessels, as well as neurons. Despite the fact that glucose remains a key energetic substrate for the brain, growing evidence suggests a different scenario. Thus astrocytes, a major type of glial cells that express their own glucose transporter, play a critical role in coupling synaptic activity with glucose utilization. It was shown that glutamatergic activity triggers an enhancement of aerobic glycolysis in this cell type. As a result, lactate is provided to neurons as an additional energy substrate. Indeed, lactate has proven to be a preferential energy substrate for neurons under various conditions. A family of proton-linked carriers known as monocarboxylate transporters has been described and specific members have been found to be expressed by endothelial cells, astrocytes and neurons. Moreover, these transporters are subject to fine regulation of their expression levels and localization, notably in neurons, which suggests that lactate supply could be adjusted as a function of their level of activity. Considering the importance of energetics in the aetiology of several neurodegenerative diseases, a better understanding of its cellular and molecular underpinnings might have important implications for the future development of neuroprotective strategies.

Keywords: Lactate; Glucose; Substrates; Ketone bodies; Astrocyte; Neuron; Monocarboxylate transporters; Review

Résumé

Alimenter sa pensée : de l'importance du glucose et des autres substrats énergétiques pour soutenir l'activité cérébrale en fionction de son niveau

Le cerveau demande un apport énergétique constant et soutenu pour subvenir à ses besoins. Depuis plusieurs décennies, le glucose a été considéré comme la principale, voire la seule source d'énergie pour les neurones. Cette idée est renforcée par la présence de transporteurs du glucose spécifiques exprimés par les vaisseaux cérébraux ainsi que par les neurones. Malgré le fait que le glucose demeure un substrat énergétique-clé pour le cerveau, de nombreuses données suggèrent une vision différente. En effet les astrocytes, type important de cellules gliales qui expriment leur propre transporteur du glucose, ont un rôle prépondérant dans le couplage entre activité synaptique et utilisation de glucose. Il a été montré que l'activité glutamatergique stimulait la glycolyse aérobique dans ces cellules. Ce processus permet de fournir du lactate aux neurones en guise de substrat énergétique supplémentaire. En fait, il avait déjà été démontré que le lactate pouvait devenir un substrat énergétique préférentiel pour les neurones dans certaines conditions. Une famille de transporteurs connue sous le nom de transporteurs des monocarboxylates a été décrite et certains de ses membres sont exprimés de manière spécifique sur les cellules endothéliales, les astrocytes et les neurones. De plus, ces transporteurs semblent régulés de manière fine, que se soit leur niveau d'expression ou leur localisation, ce qui suggère que l'approvisionnement en lactate pourrait être ajusté en fonction du niveau d'activité neuronale. Etant donné l'importance de la neuroénergétique dans l'étiologie des maladies neurodégénératives, une meilleure compréhension de ces mécanismes moléculaires et cellulaires pourrait avoir des implications importantes pour le développement de stratégies visant une neuroprotection.

Mots clés : Lactate ; Glucose ; Substrats ; Corps cétoniques ; Astrocyte ; Neurone ; Transporteurs des monocarboxylates ; Revue générale

* Correspondence.
E-mail address: Luc.Pellerin@unil.ch (L. Pellerin).

1. Introduction

The brain makes up only 2% of the total body weight, but it receives 15% of the total blood flow provided by the cardiovascular system; in addition, it consumes at least 25% of all circulating glucose and 20% of the oxygen available in the body under resting conditions [1]. Such crude estimates give an idea of the importance of energy supply for brain function. A deficit in the sequence of events allowing neurons to be adequately supplied with the necessary energy to accomplish their tasks could have dramatic consequences, as is the case after cerebral ischemia or in Alzheimer's disease. To understand how such energy supply is provided and ensured under all circumstances constitute one of the main goals of the emerging field known as neuroenergetics.

2. Glucose: an essential energy substrate for the brain

For decades, glucose has been considered as the main, if not exclusive, energy substrate for the adult brain [2]. Such a view is based notably on the classic work of McIlwain in the 1950's on brain slices demonstrating that apart from glucose, few physiological substrates could sustain metabolic and electrical activities of the nervous tissue [3,4]. However, there are situations in which alternative substrates can contribute significantly to sustain brain energy needs. First of all, this is the case in early development. Immediately after birth, blood lactate levels are elevated and it has been shown that the brain uses this source of energy in the first few hours of life. Then, once the newborn begins breastfeeding in mammals, the levels of circulating ketone bodies, i.e. acetoacetate and β-hydroxybutyrate, become elevated as fatty acids contained in the lipid-rich maternal milk are converted by the liver. It has been shown that during the entire breastfeeding period, the brain utilizes ketone bodies to fulfil a significant part of its energy requirement. Such an observation is corroborated by a transient enhancement in the expression of monocarboxylate transporters, essential ketone body carriers, both on endothelial cells forming cerebral blood vessels as well as on parenchymal cells [5]. As soon as the newborn animal switch to a solid diet however, plasmatic levels of ketone bodies drop (as does the expression of monocarboxylate transporters), and glucose becomes from that moment and throughout life the most significant energy substrate used on a regular basis. More recently, another alternative has been exposed. Under resting conditions, blood lactate levels have been shown to satisfy about 10% of the brain energy needs [6]. However, this proportion could increase significantly if circulating lactate levels rise. Indeed, during moderate to intense exercise, plasmatic levels of lactate rise to significant values. In such circumstances, it has been clearly shown that the adult brain takes up and utilizes blood lactate, at the expense of glucose [7,8]. Nevertheless, even under such conditions, glucose remains the main cerebral energy substrate, and the contribution of circulating lactate to cerebral energy supply is only transient.

Glucose must cross several membranes before becoming available for use as an energy substrate by different brain cells. In order to do so, it requires the presence of several facilitative glucose transporters belonging to the GLUTs family [9]. Glucose leaves the blood (where its concentration is around 5 mM) to enter the brain parenchyma (with a concentration of approximately 1 mM), following its concentration gradient. Its passage through endothelial cells that form cerebral blood vessels is made possible by the expression of GLUT1 55 KDa, one specific isoform of this glucose transporter. Uptake of glucose by each brain cell type is also mediated by specific glucose transporters. Thus, neurons exhibit a high affinity glucose transporter, GLUT3, which allows them to directly take up and use glucose provided by the circulation. Although glucose has long been considered the essential and unrivalled energy substrate for sustaining neuronal activity, recent data call this view into question. For example, experiments performed on cultured cortical neurons have shown that glucose uptake (mediated by GLUT3) decreases and does not increase, as would be expected, when neurons are stimulated with glutamate [10]. Moreover, as shown in the cerebellum, it seems that neurons do not massively take up glucose, but it is rather the glial cells that do so [11]. More recently, it has been shown that neurons lack an important regulatory component of glycolysis, which prevents them from enhancing their glycolytic flux [12]. But more surprisingly, it appears that most glucose consumed by neurons is metabolized through the pentose phosphate pathway and serves to maintain antioxidant status rather than participate in bioenergetic activity. Such observations raise at least two important questions. If neurons are not the main glucose consumers in the brain, what is the other cerebral cell type that would require so much glucose? And if neurons do not depend so much on glucose, what is the other substrate providing the energy necessary for neuronal function?

3. The astrocyte: a key element between blood vessels and neurons

Astrocytes belong to a category of non-neuronal brain cells known as glial cells. They are quantitatively the most important group of glial cells, which is also comprised of oligodendrocytes, microglial cells and tanycytes. Astrocytes are also often more numerous than neurons themselves, as they can outnumber them by a factor of ten in certain human brain areas. Moreover, they occupy ~ 30% of the brain volume. But one aspect that is quite remarkable about astrocytes is their morphology and location. Astrocytes exhibit a stellate shape (hence their name) with multiple processes. Some of these projections, called astrocytic end-feet, abut onto blood vessels. In fact, 99% of the surface of cerebral blood vessels is covered by astrocytic end-feet. There is a specific glucose transporter on the membrane of end-feet facing blood vessels, an isoform of GLUT1 known as GLUT1 45 KDa [13]. Because of such characteristics, end-feet constitute a preferential site for glucose

uptake as it leaves the blood to enter the brain parenchyma. On the other hand, astrocytes have several projections that come in close contact with neurons, more specifically in the peri-synaptic area where they ensheath this structure of communication between neurons. Because astrocytes express on these projections the receptors and transporters for most neurotransmitters used by neurons, they can be permanently informed of the level of activity of neurons and, concomitantly, on their energy needs.

This particular localization of astrocytes between blood vessels, which are the source of essential energetic substrates for the brain, and the important energy consumers that are neurons did not escape the attention of the first neuroanatomists that describe them at the end of the nineteenth century. Indeed, Camillo Golgi and his associates, on the basis of their morphological observations, suggested that astrocytes could play a critical role in the regulation of energetic supply to neurons. However, almost a century was required, together with the development of isolated cell culture models, before a precise mechanism implicating the astrocytes in such a function could be described. Now we know that astrocytes respond specifically to glutamate, the main excitatory neurotransmitter in the central nervous system, which triggers a particular metabolic response [14]. Thus, every time a particular brain region is activated, glutamate is released by glutamatergic neurons within that area. This glutamate is "detected" by astrocytes located nearby. As part of their homeostatic functions, astrocytes take up this glutamate and convert it to glutamine as part of a recycling of the neurotransmitter glutamate that has been well described. In doing so, glutamate uptake activates a cascade of molecular events that leads to the enhancement of glucose utilization by the astrocytes (Fig. 1). Recent observations made with the fluorescent glucose analog 6-NBDG have confirmed the predominant uptake by astrocytes in vivo following neuronal activation [15]. But quite importantly, this glucose is not oxidized entirely within the astrocyte. In fact, the astrocyte metabolises glucose into lactate, a metabolic intermediate with a high energetic value, and releases it into the extracellular space, making it available for energy-demanding neurons. This mechanism of energy supply on demand is known as the astrocyte-neuron lactate shuttle [16].

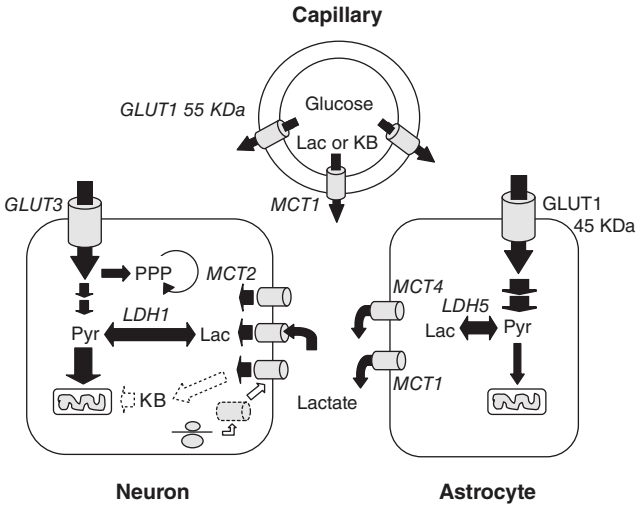

Figure 1. Energy supply to sustain brain development and activity. Glucose is provided by the circulation and enters the brain parenchyma via the transporter GLUT1 55 KDa expressed on endothelial cells forming cerebral blood vessels. Under specific circumstances (e.g. breastfeeding, exercise), circulating lactate or ketone bodies can be provided directly to brain cells after crossing the blood-brain barrier via the monocarboxylate transporter MCT1. Glucose can be taken up by neurons via the high affinity transporter GLUT3. Evidence suggests that glucose taken up by neurons might not be used solely for energetic purposes but could be partly devoted to antioxidant defence mechanisms through metabolism in the pentose phosphate pathway. In parallel, prominent glucose uptake would take place in astrocytes via GLUT1 45KDa. Glutamatergic activity would stimulate aerobic glycolysis in astrocytes with significant lactate production and release via MCT1 and MCT4. Lactate would be taken up by active neurons via the high affinity transporter MCT2 and oxidized to satisfy neuronal energy needs. Lactate supply to neurons could be adjusted according to activity, notably by enhancing MCT expression and localization at the membrane. GLUT, glucose transporter; KB, ketone bodies; Lac, lactate; LDH, lactate dehydrogenase; MCT, monocarboxylate transporter; PPP, pentose phosphate pathway; Pyr, pyruvate

4. Lactate: supplemental and alternative energy substrate to glucose for neurons

Lactate is known as the end product of glycolysis under anaerobic conditions (or conditions of insufficient oxygen supply). This is the case in muscles that produce large amounts of lactate from glucose during brief, high intensity bouts of activity. Nonetheless, even for muscles, it has been demonstrated that lactate can be produced (and consumed locally by neighbouring muscle cells) even in the presence of adequate oxygen levels. In the brain, despite the fact that lactate has long been considered a metabolic waste and potentially toxic compound, it is now recognized not only as a valuable energy substrate for neurons but even possibly as a preferential source of energy under certain circumstances [17].

As mentioned earlier, it has been known for some time that the brain can use energy substrates other than glucose to satisfy its energy needs under particular conditions. Ketone bodies as well as lactate belong to this category. However, their supply to the adult brain remains limited, both quantitatively and over time, partly due to the limited expression of specific transporters known as monocarboxylate transporters on endothelial cells of cerebral blood vessels. The astrocyte-neuron lactate shuttle mechanism provides a different source of lactate, as it is produced from circulating glucose within the brain parenchyma. The uptake of glucose in astrocytes triggered by glutamate is facilitated by an enhancement of GLUT1 45 KDa-mediated glucose transport [18]. Lactate produced by astrocytes from glucose is released in the immediate surroundings of neurons, thus becoming directly available for metabolism. As both lactate and glucose are available in the extracellular space at similar concentrations (~ 1 mM), one may wonder to what extent neurons will use each of these substrates to fulfil their energy needs. Experiments performed on isolated cultured

cell populations provide a clear answer. It has been shown under conditions where both substrates were present at the same concentration that at least 75% of oxidative metabolism in neurons is supported by lactate [19, 20]. Such a result is consistent with observations suggesting that neurons have a limited capacity to use glucose and rather use it mainly for other purposes than energy production.

5. Monocarboxylate transporters: essential highways for the lactate shuttle

Lactate as well as ketone bodies are physiological members of the family of compounds known as monocarboxylates. Since they are hydrophilic molecules, they cannot cross cellular membranes by simple diffusion. Thus, specific transporters are required for these compounds to be both released and taken up by different cell types. A family of proton-linked carriers has been identified in recent years and are collectively known as the monocarboxylate transporters or MCTs [21]. Up to now, fourteen members have been identified essentially by sequence homologies but only seven have been functionally characterized. Among them, only four have been shown to be true monocarboxylate transporters: MCT1, MCT2, MCT3 and MCT4. Their tissue distribution varies but only MCT1, MCT2 and MCT4 have been found to be expressed in the central nervous system. Their cellular distribution within the brain is quite specific. MCT1 is found on endothelial cells that compose blood vessels, where it plays an essential role in the entry of circulating lactate and ketone bodies within the brain. Astrocytes express MCT1, but they also exhibit MCT4 [22]. Both transporters are most likely involved in the release of lactate by astrocytes. However, these two transporters differ in their affinity for lactate, MCT1 displaying a lower K_m than MCT4 for this substrate (3.5 vs. 34.7 mM, respectively). Thus, it is possible that they play a distinct role depending on the metabolic state of the astrocytes (constitutive lactate release vs. activated production). To observe the expression of MCT4 on astrocytes comes as no surprise, since in the periphery MCT4 is expressed by tissues exhibiting a high glycolytic rate with significant lactate production (e.g. some muscle fibres). In contrast, a large majority of neurons have been found to express the high affinity transporter MCT2 ($K_m = 0.7$ mM) [23]. Such a distribution is entirely consistent with the concept of a lactate transfer between astrocytes and neurons.

Interestingly, monocarboxylate transporters are subject to specific regulations in brain cells. For example, it has been shown that MCT2 expression can be upregulated in cultured cortical neurons by the neurotransmitter noradrenaline, the hormone insulin, as well as the trophic factors insulin-like growth factor (IGF-1) and brain-derived neurotrophic factor [24-27]. In all cases, it has been shown to involve a translational regulation mediated by activation of the PI3K/Akt/mTOR/S6 pathway. In addition to change in protein expression levels, it was also demonstrated that the localization of MCT2 at the plasma membrane can be either enhanced or reduced by various neuroactive substances [28]. In contrast to glucose transporters, it appears that expression and localization of monocarboxylate transporters are much more finely regulated by various signals originating from neuronal activity. Such observations suggest that the supply of monocarboxylates as energy substrates to neurons could be more easily adapted to the level of activity than could be the case with glucose.

6. Perspectives

The study of brain energy metabolism in recent years has highlighted the critical role played by astrocytes in the energetic supply of neurons. The canonical view that glucose is the only valuable energy substrate for sustaining neuronal activity has changed and has been replaced by a different concept. Although glucose remains an essential energy source for the brain, its distribution and metabolism by brain cells is more complex than previously thought and involves metabolic interactions between astrocytes and neurons. Moreover, other metabolic intermediates, lactate in particular, have emerged as additional energy substrates for neurons that may even be preferred over glucose in certain circumstances. Further understanding of these aspects and the specific regulations occurring under various conditions might be of prime importance. Indeed, several neurodegenerative diseases (e.g. Alzheimer's disease) exhibit metabolic deficits that appear to precede the first symptoms. Thus, it may be that improving neuroenergetics at an early stage could provide at least partial neuroprotection.

7. Conflict of interest

None related to the content of this article.

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Impaired awareness of hypoglycaemia: a review

A. J. Graveling, B. M. Frier*

Department of Diabetes, Royal Infirmary of Edinburgh, Edinburgh, EH16 4SA, United Kingdom

Abstract

Impaired awareness of hypoglycaemia (IAH) is an acquired complication of insulin therapy, which affects people with type 1 and insulin-treated type 2 diabetes mellitus, whereby the ability to perceive the onset of hypoglycaemia becomes diminished or absent. Deficiencies of the counter-regulatory hormonal responses to hypoglycaemia usually co-exist. The development of IAH and counter-regulatory failure greatly increases the risk of severe hypoglycaemia. Scoring systems have been developed that can be used in the clinical setting and assist with identification of this group of individuals at risk of severe hypoglycaemia. The mainstay of treatment of IAH is the scrupulous avoidance of hypoglycaemia.

Keywords: Type 1 diabetes mellitus; Type 2 diabetes mellitus; Hypoglycaemia; Symptoms of hypoglycaemia; Impaired awareness of hypoglycaemia; Hypoglycaemia unawareness; Counter-regulation; Review

Résumé

Altération de la perception des hypoglycémies. Revue générale

L'altération de la perception des hypoglycémies est une complication acquise de l'insulinothérapie, qui touche les diabétiques de type 1 et les diabétiques de type 2 insulino-traités, et qui est définie par la diminution ou la disparition de la perception de survenue des hypoglycémies. Un déficit de la contre-régulation hormonale à l'hypoglycémie est habituellement associé. Le développement des altérations de la perception des hypoglycémies et de la contre-régulation hormonale majore le risque d'hypoglycémie sévère de manière importante. Des scores ont été développés pour permettre d'identifier en clinique humaine les patients « à risque » d'hypoglycémie sévère. La pierre angulaire du traitement des altérations de la perception des hypoglycémies est d'éviter les hypoglycémies de manière méticuleuse.

Mots clés : Diabète de type 1 ; Diabète de type 2 ; Hypoglycémie ; Signes d'hypoglycémie ; Altération de la perception des hypoglycémies ; Non-perception des hypoglycémies ; Contre régulation hormonale ; Revue générale

1. Definitions of hypoglycaemia

Hypoglycaemia is a major barrier to the implementation of intensive glycaemic control to treat diabetes. In the Diabetes Control and Complications Trial (DCCT) severe events were three-fold greater in the group with strict glycaemic control compared to those with conventional treatment [1]. In clinical practice, hypoglycaemia is defined by the ability of an individual to self-treat. Self-treated events are classified as "mild", while "severe" hypoglycaemia is any episode that requires external assistance for recovery, and is not confined to coma alone. The arbitrary biochemical value of blood glucose that can be used to define hypoglycaemia is the subject of topical debate [2,3]. The American Diabetes Association (ADA) have selected a blood glucose of 3.9 mmol/L (70 mg/dl) or below as representing hypoglycaemia [4], but many clinicians consider that the use of this relatively high level as the cut-off will capture many episodes that are not clinically meaningful [5].

2. Frequency of hypoglycaemia

People with type 1 diabetes mellitus (T1DM) experience an average of one to two episodes of mild hypoglycaemia per week; one third experience an episode of severe hypoglycaemia annually [6]. Retrospective recall of severe hypoglycaemia is robust for up to one year in people with both types of diabetes [7,8], but recall of mild hypoglycaemia is limited

* Corresponding author.
E-mail address: brian.frier@luht.scot.nhs.uk (B. Frier).

to one week [9]. Relatives report significantly more annual episodes of severe hypoglycaemia than people with T1DM do themselves [10]. The distribution of severe hypoglycaemia is skewed within a population so that most events are recorded by only a few individuals; identification of those at higher risk would have valuable clinical utility [7]. The frequency of sulfonylurea-induced hypoglycaemia is underestimated in people with type 2 diabetes mellitus (T2DM), and is common with long-acting preparations (e.g. glibenclamide). In a prospective study in the UK the prevalence of severe hypoglycaemic events associated with sulfonylurea therapy was 7%, comparable to the frequency observed in people with T2DM on insulin for less than 2 years [11].

3. Symptomatology of hypoglycaemia

The application of statistical methodology has enabled classification of the symptoms of hypoglycaemia in patients with T1DM; those generated by the activation of the sympatho-adrenal system are termed autonomic and those occurring as a consequence of cerebral glucose deprivation are termed neuroglycopenic. Young adults also express a non-specific or malaise group of symptoms. These three groups of symptoms can be measured using the Edinburgh Hypoglycaemia Symptom Scale [12]. Although it has been claimed that awareness of hypoglycaemia is largely the result of autonomic, rather than neuroglycopenic symptoms [13], studies identifying the cardinal symptoms that alert people with T1DM to the onset of hypoglycaemia have shown that autonomic and neuroglycopenic symptoms are represented equally [14,15].

In older people with T2DM, neurological symptoms such as ataxia and visual disturbance are prominent, which may result in misdiagnosis [16]. Elderly people with T2DM report lower symptom scores but counter-regulatory responses to hypoglycaemia are relatively intact; the lower magnitude of the symptom response may therefore result from decreased sensitivity of end-organs in response to catecholamines [17,18]. In elderly people, symptoms of hypoglycaemia commence at a lower blood glucose threshold and cognitive dysfunction occurs at a higher threshold in comparison with those observed in young adults [19]. This compresses the interval between the onset of symptomatic hypoglycaemia and the development of cognitive dysfunction, so that both develop almost simultaneously and the protective effect of the symptomatic warning is lost [19]. Symptom scores correlate positively with estimates of diabetes knowledge – those with greater knowledge of their diabetes are generally more adept at identifying hypoglycaemia [20].

4. Impaired Awareness of Hypoglycaemia (IAH)

In 1922, very shortly after insulin was first used to treat diabetes, Elliot Joslin observed that hypoglycaemia could occur without warning symptoms [21]. More than one third of episodes of severe hypoglycaemia that occur during waking hours are not accompanied by warning symptoms [22], and many people with insulin-treated diabetes develop a syndrome with a spectrum of severity in which their ability to identify the onset of hypoglycaemia becomes progressively impaired. "Impaired awareness of hypoglycaemia" (IAH) is a preferable nomenclature to the widely used "hypoglycaemia unawareness", which suggests total loss of the symptomatic warning response that is seldom observed in clinical practice. IAH is an acquired complication of insulin treatment per se, in which the perception of the onset of hypoglycaemia becomes diminished or absent.

5. Impaired defences against hypoglycaemia in T1DM

In normal health, when blood glucose falls to a level which may compromise the integrity of cognitive function, glucose counter-regulation is initiated (Fig. 1). This is triggered when blood glucose declines below the lower end of the normal range and is preceded by suppression of endogenous insulin secretion. Glucagon and adrenaline (epinephrine) are the most important counter-regulatory hormones to acute hypoglycaemia. In people with T1DM the glucagon response to hypoglycaemia rapidly declines and is lost within five years of diagnosis [23]. The adrenomedullary secretion of adrenaline (epinephrine) becomes important when these early defensive mechanisms are compromised [24]. In people with T1DM who are C-peptide negative, loss of endogenous insulin-secretory capacity and the glucagon response to hypoglycaemia underlie the fourfold increase in risk of severe hypoglycaemia [25]. Hyperinsulinaemia secondary to exogenous insulin administration frequently occurs in insulin-treated diabetes and persists in the presence of low blood glucose because normal glucose homeostasis is disrupted in T1DM and advanced T2DM. With time, sympatho-adrenal activation becomes

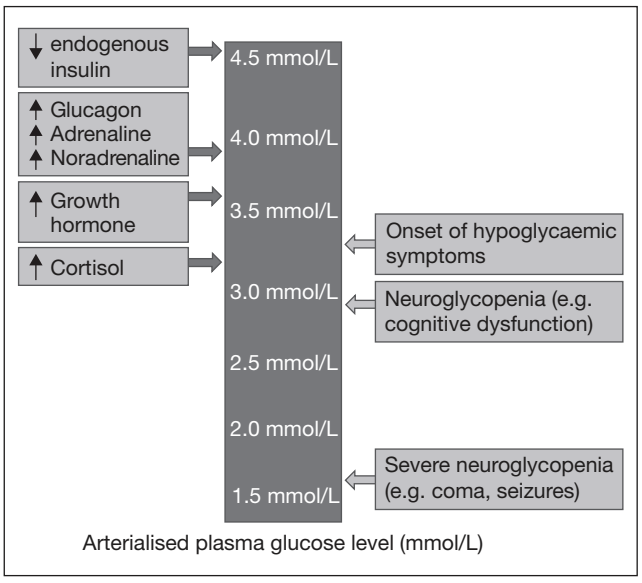

Figure 1. Figure showing glycaemic thresholds for counter-regulatory hormone release and clinical features of hypoglycaemia [24,63,64]

critical for protection of the brain from hypoglycaemia. One consequence is the generation of autonomic symptoms, the intensity of which is heightened by the secretion and circulation of catecholamines. Unfortunately, insulin-induced hypoglycaemia attenuates adrenaline release and moves the glycaemic threshold for its secretion to a lower blood glucose level, which both increases the risk of hypoglycaemia and reduces the intensity of symptoms generated during hypoglycaemia [26]. Reduced cortisol secretion also appears to contribute to counter-regulatory failure [27].

Recurrent hypoglycaemia increasingly impairs the normal defences against hypoglycaemia and diminishes the ability to detect hypoglycaemia (i.e. hypoglycaemia begets hypoglycaemia). This phenomenon of progressive counter-regulatory failure and loss of awareness of symptoms of hypoglycaemia, which co-exist in T1DM [28] has been attributed by Cryer to adverse effects of exposure to recurrent hypoglycaemia on central autonomic centres, which then fail to respond effectively to a fall in blood glucose. Cryer has called this syndrome "Hypoglycaemia Associated Autonomic Failure (HAAF) [29]. HAAF is thought to result from a failure of centrally mediated counter-regulation [29]. However, counter-regulatory hormonal failure is not the direct cause of IAH as avoidance of hypoglycaemia results in improved perception of symptoms without restoration of the normal counter-regulatory response [30]. Nevertheless, the two are closely related and probably share a common pathogenesis as suggested in figure 2.

It used to be thought that peripheral autonomic neuropathy was responsible for these attenuated responses and was the mechanism underlying IAH. Several studies have shown that autonomic dysfunction is not the primary cause, although its presence may contribute to a reduced magnitude of symptom intensity [31]. The most powerful argument against the involvement of autonomic neuropathy in the development of IAH is that this acquired syndrome is a dynamic process that can be worsened by exposure to recurrent hypoglycaemia and improved by scrupulous avoidance of hypoglycaemia, in contrast to autonomic neuropathy which, once established, is a permanent complication that progresses in severity [32].

In people with IAH, adaptation of the brain occurs, shifting the glycaemic thresholds for the generation of symptoms, counter-regulatory hormonal secretion, and the onset of cognitive impairment to lower blood glucose levels, so that more profound hypoglycaemia is required to provoke these responses [31]. Various mechanisms have been shown to cause this effect, including exposure to antecedent hypoglycaemia, recurrent hypoglycaemia and strict glycaemic control. As a consequence of the increasingly diminished (and eventually non-existent) interval between the onset of warning symptoms of hypoglycaemia and the development of significant neuroglycopenia, people with IAH have a much greater risk of developing severe hypoglycaemia [33]. By contrast, people with poor glycaemic control re-set their glycaemic thresholds upwards, i.e. they mount a counter-regulatory response and experience symptoms of hypoglycaemia at higher blood glucose levels than those with good control, often within a hyperglycaemic range [34]. Thus symptomatic responses are initiated at elevated blood glucose levels, which is termed "relative hypoglycaemia" [4]. Interestingly, the

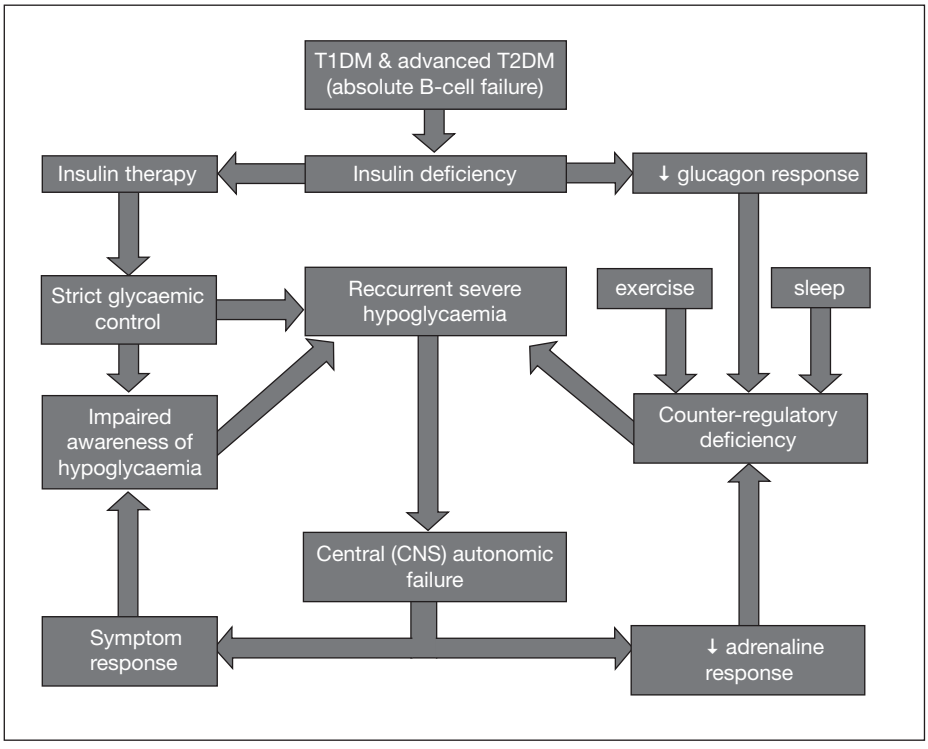

Figure 2. Pathophysiology of impaired awareness of hypoglycaemia and hypoclycaemia associated automatic failure (adapted from [31])

glycaemic thresholds of people with T2DM who have good glycaemic control but are not treated with insulin are set at levels above those of non-diabetic individuals and people with T1DM [35,36]. This may have a protective effect against the development of severe hypoglycaemia.

6. Glucose sensing

The ventromedial thalamus (VMH) is a key glucose-sensing region involved in the detection of hypoglycaemia [37]. The counter-regulatory response is ameliorated to a large extent by maintaining cerebral euglycaemia in the presence of systemic hypoglycaemia [38]. Local perfusion of the VMH with glucose to maintain localised euglycaemia markedly suppressed the counter-regulatory response despite the presence of systemic hypoglycaemia [39]. Glucose sensing also occurs outside of the brain and sensors are located in the portal vein, intestine, carotid body and in glucokinase-sensing pancreatic beta cells [40]. In animal studies, portal vein glucose sensing is necessary for the attenuation of counter-regulatory responses following antecedent hypoglycaemia [41]. However, it appears to be less important in humans in whom hormonal and symptomatic responses are unaffected by prevention of portal hypoglycaemia [42] and peripheral glucose sensors do not appear to be important in stimulating the counter-regulatory response to acute hypoglycaemia. It is not yet known if glucose sensors in the brain are irreversibly damaged in people who have developed severe forms of IAH.

7. Variable susceptibility to hypoglycaemia in people with T2DM

People with T2DM comprise a heterogeneous population with abnormalities ranging from pronounced insulin resistance to advanced insulin deficiency, and with variable residual endogenous insulin-secretory capacity. In contrast with early T1DM, residual beta cell function is usual and glucagon secretion is preserved in people with T2DM on oral therapies, so limiting the development of severe hypoglycaemia [43,44]. Increased insulin resistance associated with central obesity may also limit the severity of any iatrogenic hypoglycaemia by blunting the glucose-lowering effect of exogenous insulin.

In T2DM progression to insulin dependence occurs at a variable rate. Once insulin deficiency has developed, the same downward shift occurs in the glycaemic threshold at which the counter-regulatory response is initiated and the glucagon response becomes attenuated [35]. These developments resemble the counter-regulatory abnormalities associated with T1DM and are associated with an increased risk of hypoglycaemia [11]. When intensive insulin therapy was used in a cohort of patients with insulin-treated T2DM to lower HbA1c from 10.2% to 6.7%, the counter-regulatory and symptomatic responses to subsequent hypoglycaemia were diminished, and were associated with a threefold higher rate of severe hypoglycaemia [45]. It is difficult to determine whether the diminished responses to hypoglycaemia were a direct result of improved glycaemic control or a consequence of the effects of recurrent exposure to antecedent hypoglycaemia.

8. Definition and prevalence of IAH

The lack of an acceptable clinical definition of IAH has hindered accurate ascertainment of the prevalence of IAH and research into this condition. “Awareness” of hypoglycaemia and its progressive impairment represent a continuum ranging from normal perception of the onset of hypoglycaemia to complete inability to detect its onset [31]. For the purposes of developing a clinical scoring system, awareness of hypoglycaemia was arbitrarily divided into normal, “partial” and “absent” awareness, where “partial” represented diminution of the ability to perceive the onset of hypoglycaemia, but without total absence of a symptomatic response [33,46]. Partial and absent awareness of hypoglycaemia combined was present in 25% of a group of 302 patients with T1DM [47], which was consistent with other surveys in which the syndrome was not precisely defined [48] and more recently the syndrome of IAH was identified in 19.5% of a randomly selected cohort of 518 people with T1DM attending a secondary care diabetes clinic [49]. IAH is less common in people with insulin-treated T2DM with an estimated incidence of 8-10% [50,51]. The extent to which IAH affects people treated with insulin secretagogues such as sulfonylurea therapy is not known. Although IAH affects a smaller proportion of people with insulin-treated T2DM, in view of the number of people being treated for this condition world-wide, this clinical problem will have a greater impact than is currently appreciated.

9. Risk factors for IAH

Factors that influence the normal awareness of hypoglycaemia are shown in table 1. Many episodes of severe hypoglycaemia are under-reported by people with IAH. Furthermore, if blood glucose monitoring is infrequent, many episodes of asymptomatic (or biochemical) hypoglycaemia are not detected. Major risk factors that are associated with the development of IAH in T1DM include increasing age and duration of diabetes and strict glycaemic control [7,52]. Behavioural factors are important with reduced adherence to suggested changes in insulin regimens being observed in people with IAH [53]. Despite reporting a greater fear of hypoglycaemia, people with IAH did not modify their behaviour to try and reduce the risk of hypoglycaemia [54]. Claims in the 1980s that human insulin can cause impaired awareness of hypoglycaemia in contrast to animal insulins [55] were not substantiated by extensive research, and a subsequent meta-analysis and Cochrane review have shown no difference in the frequencies of severe hypoglycaemia or in IAH between the use of human and animal insulins [56,57].

Table 1
Factors influencing normal awareness of hypoglycaemia [31].

Internal	External
Physiological	Drugs
Recent glycaemic control	Beta-blockers (non-selective)
Degree of neuroglycopenia	Hypnotics, tranquillisers
Symptom intensity/sensitivity	Alcohol
Psychological	Environmental
Focused attention	Posture
Congruence; denial	Distraction
Competing explanations	
Education	
Knowledge	
Symptom belief	

Any medication which alters the response to sympatho-adrenal stimulation and catecholamine release could potentially affect hypoglycaemia awareness; theoretically, beta blockers by suppressing adrenoceptor responses, should reduce counter-regulation and diminish the intensity of symptoms that are adrenergically-mediated. In effect, selective beta blockers do not appear to have any significant clinical effect. Glucose clamp experiments showed that the threshold for autonomic symptoms was shifted to a lower blood glucose level while neuroglycopenic symptoms and cognitive function were unaffected [58]. Usage of non-selective beta-blockers has been associated with an increased risk of severe hypoglycaemia [59]. During moderate hypoglycaemia, beta-blockers did not modify awareness or symptom intensity during hypoglycaemia [60]. Despite some case reports suggesting a reduction in symptom intensity during hypoglycaemia, a glucose clamp study in which non-depressed, non-diabetic subjects were given fluoxetine demonstrated that counter-regulatory hormone release was increased, but with no concurrent change in symptom scores [61].

10. Clinical assessment of IAH

Glucose clamp studies have been used to determine awareness of hypoglycaemia [62] and to demonstrate the hierarchy of responses that occur as blood glucose declines. Autonomic symptoms occur before neuroglycopenic symptoms, with a difference of around 0.5 mmol/l between the thresholds at which they are generated [63,64]. However, this artificial and controlled experimental setting bears little relationship to everyday life with its myriad distractions, and this small threshold difference cannot be detected subjectively by affected individuals [14,15]. The most useful method of identifying impaired awareness of hypoglycaemia and its importance to the individual is to take a careful clinical history. People with T1DM who state that they have IAH are generally correct [46]. A structured questionnaire of hypoglycaemia experience has been developed to confirm the clinical history [46], while a simpler method employs a single question and asks the patient to score their awareness on a Likert scale (from 1 to 7), where a low score represents normal awareness and a high score designates loss of awareness [33]. To be utilised effectively the participant must have experienced hypoglycaemia on at least one occasion in the preceding year, and for reasons explained below, the answers must be based on experience of hypoglycaemia that occurs during waking hours. These two questionnaires display good concordance in the adult population [49]. A third method from Denmark, which has attempted to relate symptomatic awareness to subjective experience generally over-estimates the frequency of IAH, with almost two thirds of people with T1DM being described as having this problem, which is not consistent with clinical experience [49]. A revised, trichotomised version of this method that subdivided the patients into three groups: “aware”, “intermediate” and “impaired”, improved concordance with the two established methods [65], but the terminology used in the Danish method is open to misinterpretation. The semantics of IAH present difficulties and translation of the Clarke and Gold methods into languages other than English may introduce anomalies. The method of Clarke et al [46] has been validated by a Dutch study that also utilised prospective blood glucose monitoring and glucose clamps to assess hypoglycaemia awareness [66]. In both the Clarke and Gold methods a degree of uncertainty exists regarding assessment in the middle range, equivalent to a score of 3 in both scales. It is unclear if people with this score have definite IAH, or whether they may represent people with partial loss of awareness who have yet to progress to expression of the full-blown syndrome.

IAH is associated with a 2-4 fold higher frequency of asymptomatic biochemical hypoglycaemia (capillary blood glucose < 3.5 mmol/L) [33,52,67]. Continuous glucose monitoring (CGM) has demonstrated that much hypoglycaemia is undetected and has suggested that asymptomatic biochemical events are fourfold higher in people with IAH compared to those with normal awareness [68,69]. However, despite an increased risk of severe hypoglycaemia and evidence of more hypoglycaemia during prospective self-monitoring of capillary blood glucose, retrospective blood glucose analysis of CGM records for up to 72 hours of monitoring failed to identify those with IAH, who had a similar frequency, duration and severity of biochemical hypoglycaemia as those with normal awareness. At the time of this particular study the technology may not have been sufficiently sensitive to identify the presence of this syndrome [70], but increasingly sophisticated CGMS technology may improve detection by this approach.

11. Morbidity and mortality associated with IAH

People who have impaired awareness of hypoglycaemia have a much greater risk of severe hypoglycaemia, up to six fold, with its attendant morbidity [33,70]. Severe hypoglycaemia may result in many serious forms of morbidity including seizure, coma, fractures and joint dislocation and

cardiac arrhythmias, and is occasionally fatal. However, although these problems are more frequent in people with IAH the frequencies of these morbidities associated with severe hypoglycaemia have not been formally estimated. The strict glycaemic control that is required during the management of gestational diabetes, when insulin is frequently necessary, is often associated with IAH of considerable severity, and an associated high risk of severe hypoglycaemia. Pregnant women with diabetes are subject to hypoglycaemia-induced morbidity, particularly in the first trimester [71].

12. Effect of alcohol, sleep and distraction on awareness of hypoglycaemia

Alcohol is an important risk factor for hypoglycaemia [72]. The clinical features of hypoglycaemia can be mistaken for those of alcohol intoxication which can delay correct treatment of the hypoglycaemic episode. Despite increased counter-regulatory responses in those who had consumed alcohol compared with those who had not, during experimental hypoglycaemia they were less likely to recognise that they were hypoglycaemic (2 out of 15 versus 11 out of 15) [73].

Sleep is a physiological state where warning symptoms of hypoglycaemia are usually absent and presents a particular problem to people with T1DM as many severe episodes occur during sleep, which is mainly nocturnal [22]. Symptomatic responses to hypoglycaemia are diminished in the supine posture [58] and the plasma adrenaline response is also lower when lying down [74]. When hypoglycaemia occurs during sleep, counter-regulatory responses, particularly the release of catecholamines, are markedly attenuated in people with T1DM compared with responses when they are awake [75,76]. Adults with T1DM experienced less disruption to their quality of sleep during hypoglycaemia, spending 77% of the time asleep in comparison to 26% in non-diabetic participants [75]. During hypoglycaemia only 1 person out of 16 with T1DM awoke during hypoglycaemia in comparison to 10 out of 16 of those without diabetes [77]. Unrecognised nocturnal hypoglycaemia presents a possible explanation why people with T1DM develop IAH, by modifying glycaemic thresholds to subsequent hypoglycaemia [78].

Driving simulator studies have shown that people with T1DM whose symptomatic awareness is not impaired are often unaware of the onset of cognitive dysfunction while modest hypoglycaemia is being induced and fail to take corrective action [79]. Participants failed to recognise both deterioration in their driving performance and their current hypoglycaemic status, this may be partly attributable to distraction. People who are distracted by a stressful event report lower symptom intensity scores during acute hypoglycaemia despite greater counter-regulatory hormonal release [80].

13. Effect of IAH on cognitive function

People with IAH often state that they do not experience any cognitive impairment during hypoglycaemia and are capable of carrying out the usual activities of daily living even though they may be exposed to frequent asymptomatic hypoglycaemia. To some extent this is true, as cognitive function is less affected during moderate hypoglycaemia and recovery is quicker compared than in people with T1DM who have normal awareness [81]. The glycaemic threshold for cognitive dysfunction is re-set at a lower blood glucose level, in the same way as those for generation of symptoms and the stimulation of counter-regulatory hormonal secretion [62,82]. Other studies have indicated that cognitive dysfunction occurs at lower blood glucose levels in those with IAH compared to those with normal awareness or people without diabetes [62,83]. As already noted, nocturnal hypoglycaemia diminishes the degree of cognitive impairment during subsequent hypoglycaemia [78]. It is sometimes difficult to convince a few people with IAH both of the scale of the problem and the imperative to avoid hypoglycaemia wherever possible, especially when consultations with specialists tend to focus on the necessity of attaining good glycaemic control. However, most people with this syndrome are fully cognisant of the dangers that it imposes, and the threat to retaining their driving licence and some forms of employment.

Exposure of the brain to repeated episodes of hypoglycaemia over many years in people with T1DM had no apparent effect on long term cognitive function in the DCCT/EDIC study [84]. However, the long term effects of recurrent exposure to hypoglycaemia, both severe and mild, are more difficult to determine in patients who have established IAH. Animal studies have shown that antecedent moderate hypoglycaemia can protect the brain against subsequent severe hypoglycaemia with evidence of less neuronal damage [85]. While people with IAH develop a lesser degree of cognitive impairment during mild hypoglycaemia, with apparent resistance to the cerebral effects of moderate hypoglycaemia, because profound neuroglycopenia is a relatively common occurrence it seems likely that this will have significant adverse long term effects on cognitive function. People with IAH have been shown to perform less well on a limited number of cognitive function tests applied during both euglycaemia and hypoglycaemia [82]. More profound cognitive dysfunction during acute hypoglycaemia was observed in those with IAH compared to those with normal awareness [86]. However, few studies have examined the long-term effects on cognitive function in people who have developed impaired awareness of hypoglycaemia, which is associated with a very much high frequency of severe hypoglycaemia [33,52]. One such study has suggested that significant cognitive impairment occurs in affected patients [87].

14. Neuroimaging studies

The effect of hypoglycaemia on the brain can be directly visualised with neuroimaging techniques such as positron

emission tomography (PET) and functional magnetic resonance imaging (fMRI). During euglycaemia, glucose is the obligate metabolic substrate required to maintain cerebral function, and this is unchanged during hypoglycaemia [88]. The likely contribution of other energy sources (e.g. lactate) remains small although there is some evidence that people with T1DM may be better able to utilise these alternative fuel sources [89,90].

PET can be used to examine whole brain and regional changes in glucose metabolism. While animal models have indicated that antecedent hypoglycaemia increases glucose transport from blood to brain, thus allowing the brain to extract glucose more efficiently, this has not been shown in humans using PET [91]. Global brain glucose content falls during acute hypoglycaemia with no difference apparent between those with normal and those with impaired awareness, again implying that global glucose extraction is not enhanced by antecedent hypoglycaemia [92].

Studies of regional brain activation have identified key areas involved in glucose homeostasis and thus give insight into the pathophysiology underlying hypoglycaemia awareness. Glucose uptake by the ventromedial hypothalamus, thought to be a key glucose sensor, is reduced in people with IAH [93]. Antecedent hypoglycaemia was induced in healthy adults to induce a state of counter-regulatory failure; subsequent hypoglycaemia resulted in an increase in activity of the dorsal midline thalamus, which is thought to have an inhibitory role in reducing counter-regulatory responses following antecedent hypoglycaemia [94]. In this study, antecedent hypoglycaemia was again used to show a relative reduction in glucose metabolism in cortical areas that are involved in symptom perception [91]. This reduction was also demonstrated in people with IAH [92]. Activation of the amygdala is thought to be an unpleasant subjective experience associated with fear and anxiety. During acute hypoglycaemia, [18F] – fluorodeoxyglucose PET scanning showed greater activation in the amygdala in people with normal hypoglycaemia awareness compared to those with IAH (Fig. 3) [95]. These regional changes in people with IAH can be considered to be an example of "stress sensitisation", whereby repeated exposure to a specific stress results in a reduced response. In contrast, a relative increase in activation was observed in the lateral orbitofrontal cortex during hypoglycaemia in people with IAH; activation of these areas is thought to reduce appetite and limit an appreciation of danger associated with hypoglycaemia (Fig. 3) [95].

15. Management of IAH

The mainstay of treatment of IAH is the complete avoidance of hypoglycaemia, which is of course very difficult to achieve. Reducing the frequency of hypoglycaemia can be attempted by various measures as shown in table 2. Hypoglycaemia awareness can be restored by scrupulous avoidance of hypoglycaemia, although this may be at the cost of jeopardising glycaemic control [96,97]. Hypoglycaemia avoidance can lead to a significant improvement in hypoglycaemia symptom scores during exposure to subsequent hypoglycaemia [97]. Long term effectiveness of these hypoglycaemia avoidance programmes was demonstrated in a small cohort (n=4) three years after a period of hypoglycaemia avoidance for three months. During hypoglycaemia, the symptom scores remained higher than baseline but less than those achieved immediately after the period of hypoglycaemia avoidance [98]. Hypoglycaemia avoidance programmes are labour intensive for both patient and clinician as they tend to require frequent monitoring of blood glucose including measurements at night, with frequent insulin dose adjustments which may take months to implement [99]. Despite the improvement in symptom scores, deficient counter-regulatory hormonal responses to subsequent hypoglycaemia

Table 2
Treatment strategies for people with IAH [31].

Frequent blood glucose monitoring (including nocturnal measurements)
Avoid blood glucose values < 4.0mmol/L
Revise blood glucose targets upwards (e.g. preprandial target 6.0-12.0 mmol/L & bedtime > 8.0 mmol/L
Avoid HbA1c being within non-diabetic range
Use predominantly short-acting insulins (basal bolus regimen; CSII; insulin analogues)
Regular snacks between meals and at bedtime, containing unrefined carbohydrate
Appropriate additional carbohydrate consumption and/or insulin dose adjustment before exercise
Learn to identify subtle neuroglycopenic cues to low blood glucose

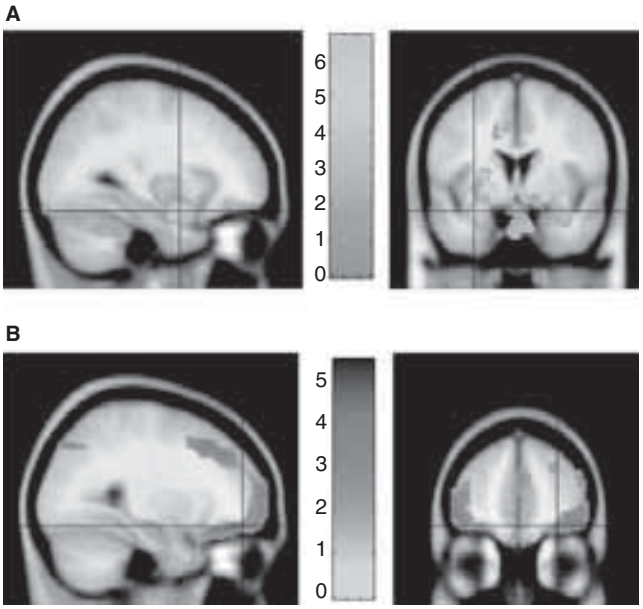

Figure 3. Cerebral correlates of unawareness [95].
A: Regions where aware subjects show relatively greater uptake with hypoglycaemia than unaware subjects, showing amygdala, cerebellum, and brainstem regions.
B: Regions where aware subjects show relatively lower uptake than unaware subjects with hypoglycaemia showing right lateral orbital-frontal cortex.

are relatively unaffected [30,97]. This illustrates a divergence between continuing subnormal counter-regulatory response and an improvement in symptomatic responses, which suggests that other factors are probably important in promoting the symptomatic recovery.

Although it has been suggested that people with IAH may have reduced sensitivity to beta agonists, one study has shown that beta-adrenoceptor sensitivity is preserved [100]. Beta agonists (e.g. terbutaline) have been shown to significantly reduce nocturnal hypoglycaemia at the cost of inducing morning hyperglycaemia [101,102]. Beta agonists have therefore been suggested as possible therapeutic options. Caffeine has been shown to augment symptom intensity and improve counter-regulatory responses [103]. Functional MRI shows caffeine can restore regional brain activation normally lost during acute hypoglycaemia [104]. However, the daily doses required may not make this a practical proposition in treating people with IAH.

One potential advantage of long-acting insulin analogues is their association with a lower rate of nocturnal hypoglycaemia [105]. Hypoglycaemia induced by insulin detemir generated higher symptom scores when compared with human insulin although the difference in total symptom scores only just achieved significance (p=0.048) and the study was not blinded to insulin type [106]. Substitution of nocturnal continuous subcutaneous insulin infusion (CSII) for isophane (NPH) insulin at bedtime resulted in a lower frequency of hypoglycaemia. Warning symptoms and counter-regulatory responses were improved during subsequent acute hypoglycaemia [107]. CSII was used for 24 months in a cohort in which 95% had established IAH and had experienced two or more episodes of severe hypoglycaemia in the preceding two years. The participants reported fewer episodes of severe hypoglycaemia, an improved quality of life, unchanged glycaemic control and an improved symptomatic response to experimentally-induced hypoglycaemia [108]. Administration of bolus doses of glucagon at times of impending hypoglycaemia during CSII lowered the frequency of hypoglycaemia [109]. IAH can also be relieved by islet cell transplantation, with a decline in prevalence from 87% before transplantation to 13% post-transplantation together with an increase in the blood glucose threshold that was required to trigger symptoms of hypoglycaemia, from 2.3 mmol/L (41 mg/dL) to 3.2 mmol/L (58mg/dL) [110].

16. Conclusion

Impaired awareness of hypoglycaemia is an acquired syndrome associated with the use of insulin and exposure to hypoglycaemia that is common in people with T1DM and is observed less frequently in insulin-treated T2DM. It should be defined by the loss of ability to perceive the onset of hypoglycaemia, which is usually manifested by a reduced intensity and number of symptoms and a change in symptom profile. Asymptomatic biochemical hypoglycaemia occurs more frequently and people with established IAH have a much higher risk of developing severe hypoglycaemia. In those affected, cognitive dysfunction is less pronounced during acute hypoglycaemia and recovery is more rapid. However, the glycaemic thresholds for the generation of symptoms, counter-regulatory hormonal secretion and cognitive impairment are re-set at lower blood glucose levels as a result of cerebral adaptation, which allows little opportunity for correcting hypoglycaemia when blood glucose falls to dangerously low levels, and neuroglycopenia rapidly supervenes which prevents appropriate self-treatment. Exposure to antecedent hypoglycaemia, especially repeated episodes, is an important factor in the pathogenesis of IAH. Neuroimaging has allowed identification of key areas of the brain that are involved in maintaining glucose homeostasis and responding to hypoglycaemia. Two methods are currently available for the assessment of awareness of hypoglycaemia in adults, which can be used to identify people with impaired awareness. As antecedent hypoglycaemia appears to have an important role in the pathogenesis of IAH, scrupulous avoidance of hypoglycaemia appears to be crucial in maintaining defences against the development or progression of IAH.

17. Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Acute consequences of hypoglycaemia in diabetic patients

S. Halimi

Clinique d'Endocrinologie Diabétologie Nutrition, Pôle DigiDUNE, CHU Grenoble, BP217X, 38043 Grenoble cedex, France

Abstract

Strict glycaemic control is a major concern in many people with diabetes, hypoglycaemia being the most limiting factor in the daily management of patients with diabetes. Acute consequences of hypoglycaemic attacks are not precisely evaluated. Acute cardiovascular (CV) complications as myocardial ischaemia or stroke seem to be rare, but possibly ignored mainly in older frail patients. Recent large trials in type 2 diabetic patients have not shown the anticipated mortality benefits of strict glycaemic control, and reported a higher frequency of severe hypoglycaemia in the intensive treatment arms with an excess of CV deaths. The authors of these trials persist to deny a direct link between CV deaths and hypoglycaemia. In young type 1 diabetics "dead in bed" syndrome represents a rare but devastating consequence probably due to arrhythmia and prolonged QTc interval. Driving mishaps represent another complication but with a controversial frequency. Neurologic syndromes are frequent during severe hypoglycaemia but usually reversible. Major brain damages are scarce, but cognitive defects or dementia should be underestimated in older and frail type 2 diabetics. Thus, iatrogenic hypoglycaemia due to insulin or sulphonylureas may cause recurrent morbidity in type 1 and type 2 diabetic subjects, and should be prevented by a reevaluation of glycaemic targets in some patients, patient education and the use of new antidiabetic drugs without hypoglycaemic risk.

Keywords: Diabetes; Hypoglycaemia; Cardiovascular complication; Brain damage; Driving; dead in bed syndrome; Review

Résumé

Conséquences à court terme des hypoglycémies cheze les diabétiques

Un contrôle glycémique strict est une préoccupation majeure chez beaucoup de diabétiques dont l'hypoglycémie est le principal facteur limitant au quotidien. Les conséquences aiguës et graves des hypoglycémies ne sont pas précisément évaluées. Les conséquences cardiovasculaires (CV), ischémie myocardique ou accidents vasculaires cérébraux semblent rares, mais peut-être ignorées surtout chez des patients âgés fragiles. De récents essais menés chez des diabétiques de type 2 n'ont pas montré les bénéfices anticipés du contrôle glycémique strict sur mortalité et rapporté une fréquence plus élevée d'hypoglycémies sévères dans le groupe de traitement intensif avec un excès de décès CV. Leurs auteurs ne retiennent aucun lien direct entre décès CV et hypoglycémies. Chez les jeunes diabétiques de type 1, le syndrome "du décès dans son sommeil" est une conséquence rare mais dramatique, sans doute due à des arythmies par allongement de l'intervalle QTc. Des accidents automobiles sont une autre complication, mais de fréquence controversée. Des syndromes neurologiques déficitaires sont fréquents au cours de l'hypoglycémie sévère, généralement réversibles. Les lésions cérébrales majeures sont rares mais les défauts cognitifs ou les démences restent sous-estimés chez les plus âgés. Ainsi, l'hypoglycémie iatrogène due à l'insuline ou aux sulfamides hypoglycémiants peut causer une morbidité significative chez des diabétiques de type 1 et 2. Elle devrait être évitée par une réévaluation des objectifs glycémiques chez certains patients, l'éducation thérapeutique et l'utilisation de nouveaux antidiabétiques sans risque d'hypoglycémie.

Mots clés : Diabètes ; Hypoglycémie ; Complications cardiovasculaires ; Lésions cérébrales ; Conduite automobile ; Syndrome de décès nocturne ; Revue générale

* Correspondence.
E-mail address: shalimi@chu-grenoble.fr (S. Halimi)

1. Introduction

Subjects with diabetes are at increased risk of micro and macrovascular complications. The benefit of glycaemic control in decreasing the risk for microvascular disease is well documented in both type 1 and type 2 diabetic patients [1-2]. By contrast, the importance of strict glycaemic control to limit the risk of macrovascular complications remains controversial. Whether numerous observational studies have clearly shown a relationship between hyperglycaemia and cardiovascular (CV) disease, some recent studies as the ACCORD, VADT trials [3-4] failed to show that intensive glucose control significantly reduces CV events. Moreover in these studies, intensive glucose control increases the risk and the severity of hypoglycaemia and, in the ACCORD study, the incidence of CV events and of all cause of mortality [3]. A benefit of strict glucose control on CV complications has been only suggested in the UKPDS Follow-up study in type 2 DM [5] and the EDIC in type 1 DM [6], in favor of a legacy effects that takes many years before being eventually translated into protection from CV events. Thus, strict glycaemic control being a major concern in many people with diabetes, hypoglycaemia is the most prevalent acute clinical complication and limiting factor in the daily management of patients with diabetes. Thus, iatrogenic hypoglycaemia may cause recurrent morbidity in type 1 and type 2 diabetic subjects [7-8]. In this article we review the acute consequences of hypoglycaemia in both type 1 and type 2 DM, defined as the immediate or short term morbidity or mortality attributable to severe hypoglycaemia conversely to delayed complications.

2. Incidence and risk factors of hypoglycaemia in type 1 diabetic patients

The incidence of hypoglycaemia varies in the literature because of a lack of universal definition and in the absence of reliable data. In most cases data are merely declarative. Severe hypoglycaemia (SH) is defined as all episodes for which, help from others was required. SH are divided into uncomplicated SH (i.e. SH episodes not complicated by coma, seizure, or treatment with glucagon or intravenous dextrose) and complicated SH (i.e. SH episodes complicated by coma, seizure, or treatment with glucagon or intravenous dextrose). Regarding this definition SH affects 40 to 56 % of type 1 people with diabetes [1,9]. In a recent study [9], an overall incidence of SH of 150 episodes/100 patient-years affected 40.5% of an unselected population. This includes 40 episodes/100 patient-years of hypoglycaemic coma. The presence of long-term complications, mainly neuropathy, a threshold for symptoms of < 3mmol/l, alcohol use, and (nonselective) β-blockers were associated with SH during the previous year. For the authors, the recurrence of SH during the period under investigation (1 year) may indicate that SH itself contributed to an increased risk of subsequent SH, as reported previously [9]. In comparison, in the DCCT, the subjects receiving intensified insulin treatment had a 3-fold increase in the incidence of SH compared with subjects treated conventionally with an occurrence of 62 SH episodes/100 patient years, including 16 episodes of hypoglycaemic coma [1]. These data have been recently confirmed by the results of the UK Hypoglycaemia Study Group, type 1 diabetic patients treated for more than 15 years having significantly higher incidence of SH when compared to those treated for 5 years or less [10]. It is however possible that the incidence of hypoglycaemia has decreased since the use of new long acting analog insulin as glargine. The ORIGIN study might answer this question in type 2 diabetics with short duration of diabetes [11]. Some study have compared patients "and relatives" assessments of rates of severe hypoglycaemia and state of awareness and explored the influence on involvement and concern of relatives [12]. Cohabitants recalled more episodes of severe hypoglycaemia than patients (2.7 *vs.* 1.6 episodes/patient year; $P < 0.001$). The discrepancy may be due to different perceptions of hypoglycaemic episodes among patients and spouses. The transient mental impairment of the patients during these episodes of hypoglycaemia may lead to underestimation by the patients. In terms of awareness, there was a poor concordance between patients and cohabitants. This confirms the unreliability of reports and the underestimation of hypoglycaemia by type 1 diabetic patients previously described. Moreover some patients with diabetes, may deliberately ignore episodes due to embarrassment or fear of impact in their professional activity or the risk of losing their driving license. In addition, discrepancies in definitions and assessments of SH and differences in duration of diabetes, age, diabetes management and patient education may explain differences in the occurrence of SH among various studies. Among these factors, duration of diabetes plays a major role. Ample evidence suggests that the glucagon response is lost within five years, as is insulin secretion measured by residual C-peptide. In some people, catecholamine responses are also diminished over a longer diabetes duration [13]. Obviously, a threshold for symptoms at lower blood glucose levels is a frequent consequence of recurrent previous hypoglycaemia, generating a vicious circle. In short, hypoglycaemias are common, particularly at night and often not felt or ignored for different reasons. Despite the huge number of studies on the frequency and severity of hypoglycaemia in type 1 diabetic patients, few details are reported regarding the acute and/or long-term consequences of these episodes. However a subgroup of young type 1 diabetic patient seems to be at high risk of severe hypoglycaemia mainly nocturnal, with potentially devastating consequences. This acute complication seems to be a major cause of an increased incidence of premature death in this population when compared to non-diabetic young people.

3. Incidence and risk factors of hypoglycaemia in type 2 diabetic patients

In type 2 diabetes, frequency of hypoglycaemia is more difficult to evaluate regarding the extreme heterogeneity of these patients, age, frailty, duration of diabetes, renal function,

treatment modalities as oral treatment containing sulfonylurea (SU), insulin use. In the recent UK Hypoglycaemia Study Group trial [10], about 7% of people with type 2 diabetes who were followed for an average of 9 months, had experienced at least one episode of severe hypoglycaemia in the first 2-3 years of insulin therapy, a proportion similar to those treated with sulfonylurea, 10 times less frequent than in patients with long standing type 1 diabetes [1]. This incidence is much higher than that reported in the UKPDS and other trials [4]. A retrospective study has reported 15% severe hypoglycaemic episodes in type 2 insulin treated patients directly related to the duration of insulin use > 5 years [14]. As in type 1 diabetes, a negative relationship was found between hypoglycaemia frequency and low residual insulin secretion. People with type 2 diabetes constitute a disparate group, the ability of each patient to secrete glucagon in response to hypoglycaemia being related to the degree of insulin deficiency [8]. Glucagon secretion was almost absent in type 2 diabetic patients who exhibit total insulin-deficiency. By contrast, glucagon secretion is intact in tablet-treated patient and in type 2 diabetic patients who have recently started insulin. These patients do not experience hypoglycaemia more frequently than patients taking SU at similar A_{1c} levels. In the UKPDS the rate of major hypoglycaemia was 1.4% in the glibenclamide group, and 1.8% in the insulin treated group [2]. In the 4-T study, median rates of hypoglycaemia per patient per year were lowest in the basal insulin treated group, 1.7, higher in the biphasic aspart insulin group, 3.0, and highest in the prandial aspart insulin group, 5.7 [15]. In a retrospective cohort of Medicaid patients, recent hospital discharge was the strongest predictor of subsequent hypoglycaemia in SU or insulin treated patients aged ≥ 65 years [16]. In the Fremantle Diabetes Study severe hypoglycaemia frequency was studied in older patients with cognitive impairment [17]. Hypoglycaemia requiring health services assistance was three times higher in patients with cognitive impairment or dementia. These patients were older, 76 ± 4.6 years, 27.5% treated with insulin + OAD and 45% by SU, 46.4% having an $HbA_{1c} \leq 7\%$. Dementia was present in 9.3% and cognitive impairment without dementia in 19.9%. Many studies support that the risk factors of hypoglycaemia in type 2 diabetic patients are: older age, decreased food intake, depression, cognitive dysfunction, as shown in the ADVANCE Trial [18], dementia, even exercise and alcohol. Ageing, *per se*, has potential effects on counter-regulatory hormones and symptomatic response to hypoglycaemia. At last, in type 2 as in type 1 diabetic patients, antecedent hypoglycaemia (i.e. repetition of hypoglycaemic episodes) can modify the glycaemic thresholds for response of counter-regulatory hormones to hypoglycaemia and may promote HAAF (hypoglycaemia-associated autonomic failure). Thus, estimation of the incidence of hypoglycaemia is likely underestimated by many patients and impossible to truly determine without blood glucose testing in regard of any "malaise" or, in prospective studies by continuous glucose monitoring.

4. Mortality in childhood-onset type 1 diabetes: hypoglycaemia as a cause of dead in bed syndrome and traffic accident?

Although the main part of excess mortality in type 1 diabetes is due to long-term complications, an excess death rate has also been reported from several studies, in different countries, in subjects with short duration of diabetes and in absence of marked signs of long-term complications [19]. If one exclude initial or subsequent ketoacidosis, this excess mortality remains unexplained and mainly due to deaths in bed and traffic accidents. Few data are available for death or serious injuries due to traffic accident secondary to driving errors in diabetic people. This incidence of traffic accident linked with hypoglycaemia remains controversial [20] A systematic trial has been conducted in Sweden for analyzing survival of children who were diagnosed with diabetes at age 0-14 years during the period of 1977-2000 (23.5 years). A cohort of 10.200 diabetic children was recorded and matched with 371 referents death in non-diabetic people [19]. A total of 78 case subjects, 49 males and 29 females, had died over the 81,600 person-years of observation and with a mean duration of diabetes of 8.2 ± 7.1 years (0-20.7). The mean, age and sex Standard Mortality Rates (SMRs) was 2.15 (95% CI 1.70-2.68). The SMRs was higher in females than males (2.65 *vs.* 1.93), whereas young males have a higher death rate than female in the general population. Mean age at death was 15.2 ± 8.6 years (1.2-27.3). Children with an onset before 2 years had an excess death rate of more than 4, whereas for older age at onset the death rate has doubled, and was about three times before 10 years. The peak in mortality is determined at 10-12 years of diabetes duration. Twenty-three deaths were clearly related to diabetes, 14 Keto-Acetosis (KA) among them 6 were onset deaths. Ten KA were found living alone. One death with alcohol intoxication was probably related to hypoglycaemia. Seventeen cases of diabetic subjects (22%) were found deceased in bed at home without a precise cause at forensic serious autopsy (17/78 *vs.* 2/364 in general matched controls). All the cases, mean age 18 years, diabetes duration 8 years, were found deceased in bed by relatives and the deaths were absolutely unexpected. This confirms the original observation of Tattersall et al in 1990 [21] that diabetic subjects, even very young, seem to run a significant risk of sudden death during sleep, related to their diabetic state. In their series, they describe patients who had gone to bed in apparently good health and been found dead in the morning, the majority of them sleeping alone at the time of death and 20/22 lying in an undisturbed bed. Most of them have uncomplicated diabetes, no lesion at autopsy, no proof or no certainty about the role of hypoglycaemia. But the timing of death and other circumstances strongly suggest that hypoglycaemia or hypoglycaemia-associated event was responsible [19,21]. The link between nocturnal hypoglycaemia and dead in bed syndrome will be discussed further when addressing the topic "QTc prolonged syndrome".

5. Hypoglycaemia as a cause of cardiovascular events?

5.1. Myocardial ischemia and CV mortality

Chest pain consistent with myocardial ischemia has been early reported in type 1 diabetic patients [22]. However many data did not confirm this assertion. If hypoglycaemia is often considered as a predictor of all-cause of mortality, no direct evidence supports that hypoglycaemia increased coronary heart disease or favor myocardial ischemia during hypoglycaemic episodes. There are, of course, more cardiovascular events in the glycaemic intensified groups than in control groups of large studies as VADT, 32 *vs.* 20% [4]. In the Bari 2D study, more frequent hypoglycaemia were reported in the insulin-provider treatment than in the insulin-sensitizer one (9.2 *vs.* 5.2%) but without difference for major cardiovascular events [23]. In 2008, an excess mortality in the intensive arm of the ACCORD study led to discontinuation of study [3]. This has prompted many conjectures about the likely reasons and potential principal mechanisms possibly responsible for this increased mortality in diabetic subject submitted to a strict glycaemic control. Thus in ACCORD the rate of hypoglycaemic episode was three times higher in the intensive arm with an annual prevalence of 3.3% *vs.* 1.1% for the standard treatment. Mortality was three times higher in both group, control and intensified, in patients who have had severe hypoglycaemia. Nevertheless, the authors of the ACCORD trial persist to deny a direct link between cardiovascular deaths and hypoglycaemia. Moreover, the delay between hypoglycaemic episodes and cardiovascular events was judged too long to retain a direct consequence of low glycaemic levels on CV events. In all these studies, conducted in relatively old type 2 diabetic patients, CV events cannot be considered as an acute effect of hypoglycaemia. In the DCCT who enrolled type 1 diabetic patients a high rate of severe hypoglycaemia in the intensified group was not associated with increased CV mortality [1]. In 1960, Egeli et al [24] have conducted a study on the effects of insulin and hypoglycaemia on ECG changes (Fig. 1). Sixty-eight patients with diabetes were made hypoglycaemic with insulin (around 2.5 mmol/L) and ECG changes on the ST segments and T waves were reported. These changes could be partly ameliorated with beta-blockers or administration of serum potassium. Ischemic changes were noted in the ECGs of 5/6 patients with type 2 diabetes when they were submitted to low blood glucose, brady-arrhythmia occurred in one patient paralleling with loss of consciousness. Few studies have simultaneously monitored glycaemia and electrocardiogram. In one study, De Souza et al have registered 54 episodes of hypoglycaemia and 10 were associated with clinical symptoms or ECG evidences of ischemia, whereas one episode of chest pain occurred during 59 period of hyperglycaemia [25].

In diabetic patients, seriously ill, admitted for an acute coronary syndrome, those who experienced severe hypoglycaemia at some point of their stay, exhibited double mortality rate compared with those who had no hypoglycaemia [26]. The

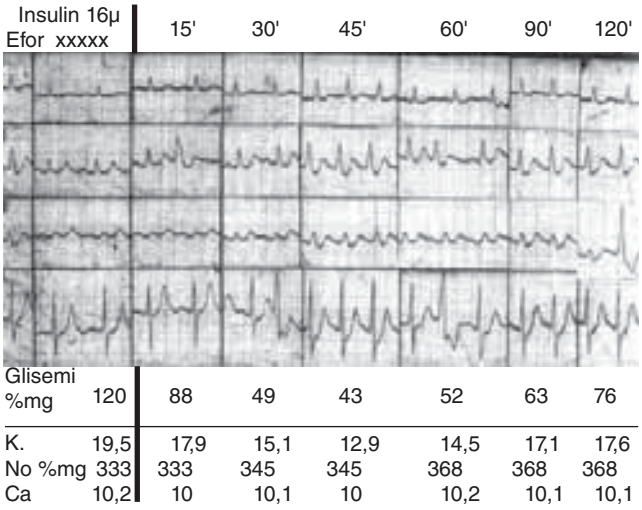

Figure 1. ECG alterations during hypoglycaemia, ECG recorded at the glucose nadir when maximal ST depression was observed (from [24]) with the permission of Elsevier.

CV cause of death in patients who had recent hypoglycaemia suggested that the susceptibility of those patients to cardiac arrhythmia may have been increased by preceding exposure to low glycaemic levels.

5.2. Hypoglycaemia, prolonged QT interval and arrhythmia

As above detailed sudden nocturnal death are sometimes reported in type 1 diabetes [27]. Mc Gill has recently demonstrated that in type 1 diabetic patients severe nocturnal hypoglycaemia was associated with a prolonged, lengthened, corrected QT interval (QTc) and in some episodes, cardiac rate and rhythm abnormalities [27]. Interestingly, this occurred during the recovery phase (CGM 3.4 mmol/l) of a more severe hypoglycaemic event. None of these abnormalities were seen during normoglycaemia with the exception of the patient with P wave abnormalities. This is also found in non-diabetic subjects [28] and in type 2 diabetic patients [29]. It was observed a strong relationship between the increase of epinephrine and the increase in QTc and a weaker relationship between the decrease of potassium and QT. QT dispersion was also recorded during hypoglycaemia, another measure of cardiac repolarization [28]. This degree of abnormal repolarization has been associated with sudden death caused by "torsade de pointes" ventricular tachycardia (VT). It is possible that special susceptibility affected some individuals having a congenital QT syndrome, an inherited condition due to mutation in genes that code the voltage-gated ion channels responsible for the cardiac action potential [30]. This could explain or contribute to the sudden death of young people with diabetes in hypoglycaemic situations. The pathophysiology of this accident should be a direct effect of hypoglycaemia on the myocardium through sympathoadrenal activation and/or hypokaliemia caused by hyperinsulinemia and catecholamines on myocyte sodium-

potassium ATPase. These abnormalities are prevented by selective beta-blockade. Whether impairment of the autonomic neural control of heart rate is associated with an increased risk of mortality, prolonged QTc interval and subsequent arrhythmia found in diabetic patients during hypoglycaemia are not found associated with autonomic neuropathy and often occur in young patients without such complication.

Autonomic neuropathy itself can be associated with QTc lengthening and possibly sudden death [31], and a recent study has found QTc prolongation to be common in adolescent patients with type 1 diabetes with early autonomic dysfunction et [32]

5.3. Hypoglycaemia in the hospital setting

Outside intensive care unit (ICU) the effect of hypoglycaemia in the hospital setting has been few investigated for diabetic patients. Hypoglycaemia during the stay was associated with increased length of stay, one year mortality and inpatient mortality: 2.96% for patients who had at least one hypoglycaemic episode during the hospital stay *vs.* 0.82% for patients who had none [33].

5.4. Coagulation and endothelial dysfunction during hypoglycaemia

Insulin is a coronary vasodilator and has proinflammatory actions [34]. The administration of intravenous insulin induces an immediate activation of sympathoadrenal and neural systems, increasing left ventricular ejection fraction, before any fall in blood glucose occurs. These changes become more pronounced with a decline in blood glucose, with maximal responses at the glucose nadir. Significant increments in cardiac output also occur during hypoglycaemia. The hemodynamic changes during hypoglycaemia are attenuated in some people with type 1 diabetes who have strict glycaemic control, this has been attributed to attenuated sympathetic stimulation. Many humoral markers changes have been reported during hypoglycaemia. Thus, C-reactive protein, TNF-α, endothelin-1, interleukin IL-6 and IL-8, factor VIII, vWF, certain growth factors (VEGF), have been reported to increase during hypoglycaemia [34]. This leads to abnormal coagulation, increased plasma viscosity, endothelial damage, neutrophils and platelets activation, reduced blood flow, capillary closure. Increased vessel wall stiffness has been described in longer duration type 1 diabetic patients during hypoglycaemia. This could explain the possible deleterious effect of hypoglycaemia in a subset of diabetics with longer diabetes duration and/or a preexisting cardiovascular disease as discussed in the ACCORD and mainly in the VADT study [3-4].

5.5. Stroke, hypertension and hypoglycaemia

Obviously, hypoglycaemia induces transient focal neurological deficits including shortly reversible ischemic attacks by correcting blood glucose. By contrast, the question whether severe hypoglycaemic episodes could increase the risk of stroke, remains highly controversial. However a potential link between hypoglycaemia and CV risk should have been "hypoglycaemia-induced hypertension", which seems to be augmented in patients having frequent and severe hypoglycaemia, as observed in intensive insulin therapy programs, DCCT in type 1 and ACCORD in type 2 diabetes [1,3]. This should increase the risk of hypertension-related complications and could have played a role in the unpredicted cardiovascular results of these intensive glucose control studies in type 2 diabetes. However, no study was designed to assess the direct relationship between hypoglycaemia and hemodynamic changes, since the occurrence of hypoglycaemic events was not documented at all.

Feldman-Billard et al have recently investigated the relationship between glycaemia and blood pressure (BP) swings in patients with diabetes under everyday conditions [35]. They have performed 24-hour home monitoring of subcutaneous glucose levels using a continuous glucose monitoring and simultaneous ambulatory BP measurement in patients with type 1 or type 2 diabetes (mean duration, 18 years). Their results demonstrate a close temporal relationship between hypoglycaemia and BP increase. Among patients with marked hypoglycaemia, no patient reported any symptom. The authors draw attention on the fact that cardiovascular disease and all-cause mortality being closely linked to BP elevation in diabetic subjects of both types, increased BP variability, paralleling with recurrent post-hypoglycaemic BP rises, may have played a role in the results of some recent studies, ACCORD VADT [3-4].

6. Hypoglycaemia and brain damages

The discovery of insulin in 1921 generated the initial interest in the possibility of brain damages resulting from hypoglycaemia. The first reason was due to the occurrence of intentional or most often, unintentional overdosage. The second was the deliberate administration of high enough dose of insulin to produce coma for treating schizophrenia and other psychosis by Sakel in 1933 [36]. It was early suspected that this treatment modality had major side effects and acts by brain damage. During the 1930s, many few controlled experiments were conducted to address the question of short or long term brain damage resulting from excess insulin administration. The effects of various degrees of hypoglycaemia have been carefully summed by B Frier [37]. A progressive decline in blood glucose triggers a series of events that occur at different glycaemic thresholds. Early changes are slight, and progressively greater cognitive impairment occurs around 2.8-2.6 mmol l^{-1}, with deteriorating performance, inappropriate attitudes and interferes with the patient's ability to self-treat hypoglycaemia. This state is well investigated by several cognitive tests. Hypoglycaemia also induces non-cognitive changes in mood and behavior, including feelings of tiredness,

sadness, fear, despondency, and, sometimes, anger, violence, aggressive behaviors leading, rarely, to forensic situations. Autonomic symptoms appear around 3.0 mmol l^{-1}, and the effects on neurophysiological function (sensory-evoked potentials and electroencephalographic abnormalities) become more prominent as blood glucose falls further. If the condition is untreated, ≤1.5 mmol l^{-1}, neuroglucopenia is considered as severe and accompanied by reduced conscious level, drowsiness, confusion, and progresses to loss of consciousness and coma. The coma may be complicated by convulsions. Significant brain damage is rare and occurs only if the neuroglucopenia is prolonged, leading to brain death, irreversible lesions and death of the patient. In very young type 1 diabetic patients, it is important to keep in mind that hypoglycaemia-associated symptoms tend to be distinctive from one child to another. Thus it may be difficult for younger child to recognize and verbalize, leaving the parents to distinguish hypoglycaemia from other transient physical states and behaviors. So far, hypoglycaemia (glucose deficiency) was considered to be a form of ischemia (i.e. oxygen deficiency) and the two insults were described as having the same neuropathology. The assumption was that in condition of either oxygen or glucose deprivation, energy deficiencies developed, resulting in necrosis of neurons before glia [38]. But accumulating data prompted a reexamination of this hypothesis. For example, in profound hypoglycaemia, enough to cause cessation of electrical activity, ATP levels are still over one third of the normal values, due to oxidation of alternative fuels (proteins and fats), whereas in ischemia ATP drops to less than 5% of normal. These data indicate that cerebral energy deprivation *per se*, as measured in whole brain, does not account for the phenomenon of selective necrosis. Furthermore, blood flow is not a critical determinant of hypoglycaemia-induces neuronal necrosis. The current concept is that hypoglycaemic coma is associated with the release of endotoxins (excitotoxins) in the CSF spaces, mainly glutamate and aspartate, 3 to 4-fold rise in tissue, which activate subtypes of excitatory amino acid receptors. This increase in aspartate occurs even in spite of normal serum glucose levels, indicating the metabolic abnormality to be due to inhibition of glycolysis, rather than to low glucose levels *per se.* The duration of electro-cerebral silence roughly determines the degree of resultant brain damage. In rodents, cells die within two hours regarding the location of the damage, however neuronal necrosis is absent in hypoglycaemia unless the EEG becomes isoelectric. Recent data suggest that a pro-oxidant state is promoted in certain brain regions during hypoglycaemia and after the glucose reperfusion phase, which might result from the activation of several oxidative stress pathways and may be related to subsequent cell death [39]. Oxidative stress is known to be present in different pathological conditions in the CNS such as ischemia and various neurodegenerative diseases. The presence of oxidative stress during hypoglycaemia has been recently suggested although its temporality and regional distribution in brain have been few explored in detail. Recent studies suggest that oxidative stress is increased by hypoglycaemia and glucose perfusion. Thus, membrane depolarization occurs and can lead to major brain damage as neuronal necrosis. Cerebral cortex and hippocampus are most sensitive to neuroglucopenia, brain stem and spinal cord are much more resistant. In fatal cases of hypoglycaemic coma, the neuropathology of the brain is variable. To date, it is not known whether regional differences in the antioxidant machinery might help to explain the differential regional susceptibility of brain to hypoglycaemic damage [39]. In the patients who survive of severe prolonged hypoglycaemic coma they develop cortical and hippocampal atrophy, with ventricular enlargement, often associated with a chronic vegetative state. The mechanisms underlying this selective vulnerability to hypoglycaemic damage are unknown. Some case report of hemiplegia has been reported as a possible result of hypoglycaemia and was first described in 1928. In a case report, a 58-year-old male with diabetes, who developed left hemiplegia during a severe hypoglycaemic event, diffusion-weighted magnetic resonance imaging has shown an increased signal intensity in the pons, indicating that the patient's hemiplegia resulted from acute brain injury [40]. Some reports provide evidence that acute brain injury may be a cause of the neurological deficit. Cortical laminar necrosis have been described after severe hypoglycaemia [41]. Many transient neurological defects have been described in young type 1 diabetics, in adult or older type 1 or type 2 diabetics. Hemiplegia and hemiparetic attacks are the most frequent and rapidly or slowly reversible even after many hours of neurological deficit until glucose infusion. Various clinical presentations have been reported as paroxysmal dyskinesia. When symptoms are clearly associated with hypoglycaemia, imaging evaluation is probably not warranted. In older patients, having previous CV complications, irreversible defects have been sometimes reported. Cases of central pontine myelinolysis have been reported after hypoglycaemic attacks, in mild forms symptoms may resolve within few months with only minimal residual neurological deficits, for some others severe irreversible sequels may persist till a vegetative state. Experimental studies show that in response to insulin-induced severe hypoglycaemia, diabetes may increase the vulnerability of specific brain areas to neuronal damage. The cumulative effects of recurrent severe hypoglycaemia may cause intellectual impairment in the developing brain of infants and young children, but in adults (principally those with insulin-treated diabetes) the effect on cognitive impairment appears to be modest, with occasional anecdotal exceptions. Nevertheless, higher-level skills seem to be more sensitive to hypoglycaemia than simple, repetitive cognitive or motor tasks explaining why some patients remain highly suited to situations such as driving or manual work. Thus usual tests (RPM) may be unable to identify low performances during acute hypoglycaemia, regarding several facets of attention as non verbal intelligence [45]. Recurrent moderate hypoglycaemia induces a maladaptive response that limits symptoms of hypoglycaemia (hypoglycaemia unawareness), limits the counter-regulatory response to subsequent hypoglycaemia (hypoglycaemia-associated autonomic failure),

and thus jeopardizes patient safety. On the other hand, antecedent recurrent moderate hypoglycaemia preconditioned the brain and markedly limited both the extent of severe hypoglycaemia-induced neuronal damage and associated cognitive impairment. Recurrent moderate hypoglycaemia can be viewed, paradoxically, as providing a beneficial adaptive response in that there is mitigation against severe hypoglycaemia-induced brain damage and cognitive dysfunction. Putative mechanisms for these beneficial adaptations could include glycogen supercompensation (increased brain glycogen content above pre-hypoglycaemic levels). This may explain the seemingly incongruous clinical findings that intensively treated patients who experience recurrent moderate and severe hypoglycaemia may be paradoxically protected from severe hypoglycaemia-induced brain damage and may not suffer from associated long-term cognitive damage [46-47]. In older type 2 diabetic people, hypoglycaemia is three times more frequent in patients with cognitive impairment or dementia than in those with normal cognition. However hypoglycaemia in older people many studies didn't find evidences that hypoglycaemia adversely significantly affects cognition or favors dementia [17]. For other authors [48] among older patients with type 2 diabetes, a history of severe hypoglycaemic episodes is associated with a greater risk of dementia. This suggests that hypoglycaemic episodes severe enough to require hospitalization, or an emergency department visit, are associated with increased risk of dementia, particularly for patients who have a history of multiple episodes. Older individuals are thought to have less brain reserve or brain plasticity, and therefore may be unable to recover from neurological insult as well as younger individuals. Epidemiologic findings from the DCCT [1] suggest that in young adults with type 1 diabetes, hypoglycaemic episodes are not associated with higher risk of subsequent cognitive impairment during 18 years of follow-up (mean age 45 years at follow-up). Thus, hypoglycaemia may not cause large adverse effects on cognitive performance in adults younger than 60 years of both types of diabetes, but could have a greater effect on neurocognition in older individuals.

Whether severe hypoglycaemia induce limited acute irremediable brain damage in diabetic subjects below 60 years, severe hypoglycaemia or even intermediate low blood glucose levels may have serious consequences by impairing driving performance or by inducing other situations leading to conflicts with law [49].

7. Hypoglycaemia and driving

Hypoglycaemia caused by insulin or sulphonylureas, can bring diabetic patients into conflict with the law. Aggressive behavior and the consequences of impaired driving skills are its commonest manifestations [49]. Most of the older studies have either found no association between diabetes and traffic accident or a small, usually not statistically significant increase, of the relative risk [50]. More recent U.S. research, however, indicated a clear trend. Cox et al in a recent study, found hypoglycaemia as a common (when monitored prospectively) and unique risk factor for driving mishaps among some drivers with type 1 diabetes with a higher incidence than the general population [51]. These accidents were not related to sex, duration of disease, A_{1c}, self reported hypoglycaemic awareness, availability of glucose in the car, or blood glucose thresholds for, when to treat or when not to drive. They were related to the use of insulin pumps, history of collisions, severe hypoglycaemia, and hypoglycaemia-related driving mishaps [51]. Hypoglycaemia preceding fatal car collisions has been clearly demonstrated in some case reports [52]. Analyze of memory meter data for 3 months before these fatalities reported frequent episode of low blood glucose values and one or more severe hypoglycaemias before these accidents [52]. The authors conclude that exposure to frequent hypoglycaemia, not low HbA_{1c}, increases the risk of severe hypoglycaemic episodes and that these deaths may have been avoided. Collisions are more common among drivers with type 1 diabetes than among their non-diabetic spouses [53]. Drivers with type 1 diabetes, with history and without a recent history of recurrent hypoglycaemia-related driving mishaps, drove a virtual reality driving simulator. During euglycaemia, participants with history, reported more autonomic and neuroglycopenic symptoms and tended to require more dextrose infusion to maintain euglycaemia with the same insulin infusion. During progressive hypoglycaemia, these subjects demonstrated less epinephrine release and greater driving impairments. This increased risk appears to be attributable to a subgroup of drivers with type 1 diabetes who must be identified and trained for avoiding accidents.

Many younger type 2 diabetic patients are obese and sleep apnea (SA) is highly frequent in this people [54]. Sleep apnea causes impairment in performance and is associated with an increased risk of motor vehicle crashes compared with the general population of drivers [55]. Despite this increased risk, the actual number of accidents due to SA is considered as low. However it is conceivable that sleep apnea or alcohol abuse in diabetic patients as in the general population, are most often involved in driving mishaps as hypoglycaemic episodes. Nevertheless patient's education centered on this risk with adapted practical preventive trainings must be widely proposed in the future to diabetic patients treated with insulin or sulfonylureas.

8. Conclusion

Strict glycaemic control is a major concern in many people with diabetes to prevent microangiopathy and long term CV complications, hypoglycaemia is a major limiting factor in the daily management of patients with diabetes. In the current literature acute consequences of hypoglycaemic attacks are not precisely evaluated. Acute cardiovascular (CV) complications as myocardial ischemia or stroke seem to be rare but possibly ignored mainly in older frail patients. Continuous ECG and

blood capillary glucose might highlight this question in the future. Whether recent large trials in type 2 diabetic patients have not shown the anticipated mortality benefits of strict glycaemic control and reported a higher frequency of severe hypoglycaemia in the intensive treatment arms with an excess of CV deaths, the authors of these trials persist to deny a direct link between CV deaths and hypoglycaemia. However after the large communication of these trials, strict blood glucose targets have been discussed in older type 2 diabetic patients with long diabetes duration and a frail situation. In young type 1 diabetics "dead in bed" syndrome represents a rare but devastating consequence probably due to arrhythmia and prolonged QTc interval, this risk is probably due to a special susceptibility, which affects some individuals having a congenital QT syndrome, an inherited condition. Driving mishaps represent another complication but with a controversial frequency. Experimental studies using driving simulator could contribute to clarify this issue in the future. Neurologic syndromes are frequent during severe hypoglycaemia but usually reversible. Major brain damages are scarce but cognitive defects or dementia should be underestimated in older and frail type 2 diabetics. Thus, iatrogenic hypoglycaemia due to insulin or sulphonylureas, may cause recurrent morbidity in type 1 and type 2 diabetic subjects and should be prevented by a reevaluation of glycaemic targets in some patients, patient education and the use of new antidiabetic treatments without hypoglycaemic risk.

9. Conflits of interests

S Halimi has received speaker and consulting fees from Abbott, Amgen, Astra-Zeneca, Bayer, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Lifescan, Merck Sharp & Dohme-Chibret, Novartis, Novo Nordisk, Pfizer, Roche Diagnostics, Roche Pharma, Sankyo, Sanofi Aventis, Servier, Takeda and Therval.

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Stroke in diabetic patients

Y. Béjot*, M. Giroud

[a]*Dijon Stroke Registry, EA4184 (Inserm and InVS), IFR 100 (STIC-Santé), Faculty of Medicine, University of Burgundy and University Hospital of Dijon, 3, rue du Faubourg-Raines, 21033 Dijon, France*

Abstract

Stroke is the leading cause of disability and the second most frequent cause of death worldwide. On the one hand, diabetic patients have a 1.5 to 3-times higher risk of stroke, especially cerebral infarction, than non-diabetic subjects. This excess risk, which is particularly pronounced in younger individuals and women, can be reduced by effective therapeutic strategies aimed at improving glycaemic control and the management of co-morbid conditions such as hypertension and dyslipidaemia. On the other hand, the prevalence of diabetes in stroke patients is between 10 and 20%, and has been increasing over the last 20 years, probably in response to rising rates of overweight and obesity in the general population and other factors such as a sedentary lifestyle. Even though diabetes has long been considered a specific risk factor of lacunar stroke, recent epidemiological studies have demonstrated that this risk factor was in fact not associated with any ischemic stroke subtype. Finally, it has been suggested that diabetic stroke patients have poorer motor and functional outcomes, and are at a higher risk of dementia, recurrent stroke and death.

Keywords: Stroke; Diabetes; Risk factors; Outcome; Review

Résumé

Accidents vasculaires cérébraux chez le patient diabétique

Les accidents vasculaires cérébraux représentent la première cause de handicap et la seconde cause de décès à travers le monde. Les patients diabétiques ont un risque 1,5 à 3 fois plus élevé d'accident vasculaire cérébral, et en particulier d'infarctus cérébral, que les non diabétiques. Cet excès de risque, qui est particulièrement marqué chez les sujets jeunes et les femmes, peut être réduit par des stratégies thérapeutiques efficaces qui visent au contrôle glycémique et à la prise en charge des co-morbidités telles que l'hypertension artérielle ou encore les dyslipidémies. D'autre part, la prévalence du diabète au sein des patients victimes d'un accident vasculaire cérébral est évaluée à 10 à 20%, et est en augmentation au cours des 20 dernières années, probablement du fait de l'accroissement de la prévalence du surpoids et de l'obésité dans la population générale, et en lien avec d'autres facteurs tels que la sédentarité. Alors que le diabète a longtemps été considéré comme un facteur de risque spécifique des infarctus cérébraux lacunaires, les études épidémiologiques récentes ont démontré que ce facteur de risque n'était en fait associé à aucun sous-type étiologique particulier d'infarctus cérébral. Enfin, les patients diabétiques qui présentent un accident vasculaire cérébral ont un pronostic moteur et fonctionnel moins bon, et sont à plus haut risque de démence, récidive ou décès.

Mots clés : Accidents vasculaires cérébraux ; Diabète ; Facteurs de risque ; Pronostic ; Revue générale

1. Introduction

Stroke is the leading cause of disability and the second most frequent cause of death worldwide. In France, both stroke and transient ischemic attack result in over 125,000 hospitalizations annually, and standardized mortality rates for stroke are estimated at approximately 25 to 30/100,000/year [1]. Diabetes mellitus (DM) is one of the major risk factors for stroke, as it contributes to the progression of atherothrombotic cerebrovascular lesions.

In this article, we review epidemiological data about stroke in diabetic patients by discussing: 1) the risk of stroke in individuals with diabetes, the influence of this risk and ways to reduce it; 2) the frequency of DM in stroke patients and

* Corresponding author.
E-mail address: ybejot@yahoo.fr (Y. Béjot)

the clinical characteristics of diabetic stroke patients; and 3) the prognosis of stroke patients with DM in terms of the risk of recurrence, mortality, disability, handicap, and cognitive impairment.

2. Risk of stroke in diabetic patients

Epidemiological studies have suggested that the overall relative risk of stroke is 1.5 to 3 times greater in patients with DM than in healthy controls [2-4]. This increase in risk is particularly pronounced in younger subjects as well as in women. Hence, compared with healthy controls, the risk of developing a stroke is 2 to 3 times higher in men with DM, and 3 to 6.5 greater in women with DM [2,5,6]. In a large cohort study in the UK, which included 41,799 type 2 diabetic subjects and 202,733 controls, the absolute rate of stroke was 11.9 per 1,000 person-years in people with DM, and 5.5 per 1,000 person-years in the control group. The maximum likelihood estimate of the hazard ratio for stroke was observed in the 35-54 year age group (4.66 in men, and 8.18 in women), and the risk decreased with age [7].

The risk of stroke is also influenced by other factors such as the severity of the diabetes. The Atherosclerosis Risk in Communities (ARIC) study, which included 15,792 people aged 45-64 years at baseline, with a mean follow-up of 8-10 years, showed a robust association between diabetes-specific HbA_{1C} tertiles and incident stroke risk, both in diabetic and non-diabetic subjects [8]. In diabetic patients, the adjusted relative risk of stroke was 2.33 (95% CI: 1.29-4.21) in the highest tertile of HbA_{1c} (HbA_{1c} > 6.8%) compared with the lowest one (HbA_{1C} < 4.7%). A high level of proteinuria, defined as over 300 mg/d, is also considered an independent and strong risk factor for stroke in type 2 diabetic patients, even though no correlation between proteinuria and stroke mortality has been established yet [9].

The other classical vascular risk factors, including hypertension, dyslipidaemia, smoking and atrial fibrillation, also contribute to the increase in the stroke risk in patients with DM. Hypertension is twice as prevalent in diabetic as in non-diabetic individuals and in patients with diabetes; it is associated with accelerated progression of both microvascular and macrovascular complications, leading to a greater risk of stroke. Several randomized clinical trials have demonstrated that antihypertensive treatment dramatically reduces this risk in diabetic patients [10,11]. Therefore, in the UK Prospective Diabetes Study (UKPDS), a 10 mmHg reduction in mean systolic blood pressure was associated with a 44% reduction in stroke incidence [10]. In the secondary prevention setting, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) showed a 38% risk reduction in diabetic patients treated with the combination therapy perindopril plus indapamide [11]. A meta-analysis of 14 randomised trials on statin therapy conducted in over 18,000 diabetic patients reported a highly significant reduction in stroke risk in diabetic patients (21%; 95% CI: 7-33%); this reduction was more marked than in the non-diabetic group (16%; 95% CI: 7-24%) [12]. Finally, the cumulative effect of lifestyle risk factors, such as cigarette smoking, alcohol abuse, obesity, physical inactivity, poor diet and stress, could be greater in individuals with diabetes than in those without.

Contrasting with these data, which clearly demonstrate that the control of vascular risk factors in diabetic patients is associated with a reduction in the incidence of stroke, there is longstanding controversy about the efficacy of improving glycaemic control in the risk reduction of macrovascular complications, including stroke, in patients with DM. A recent systematic review and meta-analysis of all randomized controlled trials comparing interventions to improve glycaemic control with conventional treatment included 1800 patients with type 1 DM and 4472 patients with type 2 DM [13]. The author found clear evidence that glycaemic control is associated with a substantial decrease in macrovascular risk in diabetic patients. Interestingly, in type 1 DM, improved glycaemic control significantly reduced the risk of cardiac events and peripheral vascular disease, whereas it did not reduce the risk of stroke. In contrast, for type 2 DM, a significant 42% reduction in the risk of stroke was noted with active treatment and a similar reduction was observed for peripheral vascular disease, but not for cardiac events [13].

3. Prevalence of diabetes mellitus in stroke patients

DM is a frequent condition in stroke patients. Population-based registries of stroke have reported a global prevalence of DM ranging from 9.5% to 20% [14-16]. In France, based on the national database called “Hospital Discharge Diagnosis Records” (Programme de Médicalisation des Systèmes d’Information, PMSI), the prevalence of diabetes among all hospitalized patients from 2005 through 2008 with a diagnosis of stroke has been estimated at 15% (unpublished data). In addition, in a recent study 16% to 24% of patients with undiagnosed DM at admission for acute stroke were found to have DM according to an oral glucose tolerance test performed 12 weeks after the stroke [17]. The prevalence varied greatly according to the subtype of stroke considered. Hence, the prevalence of DM is lower in patients suffering from spontaneous intracerebral haemorrhage than in those with ischemic stroke. In the latter group, the prevalence is around 25% [18-22]. However, some variations have been noted according to the etiological subtype of ischemic stroke (lacunar, cardioembolic, or large vessel ischemic stroke). Several studies, most of which were hospital-based, have suggested that lacunar stroke is associated with a particular risk factor profile characterized by a higher frequency of hypertension and DM, both of which contribute to the development of lipohyalinosis involved in small vessel brain disease [23,24]. Contrasting with these results, in a previous study conducted on the population-based stroke registry of Dijon, France, we reported a DM prevalence of 19.1% in lacunar strokes, 21.9% in large vessel strokes, and 13.6% in cardioembolic

strokes [25]. After multivariate regression analysis, this study, like other population-based studies, did not find an association between DM and a particular ischemic stroke subtype, including lacunar stroke [24-26]. In a systematic review of 28 studies comparing the risk factor profiles of lacunar and non-lacunar infarcts, the authors found that the apparent excess of diabetes in lacunar *versus* non-lacunar stroke was encountered only in studies that applied a classification of stroke subtypes in which diabetes and other risk factors were used to classify patients [24]. Conversely, among studies with a risk-factor-free classification, there was no difference in the prevalence of diabetes in lacunar *versus* non-lacunar infarction (pooled RR O.95; 95% CI: 0.83-1.09). Therefore, the authors concluded that the controversial assertion that diabetes, as well as hypertension, are particularly associated with lacunar stroke may arise almost entirely from classification bias [24]. Finally, clinically silent infarcts, infratentorial infarcts, as well as cerebellar infarcts have been reported to be more common in diabetic patients [27].

Few data about temporal trends in the prevalence of prior-to-stroke DM are available. Whereas a stable prevalence of approximately 10% was observed in Oxford, UK between the study periods 1981-1984 and 2002-2004, a significant increase was noted in Auckland, NZ between 1981-1982 and 2002-2003 (from 10% to 17.4%, $p < 0.001$) [15, 16]. In Dijon, where the assessment of stroke has been continuous since 1985, the prevalence of prior-to-stroke DM rose from 10.4% to 17.5%, with an odds-ratio adjusted for age and sex of 1.04 (95% CI: 1.03-1.06, $p < 0.01$) [18]. Similarly, in the Framingham Heart Study the proportion of cardiovascular disease, including stroke, attributable to DM increased from 5.4% to 8.7% between 1952 and 1998 [28]. These results are probably related to a rising prevalence of DM in the general population, probably in response to increasing rates of overweight and obesity, and other factors such as a sedentary lifestyle [29].

4. Prognosis of diabetic stroke patients

Several studies have suggested that diabetic patients suffering from stroke have a poorer prognosis than non-diabetic patients. In the FINSTROKE study that recorded 4390 patients with ischemic stroke, 25.1% of whom were diabetic, the four-week case fatality was significantly higher in patients with DM than in those without (20.0% *versus* 16.9%, $p = 0.020$) [30]. In this period after stroke onset, diabetic patients were also more likely to be disabled (43.3% *versus* 33.5%, $p < 0.001$). In addition, in this study, as in others, after adjustment for other cardiovascular risk factors, diabetes was positively and independently associated with both disability and a fatal outcome after the stroke event [30, 31]. In the UKPDS trial, the level of HbA_{1C} in patients with type 2 DM was shown to correlate with stroke fatality, as were several other factors such as sex, systolic blood pressure, recurrent stroke or white cell count [32]. Hence, each 1% increase in HbA_{1C} was associated with a 37% rise in stroke case fatality. In the Malmö Stroke Registry, DM was associated with both mortality and recurrence rates of stroke after 3 years of follow-up [33]. Nevertheless, other authors found no differences between patients with and without diabetes in terms of mortality one year after ischemic stroke [3].

Similarly, some studies have demonstrated that DM influences the long-term functional outcome after stroke. Hence, the European BIOMED Stroke Project reported in a sample of 4537 patients from 7 European countries that handicap (OR = 1.47; 95% CI: 1.13-1.91; $p = 0.005$) and disability (OR = 1.39; 95% CI: 1.05-1.83; $p = 0.016$) were significantly higher in diabetic than in non-diabetic patients at 3 months from onset, whereas no significant difference was noted for mortality [34]. However, other studies found no influence of DM on motor and functional outcomes in the acute and post-acute phases after stroke [35,36].

Finally, the cognitive status of stroke patients also appears to be influenced by DM. In a recent meta-analysis, Pendlebury and Rothwell showed that diabetes was a strong predictor of post-stroke dementia with an odds-ratio of 1.4 (95% CI: 1.2-1.7, $p < 0.0001$) [37].

5. Conclusion

Patients with DM are at a higher risk of stroke than those without, but glycaemic control and the treatment of comorbid conditions such as hypertension and hypercholesterolemia can markedly decrease this risk. Although diabetes is frequent in ischemic stroke patients, it does not predict the etiological subtype of the ischemic stroke. Finally, diabetic stroke patients are characterized by poorer functional outcomes and a greater risk of death. These data, associated with the rising prevalence and incidence of DM in western countries, underline the need for particular attention to be paid to this vascular risk factor.

6. Conflicts of interest

None related to the content of this article.

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Reducing post-stroke disability in diabetic patients

Y. Samson

APHP Urgences Cérébro-Vasculaires Salpêtrière, Groupe Hospitalier Pitié-Salpêtrière, 47-83, boulevard de l'Hôpital, 75013 Paris France, and UPMC Paris Universités, France

Abstract

Stroke is the main cause of acquired disability in adults and is particularly frequent in diabetic patients. Recent data have shown that stroke-related disability may be substantially reduced by emergency treatment of acute stroke in dedicated stroke units and by rapid management of transient ischaemic attack (TIA) and minor strokes, which remain too often neglected. Simple clinical scores have been developed to improve pre-hospital diagnosis of acute stroke and risk estimation in patients with TIA or minor stroke. They are simple enough to be adapted in patient education programs and stroke education may reduce stroke-related disability by increasing the number of patients immediately seeking appropriate stroke care. Immediate access to diffusion MRI and intra-cranial MR angiography further improves diagnosis and risk estimation in TIA and minor stroke. Urgent investigations should also include systematic non-invasive and high quality detection of severe carotid stenosis, which requires rapid endarterectomy, and of permanent or paroxysmal atrial fibrillation (AF), which requires oral anticoagulation.

Keywords: Diabetes; Stroke; TIA; Patient education; Thrombolysis; Endarterectomy; Atrial fibrillation; Review

Résumé

Réduire le handicap de l'accident vasculaire cérébral dans le diabète

Les accidents vasculaires cérébraux (AVC) représentent la principale cause de handicap de l'adulte et sont particulièrement fréquent chez les diabétiques. Les données récentes montrent que le handicap post-AVC peut être considérablement réduit par le traitement en urgence des AVC aigus en unité neuro-vasculaire et par la prise en charge rapide des accidents ischémiques transitoires (AIT) et des mini-AVC, qui sont encore trop souvent négligés. Des scores cliniques ont été mis au point pour améliorer le diagnostic pré-hospitalier de l'AVC et l'estimation du risque immédiat après un AIT ou mini-AVC. Ces scores sont suffisamment simples pour être adaptés à des programmes d'éducation des patients et l'éducation AVC devrait permettre de réduire le handicap post-AVC en augmentant le nombre de patients demandant une prise en charge adaptée immédiate. L'IRM de diffusion en urgence et l'angio-IRM intracrânienne améliorent considérablement le diagnostic et l'estimation du risque après un AIT ou un mini-AVC. Il est également essentiel de rechercher très rapidement, par des méthodes non-invasives de haute qualité, une sténose serrée de la carotide, qui nécessite un traitement chirurgical très rapide et une fibrillation auriculaire permanente ou paroxystique qui nécessite l'institution d'un traitement anticoagulant oral.

Mots clés : Diabète ; AVC ; Infarctus cérébral ; AIT ; Thrombolyse ; Éducation patient ; Sténose carotidienne ; Fibrillation auriculaire ; Revue générale

1. Introduction

Stroke occurs frequently in diabetic patients [1], and stroke patients often have diabetes [2]. In a population-based study with a 20-year follow-up [3], stroke occurred in 27% of the patients with type 2 diabetes mellitus (DM), and 37% of patients had previously known or newly diagnosed DM in a series of 286 consecutive acute stroke patients [2]. Furthermore, stroke is also more severe in diabetic patients and this well-known association has been recently confirmed in the SITS-ISTR registry, which included more than 16,000 thrombolysed patients [4]. The adjusted OR for mortality was 1.31 (1.12-1.53) in patients with history of DM and the adjusted OR for independence was 0.83 (0.73-0.94). Thus an important goal would be to reduce the post-stroke disability in diabetic patients.

The first strategy is pharmacological and will be detailed elsewhere. It relies on tight post-stroke glycaemic control.

* Correspondence.
E-mail address: yves.samson@psl.aphp.fr (Y. Samson).

There is growing evidence suggesting that even mild hyperglycaemia is toxic in acute stroke and that early and strict control of serum glucose levels within the therapeutic window may decrease infarct growth [5]. This hypothesis is currently being tested in several randomised trials, which may turn out to be positive if strict euglycaemia is achieved fast enough (within 3-6 hours post-stroke) and hypoglycaemic episodes are avoided [6].

We will focus here on a "knowledge-based" strategy. All recent advances in stroke care emphasize *emergency access to dedicated stroke units as the major factor of therapeutic efficiency*. Unfortunately, many stroke patients do not receive adequate emergency care. This is partly explained by insufficient medical resources, but the number of stroke units is rapidly increasing. There is also a lack of public knowledge of stroke symptoms and the course of action to take when stroke is suspected [7]. There is finally a lack of medical knowledge of new methods of triaging transient ischaemic attacks (TIA) and mini-strokes according to the subsequent risk of stroke [8]. Since diabetic patients are at very high risk of stroke and since diabetologists have a long experience in patient education, we believe that the "diabetes community" could be an excellent target for testing the efficiency of improvement in stroke knowledge for reducing stroke disability. We will successively consider potential thrombolysis candidates and TIA and mini stroke.

2. Thrombolysis candidates

Thrombolysis is an efficient treatment of ischemic stroke but remains underused: about 3% of stroke patients in France. One of the reasons is the very short therapeutic window [7]. The treatment needs to be initiated within 4.5 hours after stroke onset. Moreover, the efficiency decreases sharply with time. The number of patients needed for treatment in order to have one more patient returning to normal life at three months is 4.5 during the first 90 min, 9 during the 90 min-3 hour period, and 14 between 3 and 4.5 hours [9]. Therefore, stroke-related disability can be reduced by increasing the number of patients treated and even more by reducing treatment delay. In the SITS-most registry, 11% of the patients had already been treated within 90 minutes [10]. To increase this proportion, it is necessary to set a *one hour maximum delay* between stroke onset and admission in a well organized stroke unit. Therefore, each minute and each second count.

There are various modes of organization, but all efficient ones have organized *direct access to the stroke unit via an emergency call system* [7]. In Newcastle on Tyne, England, the patients who called the emergency medical services arrived within one hour at the stroke unit in 27% of cases, compared to 3% of those who contacted their general practitioner or went directly to the hospital emergency department [11]. We also believe that the development of thrombolysis telemedicine networks will be indispensable for increasing the number of treated patients and reducing treatment delay, not only in remote geographic areas but also large, traffic-congested urban concentrations. This should be given a very high priority in stroke care organization since the safety and efficiency of telethrombolysis is now well established [12].

Efficient treatment of acute stroke however requires hat the patient or the bystanders recognize the stroke and act in an appropriate way. Mass media campaigns are efficient, but they are expensive and their effect diminishes after a few months. In addition, we still have questions as to what extent public education really influences people behaviour [7]. Focusing on high-risk populations may be a cost-effective strategy, and we believe that, given the high risk of stroke in diabetic patients, diabetic education programs should include stroke education.

Simple and repeated messages are likely to be the most efficient. They should focus on three issues: 1) Stroke is an extreme emergency; 2) In case of stroke, look at your watch, note the time of stroke onset, and immediately contact the emergency medical services (in France dial 15). This message is likely to be efficient since the word "stroke" is already one of the most used by patients or bystanders in emergency medical service calls [13]; 3) Increase knowledge of stroke symptoms. We advocate the use of the "FAST" method, which is a simple and efficient method of pre-hospital stroke diagnosis [11]. FAST stand for Facial paresis, Arm drift, Speech abnormalities, and Time. Systematic use of the FAST questions improves stroke detection rate in paramedics and ambulance dispatchers. It also improves knowledge of stroke symptoms in the public, and is increasingly popularized by media campaigns in many countries. Even if FAST sensitivity is not perfect, it is well suited for thrombolysis screening since FAST-negative strokes are unlikely to reach the minimum level of severity required to consider thrombolysis, given the risk of symptomatic haemorrhage. In summary, in addition to primary prevention in diabetic education programs, teaching the concept of stroke emergency, the need for an *immediate* emergency medical service call and the FAST knowledge of stroke symptoms may be effective ways for reducing stroke disability in this high-risk population.

3. TIA's and mini strokes

Patients with TIA or mini strokes do not always seek rapid medical attention, and even when they do, they often wait weeks or months before being investigated and treated. For example, in the Oxford population-based study, only three per cent of the endarterectomies were performed within 2 weeks of the presenting event, and only 43% within the first 12 weeks [14]. This is worrying since in the randomised trials, the number of patients needed to treat in order to prevent one stroke in 5 years was 5 for those randomised within 2 weeks and 125 for those randomised after 12 weeks [15].

There is a very low level of public knowledge on TIA, and the medical community has until recently underestimated the risk of early recurrent stroke after a TIA or a mini-stroke, as well as the benefit of emergency treatment in specialized

centres [8]. The high risk of early recurrent stroke after TIA and mini stroke was first demonstrated in patients with severe carotid stenosis. In the patients of the Oxford population study with ≥ 50% carotid stenosis, the risk of stroke prior to endarterectomy was 21% at 2 weeks and 32% at 12 weeks [14]; in addition, as already stated, in randomized clinical trials there is a 25-fold decrease in the benefits of endarterectomy when randomisation is done more than 3 months after the index event [15].

3.1. The ABCD² score

Prognosis scores have shown that the risk of recurrent stroke is not only related to the underlying disease but also to very simple clinical characteristics of the TIA or minor stroke. Among these scores, the ABCD² score has become widely used [16]. This 7-point score is based on: Age ≥ 60 years: 1 pt; Blood Pressure ≥ 140/90 at the first measurement after index event occurrence: 1 pt; Clinical Features: unilateral weakness: 2 pts, speech impairment without weakness: 1 pt; duration ≥ 60 min: 2 pts, 10-59 min: 1 pt; and diabetes 1 pt. It was developed and validated in four independent groups of patients (n = 2893) in the USA and UK, and it has been shown to be highly predictive of the risk of recurrent stroke after seeking medical attention for possible TIA. In the original study [16], the risk of stroke at 48 h was 1% in the low-risk group (ABCD² < 4; 34% of patients), 4.1% in the moderate-risk group (ABCD² 4-5; 45% of patients) and 8.1% in the high-risk group (ABCD² > 5; 21% of patients). The risk of stroke at 3 months was 3.1%, 9.8%, and 17.8% in these 3 groups. Another important finding was that the predictive value was similar in patients with a confirmed diagnosis of TIA by a neurologist and those thought not to have had a TIA. The ABCD² score also predicts the risk of *very early* recurrent stroke. In a recent study [17], the stroke rate at 24 h was 2% with a score < 5 and 10% with a score ≥ 5. Such a high rate suggests that patients with high ABCD² scores should be managed with almost the same degree of emergency attention as the thrombolysis candidates. However, patients with a low ABCD² score still have a high 3% risk of stroke at 3 months, and therefore should also undergo rapid investigation. This is supported by recent data of the Bichat group that found that 20% of the patients with an ABCD² < 4 had an underlying disease requiring immediate admission such as atrial fibrillation (AF) or severe carotid or intracranial arterial stenosis; they recommended EKG and carotid imaging within 24 hours before postponing a complete TIA investigation [18].

Urgent assessment and treatment markedly reduce the risk of subsequent stroke. In the EXPRESS study [19], the 90-day risk of stroke fell from 10.3% to 2.1%, while the median delay for assessment fell from 3 days to less than 1 day and treatment initiation from 20 to 1 day. In the SOS-TIA report [20], the 90-day stroke rate was 1.2%, whereas the predicted rate from the ABCD² score was 6%. A systematic review found that the lower risk of recurrent stroke was seen in studies of emergency treatment in specialist stroke services (0.9%) and the highest in population-based studies without urgent treatment (11%) [21].

In summary, the ABCD² score may be considered as "the FAST score of TIA and mini stroke". Patients with ABCD² scores ≥ 4 should be admitted as soon as possible in a stroke unit and considered as potential thrombolysis candidates in case of early recurrent stroke during the first 24-48 hours. Patients with lower scores should ideally have access to MRI, carotid imaging and EKG within 24 hours. The diabetic community should generalize the use of the ABCD² score, and diabetic education programs may consider the fact that any hypertensive diabetic patient ≥ 60 years with transient unilateral weakness or speech impairment will likely have an ABCD² score ≥ 4 and should be admitted as soon as possible in a stroke unit.

3.2. MRI

The recent American Heart Association/American Stroke Association (AHA/ASA) guidelines stated among the Class 1 recommendations that "patients with suspected TIA should be evaluated as soon as possible after an event" and that "MRI, including DWI (diffusion weighted imaging) is the preferred brain diagnostic imaging modality" and should be performed within 24 hours of symptom onset [22]. The DWI sequence is often but not always abnormal in recent TIA. A DWI abnormality proves the diagnosis of acute ischemic event and its localization. Conversely, a normal DWI does not rule out the diagnosis of TIA. It is however associated with a very low risk of recurrent stroke, even in patients with high ABCD² scores. For example, in a multi-hospital study of 944 TIA patients, disabling stroke occurred at 90 days in 0% of DWI-negative patients with low ABCD² scores, and in only 0.6% of those with high ABCD² scores [23]. In another collaborative study [24], the rate of stroke at 7 day was 9 of 2322 (0.4%) in DWI-negative patients. A hypothesis is that many DWI-negative patients have TIA mimics, since it is increasingly clear that focal ischemia is not the only cause of transient neurological symptoms [25].

On the other hand, patients with DWI abnormalities have a high or very high risk of recurrent stroke. In the former study [23], disabling stroke occurred at 90 days in 6% of DWI-positive patients with 0-3 ABCD² scores, and in 15% of those with 4-6 ABCD² scores; in the latter study [24], the rate of stroke at Day 7 was 63 of 884 (7.1%). This study also showed the improved predictive power of the ABCD2-I score, which added 3 points to the ABCD² score for brain infarction at DWI or CT.

Intracranial arterial occlusion is associated with an even higher risk of recurrent ischemic stroke. In a study of 120 patients with TIA or minor stroke and MRI within 24 hours [26], recurrent stroke occurred at 90 days in 10.8% of patients with DWI lesions and no vessel occlusion at MR angiography, and

in 32.6% of patients with DWI lesions and vessel occlusion. The percentage of patients who were functionally dependant at 90 days were 1.9% in patients without DWI abnormalities, 6.2% in patients with DWI lesions and 21% in patients with DWI lesions and vessel occlusion. In the SOS-TIA clinic, 8.8% of 1823 patients had intracranial artery narrowing or occlusion on transcranial Doppler (TCD) [27]. This finding was independently associated with age, hypertension and diabetes. The incidence of recurrent vascular event at one year was 7% in patients with positive TCD and 2.4% in patients with normal TCD. The hazard ratio was 2.29 after adjustment for age, diabetes and hypertension, and 2.5 after adjustment for an $ABCD^2$ score ≥ 4. Intracranial artery obstructions are frequently associated with misery perfusion [28], indicating exhausted cerebrovascular autoregulation and a high risk of subsequent stroke [29]. We believe that treating hypertension may be dangerous in this situation although the issue remains controversial.

FLAIR and T2* sequences should also be done since they detect previous silent infarcts and signs of microvessel disease such as leucoaraiosis, lacunar infarcts, and microbleeds. In summary, in less than 10 minutes of imaging time, a standardized MRI procedure including diffusion, FLAIR, time of flight MR intracranial angiography and T2* provides without any contrast injection very accurate diagnostic and prognostic indices immediately after a TIA or a minor stroke. An important unsolved issue concerns the best magnetic field (1.5 T *vs.* 3 T), since we recently found that 1.5 T has a much higher diagnostic accuracy than the 3 T MRI unit in thrombolysis candidates [30]. Whether this is also true in minor strokes and TIAs imaged within 24 hours remains to be established.

3.3. Carotid artery imaging

Imaging of the carotid bifurcation is mandatory in all patients with TIA and minor stroke because of the demonstrated benefits of endarterectomy in recently symptomatic patients with severe (> 70%) and moderate (> 50%) North American Surgery Carotid Endarterectomy Trial (NASCET) method of measurement of stenosis. Furthermore, there is growing evidence that endarterectomy should be performed as soon as possible after the index event since the time-window for effective stroke prevention is short. Therefore, carotid imaging should ideally be performed within 24 hours of the index event.

Non-invasive imaging methods have replaced digital subtraction angiography (DSA), which is an invasive, time-intensive and expensive technique, and has a small but real risk of permanent neurological deficit. Doppler-ultrasound (DUS), contrast enhanced magnetic resonance angiography (CE-MRA) and CT angiography (CTA) are the most used non- or minimally-invasive imaging methods. Each of these techniques has advantages and disadvantages, but all remain operator-dependant during image acquisition and/or post-processing of the data [31]. Compared to DSA, a meta-analysis concluded that CE-MRE was more sensitive (0.94) and specific (0.93) for > 70% stenosis than DUS (sensitivity: 0.89, specificity: 0.84) and CTA (0.76; 0.94) [32]. However, DSA is at best an imperfect gold standard, and the meta-analysis was done on relatively old data published between 1980 and 2004, whereas non-invasive imaging technologies are rapidly improving. Even with high quality imaging methods however, the accuracy of grading the degree of ICA stenosis remains an important issue. In practice, we consider, as in many other centres, that two non-invasive techniques are required to make the decision for medical or surgical treatment. The results of the two methods are not always concordant, but in our experience, the most severe grading is the most reliable evaluation and discordances are often resolved by reviewing the original image files.

3.4. Atrial fibrillation

Atrial fibrillation (AF) is a major and treatable cause of recurrent stroke and is especially frequent in DM [33]. AF was reported in 30.1% of patients with DM history and in 24.8% of patients without DM history ($p < 0.001$) in the thrombolysis SITS-MOST registry [4]. AF also occurs in TIA and minor strokes. In the TIA-SOS registry, AF was found in 10.7% of cases with $ABCD^2$ scores ≥ 4 and in 5.9% of patients with $ABCD^2$ scores < 4 [18]. About one-third of patients will have a recurrent stroke in 5 years without oral anticoagulation. This treatment, although burdensome, is extremely efficient: 3 warfarin treatments prevent one case of recurrent stroke in 5 years [34]. By comparison, it is necessary to perform 6 endarterectomies in recently symptomatic severe carotid stenosis to prevent one stroke in 5 years.

Therefore it is important to assess all stroke patients for AF, including those with cervical or intracranial artery stenosis, since atherosclerosis does not offer protection from AF. An important issue is the diagnosis of paroxysmal AF (PAF), which carries the same stroke risk as permanent AF in randomised trials [35]. A systematic review reported that routine Holter monitoring can identify PAF in approximately 1 in 20 patients, and that extended duration of monitoring may improve detection rate [35]. Event loop recording and implantable devices may further improve detection rates, but the significance of very short AF bursts remains to be established [36]. An alternative approach is transtelephonic EKG in which patients frequently self-record short EKGs for 1 month and then transmit the result by phone to a cardiology centre. In a study of 98 stroke or TIA patients with normal 24 h Holter results, we found PAF in 9.2% of cases [37]. The estimated duration of PAF episodes ranged from 4 to 72 hours. The rate of PAF reaches 42.6% in patients with non-lacunar anterior circulation diffusion abnormalities and more than 100 premature atrial ectopic beats in routine 24 h Holter monitoring.

New anticoagulants will facilitate treatment and further decrease the risk of recurrent stroke. In the RE-LY study [38], the overall risk of stroke (ischaemic and haemorrhagic) was 1.4% per year in the warfarin group, 1% in the dabigatran (110 mg) group and 0.7% in the dabigatran (150 mg) group. The risk of brain haemorrhage was particularly low in the dabigatran goups (0.10 and 0.12% per year).

The emergence of low risk anticoagulants suggests that systematic screening for AF and PAF may become in the few next years one of the most efficient methods for decreasing the incidence of disabling stroke in diabetic patients.

4. Conflict of interest

None related to the content of this article.

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Management of blood glucose in patients with stroke

R. P. Radermecker*, A. J. Scheen

Division of Diabetes, Nutrition and Metabolic Disorders, Department of Medicine, CHU Sart Tilman, University of Liège, Liège, Belgium

Abstract

Stroke is a leading cause of death worldwide and the most common cause of long-term disability amongst adults, more particularly in patients with diabetes mellitus and arterial hypertension. Increasing evidence suggests that disordered physiological variables following acute ischaemic stroke, especially hyperglycaemia, adversely affect outcomes. Post-stroke hyperglycaemia is common (up to 50% of patients) and may be rather prolonged, regardless of diabetes status. A substantial body of evidence has demonstrated that hyperglycaemia has a deleterious effect upon clinical and morphological stroke outcomes. Therefore, hyperglycaemia represents an attractive physiological target for acute stroke therapies. However, whether intensive glycaemic manipulation positively influences the fate of ischaemic tissue remains unknown. One major adverse event of management of hyperglycaemia with insulin (either glucose-potassium-insulin infusions or intensive insulin therapy) is the occurrence of hypoglycaemia, which can also induce cerebral damage. Novel insights into post-stroke hyperglycaemia management have been derived from continuous glucose monitoring systems (CGMS). This article aims: 1) to describe the adverse effects of hyperglycaemia following acute ischaemic stroke and the risk associated with iatrogenic hypoglycaemia; 2) to summarise the evidence from current glucose-lowering treatment trials; and 3) to show the usefulness of CGMS in both non-diabetic and diabetic patients with acute stroke.

Keywords: Stroke; Diabetes; Hyperglycaemia; Hypoglycaemia; Insulin therapy; CGMS; Review

Résumé

Contrôle de la glycémie chez les patients présentant un accident vasculaire cérébral

Les accidents vasculaires cérébraux (AVC) sont une cause fréquente de mortalité et d'invalidité au long cours dans la population adulte, en particulier parmi les patients atteints de diabète sucré et/ou d'hypertension artérielle. De nombreuses observations ont montré que les perturbations des fonctions physiologiques secondaires à l'AVC, et tout spécialement l'hyperglycémie, affectent défavorablement le pronostic. L'hyperglycémie post-AVC est fréquente (touchant jusqu'à 50 % des patients) et peut être relativement prolongée, que le sujet soit diabétique ou non. Il a été démontré que l'hyperglycémie exerçait des effets délétères à la fois sur la récupération clinique et sur l'évolution des lésions cérébrales évaluées par l'imagerie médicale. Dès lors, l'hyperglycémie représente une cible physiologique intéressante dans la prise en charge des AVC. Cependant, il reste à apporter les preuves qu'une manipulation intensive de la glycémie influence positivement le pronostic cérébral. En effet, un événement indésirable sérieux de la correction de l'hyperglycémie par l'insuline (que ce soit par une perfusion combinée « glucose-potassium-insuline » ou par une insulinothérapie intraveineuse intensive) est la survenue d'une hypoglycémie qui, elle-même, peut entraîner des dommages cérébraux graves. Aussi, la détection et le traitement de l'hyperglycémie post-AVC pourraient bénéficier du recours à un système d'enregistrement continu des concentrations de glucose (CGMS). Cet article a pour but de rappeler brièvement les conséquences d'une hyperglycémie aiguë post-AVC et les risques associés à une hypoglycémie iatrogène, de résumer les principales données des essais cliniques qui ont tenté de contrôler l'hyperglycémie post-AVC et de décrire l'utilité des systèmes CGMS chez les patients avec ou sans diabète exposés à un AVC.

Mots clés : Accident vasculaire cérébral ; Diabète ; Hyperglycémie ; Hypoglycémie ; Insulinothérapie ; CGMS ; Revue

* Corresponding author.
E-mail address: regis.radermecker@chu.ulg.ac.be (R. P. Radermecker).

1. Introduction

Stroke is one of the most prevalent disabling disorders in western countries and shares many similarities with myocardial infarction [1]. Several aspects of physiology, notably blood pressure, body temperature, blood oxygen saturation, and blood glucose, may be altered after an ischaemic stroke or intracerebral haemorrhage. Patients with acute ischaemic stroke frequently test positive for hyperglycaemia, which is associated with a poor clinical outcome [2-4]. Most studies show the deleterious effect of early hyperglycaemia, especially in patients with non-lacunar focal or global ischaemia [5]. This association between poor glycaemic control and a poor prognosis is particularly evident in patients with persistent hyperglycaemia, patients without a known history of diabetes mellitus, and patients with cortical infarction [6]. It is well established that management of patients in the stroke care unit improves outcomes. How this is achieved, however, remains unclear. It may be hypothesized that closed monitoring and maintenance of physiological homeostasis, including glucose levels, could contribute to this benefit [7].

In a broader context, hyperglycaemia in critically ill patients has been shown to be associated with increased morbidity and mortality. An astounding 42% relative risk reduction in mortality in surgical intensive care unit (ICU) patients was reported in a single centre study when blood glucose was tightly controlled between 4.5 and 6.1 mmol/L with insulin infusions [8]. In a subsequent study, the same group reported the absence of mortality benefit of intensive insulin therapy in medical ICU patients, except in a subgroup of patients requiring critical care for 3 or more days [9]. While the importance of glucose control in this ICU population is well recognized, many questions remain, including the external validity of these single centre trials, the feasibility and safety of intensive insulin therapy outside the setting of a clinical trial, and the most appropriate target for glycaemic control in such critically ill patients. Indeed, two other trials of intensive insulin therapy reported unacceptably high rates of severe hypoglycaemia, leading to the premature interruption of one of them [10,11]. This was confirmed by the recent observations of the multi-national NICE-SUGAR, a large study that randomized 6104 ICU patients to tight glycaemic control (4.5-6.0 mmol/L) or conventional control (8.0-10.0 mmol/L). An increase in mortality at 90 days was observed with intensive *versus* conventional glucose control (27.5 *vs.* 24.9%; odds ratio 1.14; $P = 0.02$) [12]. There is thus growing debate over the value of intensive insulin therapy in critically ill patients. Available trials have been performed in general medical and surgical ICUs, and these results may not be directly applicable to individuals with severe acute brain disease. Indeed, patients with acute stroke may have heightened susceptibility to hyperglycaemia and hypoglycaemia [13]. Therefore, considering the well-known susceptibility of cerebral tissue to glucose changes [14,15], the influence of acute variations of plasma glucose levels in patients with brain injuries certainly deserves careful investigation [7]. If there is evidence that hyperglycaemia can increase the likelihood of poor outcomes after stroke, including in patients receiving tissue plasminogen activator [16], the role of diabetes and hyperglycaemia is difficult to investigate due to the heterogeneous nature of diabetes/hyperglycaemia in regard to the site of ischaemia, the degree of vasculopathy, and the state of reperfusion.

The main aims of the present review are: a) to analyze the relationship between hyperglycaemia and stroke outcomes; b) to describe the potential risk of iatrogenic hypoglycaemia in stroke patients; c) to consider the possible contribution of continuous glucose monitoring system (CGMS) in a stroke unit; and d) to conclude with some clinical recommendations.

2. Stroke-associated hyperglycaemia

The phenomenon of increased glucose levels after acute stroke was already described in 1976 [17]. A neuroendocrine stress response and an inflammatory response may play a role in generating hyperglycaemia, which may be attributed to several underlying mechanisms: a non-specific reaction to acute stress and tissue injury with the associated autonomic, hormonal and metabolic alterations; uncovering of underlying latent diabetes by the acute stroke; increased secretion of growth hormone due to stroke-induced hypothalamic dysfunction; and irritation of the glucose regulatory centres in the hypothalamus and brain stem by blood-laden cerebrospinal fluid or local ischaemia [17]. One study involving non-diabetic patients demonstrated a rise in median blood glucose level from 5.9 mmol/L at 2.5 h to 6.2 mmol/L at 6 h post-stroke [18]. Indeed, post-stroke hyperglycaemia is a frequent phenomenon, with up to 50% of the patients having an initial blood glucose of over 6.0-7.0 mmol/L [19]; notably, such glucose levels, while fasting, would be consistent with a pre-diabetic state [20]. Hyperglycaemia appears to be associated with more severe stroke, as assessed either with a clinical stroke scale or by brain lesion volume measurement. Post-stroke hyperglycaemia has been associated with poor outcomes [21] but seems to particularly affect outcomes in patients without diabetes. In a meta-analysis, the relative risk of in-hospital 30-day mortality in patients with admission hyperglycaemia (> 6.1-7.0 mmol/L) was 3.28 (95% CI 2.32 to 4.64) in ischaemic stroke patients without diabetes, but it was not significantly increased in patients with diabetes [22]. This observation may suggest that hyperglycaemia per se is a marker of the severity of the stroke rather than a real risk factor. Consequently, the poor outcomes in patients with hyperglycaemia may in part reflect the seriousness of the vascular event itself. Alternatively, diabetes is associated with microcirculatory abnormalities in the brain, including arteriovenous shunting and a reduction in glucose transport across the blood-brain barrier. These processes would reduce the delivery of glucose from the blood to the brain of a patient with diabetes, thus possibly protecting cerebral tissue from high glucose levels after acute stroke. Nevertheless, hyperglycaemia has a particularly potent adverse effect after thrombolysis, also in patients with diabetes [23]. Hyperglycaemic patients develop intracerebral

haemorrhage after thrombolysis more often and have overall poorer clinical and radiological outcomes [24]. Hyperglycaemic patients are also less likely to experience recanalisation with thrombolysis. Even if it does occur, hyperglycaemic patients are more likely to deteriorate, particularly if hyperglycaemia appears early after recanalisation. So even if the mechanisms of cerebral glucotoxicity remain unclear, it seems logical to provide early management of hyperglycaemia in patients presenting with acute stroke.

Unfortunately, there are no relevant scientific data proving clear-cut efficacy of managing hyperglycaemia in acute stroke. A few exploratory randomised trials showed that glucose-potassium-insulin (GKI) infusions can be safely administered to acute stroke patients with mild to moderate hyperglycaemia producing a physiological but attenuated glucose response to acute stroke, the effectiveness of which remains to be elucidated [25,26]. The large multicentre GIST-UK trial (Glucose Insulin in Stroke Trial) aimed to demonstrate that treatment with GKI infusions to maintain euglycaemia immediately after the acute event reduces death at 90 days [27]. The trial was stopped due to slow enrolment after 933 patients were recruited. For the intention-to-treat data, there was no significant reduction in mortality at 90 days (GKI *vs.* control: odds ratio 1.14; 95% CI 0.86-1.51; $p = 0.37$). There were no significant differences for secondary outcomes either. In the GKI group, the overall mean plasma glucose and mean systolic blood pressure were significantly lower than in the control group (mean difference in glucose 0.57 mmol/L, $p < 0.001$; mean difference in blood pressure 9.0 mmHg, $p < 0.0001$). This neutral result does not prove inefficacy of acute glucose control for several reasons: acute blood pressure changes may be a confounding factor; the study was underpowered; glucose-lowering therapy was administered relatively late after the stroke event; and perhaps more importantly, GKI infusions achieved only modest decrements in glucose levels. A recent randomised, placebo-controlled trial of GKI infusion in patients with blood glucose > 7 mmol/L within 24 hours of ischaemic stroke measured infarct growth assessed by magnetic resonance imaging (MRI) between baseline and day 7 as the primary endpoint, and brain lactate concentrations with magnetic resonance spectroscopy [28]. GKI infusions lowered blood glucose (approximately 5.6 mmol/L *versus* 7.0 mmol/L in control subjects from 6 to 12 hours post-intervention) and attenuated an increase in brain lactate; they did not affect cerebral infarct growth however. On the contrary, exploratory analysis found that GKI therapy was associated with greater infarct growth in patients with persistent arterial occlusion, and with a high incidence of asymptomatic hypoglycaemia (< 4 mmol/L in 76% of patients; almost 50% of GKI patients required intravenous dextrose infusion)

More substantial reductions in plasma glucose concentrations can be achieved using intensive intravenous insulin, but perhaps at the expense of a higher risk of hypoglycaemia. In a single centre pilot study, 25 acute ischaemic stroke patients were randomised to an insulin sliding scale approach or standard management [29]. Sliding scale insulin therapy significantly reduced blood glucose throughout the 48-hour treatment. Stability of blood glucose within a pre-defined range was achieved with only one possible adverse event related to hypoglycaemia. Although not adequately powered to assess outcome, no significant differences in mortality or disability were observed between the two groups. In another study of 40 ischaemic stroke patients with onset less than 24 hours earlier, an intensive intravenous insulin infusion protocol with the aim of reaching and maintaining blood glucose levels between 4.44 mmol/L and 6.11 mmol/L effectively lowered blood glucose levels compared to subcutaneous insulin if concentrations were above 11.10 mmol/L [30]. Hypoglycaemic events were five times more common (but with few symptomatic events) in patients treated intensively, whereas severe hyperglycaemia was five times more frequently associated with conventional treatment. In addition to the increased risk of manageable hypoglycaemic events, the authors concluded that intensive insulin treatment imposes a considerable strain on both patients and caregivers. A highly motivated and trained staff seems essential, limiting feasibility outside of specialty care settings [30].

Despite the absence of clear evidence from interventional studies, current guidelines recommend management of hyperglycaemia in acute stroke. The main reason is that several reports provide reasonable evidence that persistent elevations of blood glucose levels are associated with neurological worsening. Nevertheless, most recommendations are prudent. Indeed even if experts concluded that the level of hyperglycaemia that previously mandated emergency treatment in the setting of stroke was too high, most of them considered that a reasonable approach would be to initiate insulin treatment among patients with a blood glucose level > 11.10 mmol/L, although this remain a matter of controversy (see below). However, close monitoring of glucose concentrations with adjustment of insulin doses to avoid hypoglycaemia is recommended. Simultaneous administration of glucose and potassium also may be appropriate [31].

3. Iatrogenic hypoglycaemia and stroke

Hypoglycaemia is a common complication of the use of glucose-lowering agents in diabetic patients, and its symptoms may mimic those of a stroke, which may cause problems regarding the clinical evaluation of patients admitted in stroke units. The reason that thresholds proposed in guidelines to initiate insulin therapy remain so “comfortable” is that severe hypoglycaemia may occur if the blood glucose targets are too strict. However, if glucose management is to be undertaken, this should be instituted while there is still salvageable tissue and the glucose reduction must be substantial. As already mentioned, intensive intravenous insulin may be more effective than GKI infusions. In either case, both interventions carry a risk of hypoglycaemia, and any proposed intervention must balance the efficacy/safety ratio as well as the convenience of glycaemic control. Indeed, in clinical practice, it is a real challenge to obtain

near normal glycaemic values using aggressive management of hyperglycaemia without experiencing any hypoglycaemic event. A pilot study assessed the feasibility of early intravenous insulin in patients with post-stroke hyperglycaemia (admission glucose concentration: 9.4-22.2 mmol/L). In 24 patients, there was a substantial decrease in glucose level (from 14.7 ± 4.9 mmol/L pre-intervention to 7.3 ± 1.1 mmol/L post-intervention), with a 21% incidence of symptomatic hypoglycaemia [29]. With no control group, it is difficult to know how much of this change can be attributed to the natural history of post-stroke hyperglycaemia rather than a specific intervention. Based on these pilot data, the latter group completed a larger randomised controlled trial. The recently published Treatment of Hyperglycaemia in Ischaemic Stroke (THIS) study randomised a predominantly diabetic cohort to intravenous insulin for 72 h or usual care (subcutaneous insulin) [32]. In this study, aggressive glucose management achieved better glycaemic control (mean difference in glucose concentration averaging 3.7 mmol/L). However, this was at the cost of an increased rate of hypoglycaemia (12 episodes *versus* 0 episodes). Clearly the limiting factor of intensive management of hyperglycaemia in acute stroke is the risk of hypoglycaemia, which may also be deleterious for the brain [14, 15]. Nevertheless, in available studies it is difficult to link poor outcome after stroke and the occurrence of treatment-induced hypoglycaemia.

Because hypoglycaemia may produce neurological signs that mimic ischemic stroke and because hypoglycaemia itself may lead to brain injury, prompt measurement of the plasma glucose concentration and rapid correction of a low serum glucose level are important. Current guidelines point out that hypoglycaemia should be treated in patients with acute ischemic stroke (class I, level of evidence C) [31]. The goal is to restore normoglycaemia, but excessive post-hypoglycaemia elevation of blood glucose levels should be avoided.

4. Lessons from continuous glucose monitoring

Most of the actual data have been obtained by research groups that have used a single time point measurement of blood glucose to define glycaemic control. This method cannot precisely evaluate the severity and the duration of hyperglycaemia however [33]. The development of the continuous glucose monitoring system (CGMS) with a subcutaneous sensor device has provided a novel tool for recording interstitial glycaemic kinetics [33]. GGMS revealed that normoglycaemia was only achieved 22% of the time in diabetic/non diabetic ICU patients [34] and that early and frequent hyperglycaemia occurred in non-diabetic patients with acute coronary syndromes [35]. Recent evidence suggests that continuous monitoring of glucose levels may help to signal glycaemic excursions and eventually to optimize insulin titration in the ICU [36].

Using this technology, Baird et al. performed a pilot study in which they aimed to directly address the relationship between stroke outcome and contemporaneous glycaemia [37]. This trial enrolled 25 subjects within 24 hours of ischaemic stroke symptoms. Multiple regression analysis indicated that both mean CGMS and blood glucose levels ≥7 mmol/L were independently associated with increased final infarct volume change. The conclusion was that there is an urgent need to study normalization of blood glucose after stroke. Later, Allport et al. [38] used CGMS devices in 59 patients with acute hemispheric ischaemic stroke. The patients were prospectively studied regardless of medication, admission plasma glucose value, and diabetes status. On admission 36% of patients had pre-existing diabetes. At the earliest analyzed time point of 8 h from stroke onset, 50% of non-diabetic subjects and 100% of diabetic patients were hyperglycaemic (≥ 7 mmol/L). This early-phase hyperglycaemia was followed by a decrease in glucose level 14-16 h post-stroke when only 11% of non-diabetic and 27% of diabetic patients were still hyperglycaemic. However, a late hyperglycaemic phase 48-88 h post-stroke was observed in 27% of non-diabetic and 78% of diabetic patients. Thirty-four percent of non-diabetic and 86% of diabetic patients were hyperglycaemic for at least a quarter of the monitoring period. Multivariate regression analysis demonstrated that diabetes, insular cortical ischaemia, and increasing age independently predicted higher glucose values. Thus post-stroke hyperglycaemia is common and rather prolonged despite treatment based on current guidelines. There are early and late hyperglycaemic phases in non-diabetic as well as diabetic patients. Treatment protocols with frequent glucose measurements and intensive glucose-lowering therapy for a minimum of 72 h post-stroke need to be evaluated. With the recent improvement of glucose monitoring systems [36], it will probably be easier to manage post-stroke hyperglycaemia in a more effective and safe manner in the near future [33].

5. Practical implications regarding glucose management during acute stroke

Stroke is the second most common cause of death and a major cause of disability worldwide. Advances have occurred in the prevention and treatment of stroke during the past decade [39]. However, the lack of high quality evidence on the effects of blood glucose manipulation in acute stroke is reflected by the wide variation in current clinical practices. Similarly, local and international guidelines differ in their recommendations for treatment of post-stroke hyperglycaemia. Comparing guidance from the American Stroke Association [31], the UK Royal College of Physicians [40] and the European Stroke Organisation (ESO) [41], all agree that post-stroke hyperglycaemia is associated with poorer outcomes, that (major) hyperglycaemia should be prevented/treated and that iatrogenic hypoglycaemia must be avoided or promptly treated (Fig. 1). However, there is no consensus on the frequency of glucose monitoring, thresholds for intervention or methods to achieve glucose control [42,43].

According to the American Stroke Association [31], because evidence indicates that persistent hyperglycaemia

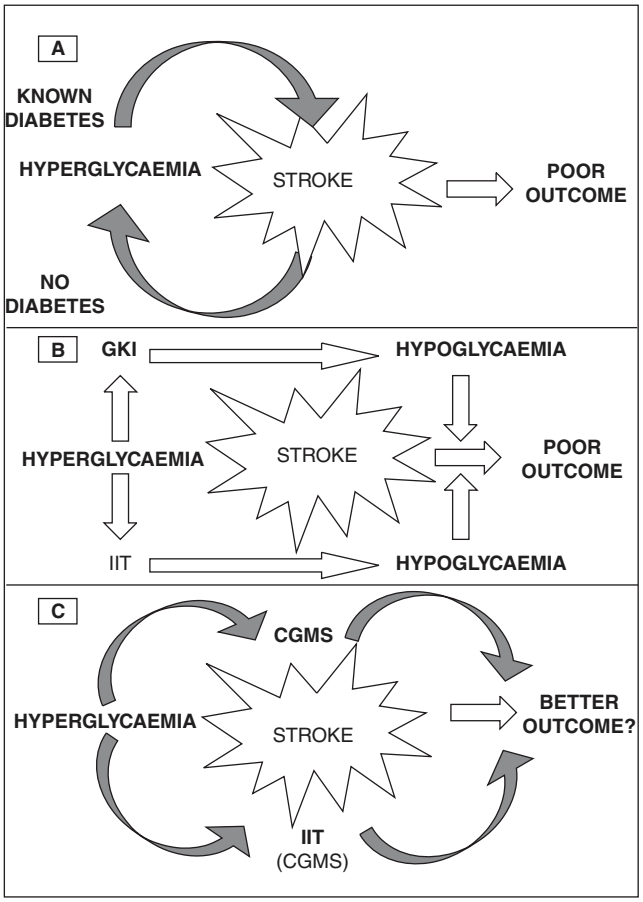

Figure 1. Illustration of the interrelationships between stroke and glucose control.
A: Deleterious effects of post-stroke hyperglycaemia.
B: Deleterious effects of iatrogenic hypoglycaemia.
C: Potential benefit of Continuous Glucose Monitoring System (CGMS) and Intensive Insulin Therapy (IIT) driven by CGMS. GKI: Glucose-Potassium-Insulin.

(> 7.8 mmol/L) during the first 24 hours after stroke is associated with poor outcomes, lower plasma glucose concentrations than the commonly accepted 10-11 mmol/L threshold (possibly > 7.8 to 10.3 mmol/L) should probably trigger administration of insulin. This approach is similar to the procedure in other acute situations accompanied by hyperglycaemia (recommendation class IIa, level of evidence C) [31]. However, the most recently revised guidelines of the European Stroke Organisation still suggest considering intervention if blood glucose concentration is greater than 10 mmol/L, provided that hypoglycaemia can be avoided [41].

In clinical practice the first step is to objectify hyperglycaemia on admission and in the post-stroke state in a sufficiently accurate manner in order to evaluate its severity and duration. Intravenous insulin therapy and frequent blood glucose control for adapting insulin delivery are required. A number of approaches to acute glycaemic control have been described, and there is presently no consensus as to the optimal intervention. Glucose-potassium-insulin (GKI) – based regimes infuse a solution of predetermined concentrations of glucose, insulin and potassium, with peripheral glucose monitoring to guide the rate of infusion. An alternative approach is that of a "sliding scale" insulin administration, wherein the infusion uses a rapidly acting insulin preparation. Proponents of GKI state that this approach is more "physiological" and less prone to dangerous extremes of blood sugar. However, the frequent changes of infusion required for maintaining glucose is time consuming. Alternatively, treating hyperglycaemia with intravenous insulin therapy only (without concomitant glucose infusion) requires frequent control of blood glucose concentrations to adapt rates of insulin in order to avoid hypoglycaemia. Ideally, clinicians should not infuse any glucose solution during the management of such patients (except to correct hypoglycaemia) in order to avoid acute hyperglycaemia, which may be deleterious for the injured brain [7]. Even if CGMS has only been used to carefully evaluate post-stroke hyperglycaemia up until now, this technology will probably be interesting in the future for managing hyperglycaemia in stroke units in a more effective and safer manner [33], as in other critically ill patients [34-36].

6. Conclusion

The danger of post-stroke hyperglycaemia is well established, with numerous data confirming an association between hyperglycaemia and poor outcomes, including in patients treated with thrombolysis. However, although there is compelling evidence that hyperglycaemia has an effect on stroke outcome, the debate continues as to whether the effect is independent of the influence of diabetes or initial stroke severity. The aetiology of hyperglycaemia and the pathophysiology that underlie its detrimental effects remain unclear. A distinction between unknown diabetes and non-diabetic hyperglycaemia seems important, as prognosis and effect of intervention have been shown to differ in these two groups. When attempts are made to treat hyperglycaemia, care should be taken to avoid rapid fluid shifts, electrolyte abnormalities, and hypoglycaemia, all of which can be detrimental to the brain. Patients with critical brain disease should have frequent glucose monitoring because (severe) hyperglycaemia and even modest hypoglycaemia may be detrimental. The safety and efficacy of intravenous insulin therapy in patients with critical brain disease have not been well studied. Careful use of insulin infusion protocols appears advisable, but maintenance of strict normoglycaemia cannot be recommended in this population because of a too high risk of hypoglycaemia. Rigorous studies must be conducted to assess the value of insulin therapy and to determine the optimal blood glucose targets in patients with the most common acute vascular insults. Finally, experts have to propose clear guidelines, which are feasible in clinical practice. One of the key successes will probably be the ability to check glucose continuously in order to adapt insulin therapy on time. This approach needs CGMS devices with good accuracy and a short lag time in order to minimize the risk of both stroke-induced hyperglycaemia and iatrogenic hypoglycaemia.

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Diabetes and cognitive impairment: how to evaluate the cognitive status?

F. Pasquier

Université Lille-Nord-de-France, UDSL, EA 1046, CHRU, Hôpital Roger Salengro, 59037 Lille cedex, France

Abstract

Aim. – Patients with diabetes have shown lower performance in tests of cognitive function especially those testing memory, executive functions, and psychomotor efficiency. They also have an elevated risk of both vascular dementia and Alzheimer's disease. Cognitive impairment may have consequence on treatment compliance.

Methods and results. – This article provides indication for holding an interview, and reports a few screening bedside tests to detect a cognitive impairment. Some neuropsychological tests useful for characterizing the cognitive profile of a patient are described, as well as the main cognitive profiles expected in patients with diabetes and cognitive decline.

Conclusion. – A systematic assessment of cognition with a rapid interview and screening tests in patients with diabetes, especially the oldest, with a long history of diabetes, co-morbidities, or with unexplained poor metabolic control would be a good clinical practice. Patients with cognitive decline may be referred to memory clinics for identifying the cause of the decline and contribute to provide appropriate medical and medicosocial management.

Keywords: Diabetes; Cognition; Neuropsychology; Dementia; Review

Résumé

Diabète et altérations des fonctions cognitives : comment évaluer le statut cognitif ?

Objectif. – Il a été montré que les patients diabétiques avaient des performances moins bonnes que les sujets non diabétiques notamment sur les épreuves testant la mémoire, les fonctions exécutives et qu'ils présentaient un ralentissement psychomoteur. Les patients diabétiques sont aussi à risque plus élevé de démence vasculaire et de maladie d'Alzheimer. Or les troubles cognitifs pourraient avoir des conséquences sur l'observance thérapeutique.

Méthode et résultats. – Cet article donne des indications sur la manière d'interroger un patient en vue de repérer un déclin cognitif, et décrit quelques tests de dépistage d'un déclin cognitif réalisables en consultation ou au lit du malade. Il décrit également quelques tests neuropsychologiques (réalisés généralement par des psychologues) utiles pour caractériser le profil cognitif d'un patient et les principaux profils cognitifs attendus chez un patient diabétique.

Conclusion. – L'évaluation systématique de la cognition par quelques questions pertinentes et des tests de débrouillage est de bonne pratique chez les patients diabétiques notamment les plus âgés, ayant une longue histoire de diabète, présentant des co-morbidités, ou un mauvais contrôle métabolique avec des complications. Les patients chez qui des troubles cognitifs sont suspectés peuvent être adressés à une consultation mémoire pour la recherche de la cause de ce déclin et contribuer à la prise en charge thérapeutique et médico-sociale la plus appropriée.

Mots clés : Diabète ; Cognition ; Démence ; Neuropsychologie ; Revue générale

1. Introduction

The impact of diabetes on cognitive function, especially memory, psychomotor efficiency, and executive function, is addressed for a long time [1]. Compared to people without diabetes, people with diabetes have a greater risk of cognitive decline [2], especially memory and executive functions [3, 4]. There is also evidence for an elevated risk of both vascular dementia and AD in patients with type 2 DM albeit with strong interaction of other factors such as hypertension, dyslipidaemia and apolipoprotein E genotype [1].

Some tests that have shown lower performances in not demented patients with diabetes than in controls [5-7] including the Digit Symbol Substitution Test (DSS) from the

* Correspondence.
E-mail address: Florence.pasquier@chru-lille.fr (F. Pasquier).

Wechsler Adult Intelligence Scale-Revised [8], the Benton Visual Retention Test (BVRT) [9], the verbal fluency test, and the MMSE [10, 11]. Delayed verbal memory was associated with a previous diagnosis of type 2 DM, and diabetes duration was associated with poor performance on immediate verbal recall, delayed verbal recall and abstract reasoning [6]. Results are inconsistent, and other factors are involved in cognitive impairment of patients with diabetes, including age, co-morbidities, level of education, duration, and control of the disease. However, it remains a good clinical practice to systematically assess cognition in older patients with a long history of diabetes or with co-morbidities, as well as patients with poor control of their glycaemia and in patients having complications of DM.

2. Why assessing cognition?

Assessing cognition has several aims. It may indicate whether the patients need supervision for managing their treatment, and improving metabolic control leads to better cognitive functions in patients with Type2 diabetes [12]. Executive functions are involved in organization of information, carrying out plans, judgment according to outcome and cognitive shifting. They are regulated by the dorsolateral prefrontal cortex (PFC), whereas ventral PFC regulates decision making [13] by predicting future rewards and punishments and inhibits impulsive thoughts and responses. Insulin is an important central signal to regulate PFC functions, attenuated in diabetes [14]. In addition to impairment in memory and judgment which have consequence to treatment compliance, impairment in PFC function is particularly important in patients with type 2 diabetes, who are required to make strict daily decisions for optimal glycemic control [15].

Characterising the profile of cognitive impairment helps to diagnose the underlying pathology, more or less related to diabetes. Diabetes is a vascular risk factor and cerebrovascular lesions may cause cognitive impairment. Patients with diabetes may suffer, as others, from degenerative diseases such as Alzheimer's disease (AD) and other degenerative disorders namely Lewy body disease or frontotemporal lobar degeneration. Furthermore, there is some evidence that patients with diabetes may be at risk for AD. The mechanisms underpinning this association remain to be clarified. It is likely that multiple different, synergistic processes may interact to promote cognitive decline [16].

3. How to assess cognition in clinical practice?

3.1. Interview

First an interview with the patient and an informant is necessary to detect and orient towards a cognitive decline. Questions should be first about episodic memory and executive functions, orientation and language. Some scales like the one of McNair et al. [17], previously an auto-questionnaire, or the "Questionnaire de Plainte Cognitive (QPC)" [18] help to structure the interview. For example, the following questions could be asked:

3.1.1. Concerning memory

Did you notice any change in your memory functioning compared to what it was 6 months ago? Do you think your memory is functioning as well as that of other people of your age? In the last 6 months did you feel that registration of new memories is worse than previously? In the last 6 months, did you forget more appointments than you used to forget before? Did you loose your belongings more often than previously? Did you ever completely forget an event even after your relatives told it to you or showed you pictures related to it?

3.1.2. Concerning executive functions

Did you give up some activities or asked for being helped in some activities because of fear to make mistakes or because you are less self-confident than before? Do people find you less interested in some of your previous activities or that you have less initiative than before? Do you feel having more difficulties to do things that you performed quite easily before, because you do not know how to start and to plan each step to achieve them (e.g. organising a trip, inviting people to eat, or sending tax return…).

3.1.3. Concerning language

Do you have the feeling that you miss some words, so that you need to replace these words, use words like "thing", or locution like "what do you call it?" more often than usual? Do you have difficulties with comprehension? Do you sometimes misunderstand what is said or written?

3.1.4. Concerning orientation

Do you have more difficulties in orientation in space, notably in unfamiliar places?

As for any complaint, it must be asked for how long the patient noticed the change; if this change is noticed also by the relatives or by colleagues; if it happened suddenly, in a subacute fashion, or insidiously; and if the progression is stable, improves or worsens.

It is also important to know whether this cognitive change is associated with other symptoms, especially mood or behaviour changes, and if the neurological examination has changed (e.g. appearance of new focal symptoms).

3.2. Global assessment

The multi-item rating scales and batteries of brief cognitive tests evaluate several cognitive functions. Scores on various

separate items or tests are summed to provide a total score representing overall cognitive status. The sensitivity of these cognitive tests in short formats is not uniform and varies by age, education, social class and living situation (e.g. at home, independent of family members, in a geriatric institution, in hospital) [19]. However, they are useful in assessing the rate of cognitive decline, and grading the severity of dementia.

- *The mini-mental status examination* (MMSE) [10] is one of the most widely used screening tests of cognitive decline. The MMSE scale ranges from 0 to 30 points, with higher number indicating better performance. The MMSE consists in questions designed to assess the patient's mental status in the following 7 categories:
  - Orientation in time (5 points): year, season, date, day, month
  - Orientation in space (5 points): country, city, street (or building), floor and location
  - Short term memory (3 points): repetition of 3 words (concrete and frequent words); the patients are informed that they have to learn these words, which have to be recalled later.
  - Counting backwards (5 points): subtraction of seven serially (100-7; 93-7; 86-7; 79-7; 73-7; 65) which is also a distraction task between learning and recall of the 3 words (to prevent repeating the 3 words mentally)
  - Episodic memory (3 points): delayed recall of the 3 previously repeated words
  - Language (8 points): confrontation naming of 2 items (watch and pencil, 2 points), repetition of the sequence "No ifs, ands, or buts" (adapted to French language as "pas de mais, de si, ni de et" http://cat.inist.fr/?aModele=afficheN&cpsidt=15201642, 1 point); writing a sentence (1 point), oral comprehension of a 3 step-command (take the sheet of paper, fold it in 2 and put it on the floor, 3 points), read and follow the sentence "close your eyes" (1 point)
  - Constructional praxis: copy of overlapping pentagons (1 point).

The performance in the MMSE can be influenced by age and education level. Usually the cut-off to consider a possible dementia is 26 for patients with more than 8 years of education (and 18 in patients with 1 to 8 years of study). MMSE has disadvantages for the screening of vascular cognitive impairment: it emphasizes language and verbal memory, it lacks the recognition part of memory, it has no timed elements, and it is not sensitive to impairments in executive functions or mental slowing. A low MMSE score was shown to be significantly associated with reduced activities of daily living, increased need for assistance in personal care, and higher hospitalisation rates [20].

An other more an more widely used test it the *Montreal Cognitive Assessment* (MoCA, http://www.mocatest.org/) which is a cognitive screening test designed to assist for detection of mild cognitive impairment. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal. It was shown to be superior to the MMS for the detection of vascular cognitive impairment since it detects more cognitive abnormalities, particularly in executive function, attention and delayed recall [21]. It is more capable of testing for complex cognitive impairments in domains such as visuo-spatial, executive function and abstract reasoning than the MMSE. In addition, the MMSE subtests of Attention and Delayed Recall contain test items which are not as challenging as contained in the MoCA. For example, the only MMSE test for attention is the serial 7s test while the MoCA includes 2 additional tests: Digit Span (forward , 5 numbers, and backward, 3 numbers) and Vigilance (The examiner reads the list of letters at a rate of one per second, after giving the following instruction: "*I am going to read a sequence of letters. Every time I say the letter A, tap your hand once. If I say a different letter, do not tap your hand*"). Similarly, the 3-item Delayed Recall in the MMSE is less difficult than 5-item Delayed Recall in the MoCA, which also includes a brief executive function assessment (the trail-making test, and a verbal fluency test), and an abstraction test (*Tell me how an orange and a banana are alike*).

4. Neuropsychological tools

4.1. Bedside tools

A selection of common widely used tools sensitive to cognitive decline is presented.

4.1.1. 5 Words Test [22]

It is a serial verbal episodic memory test, with semantic cueing. Five words of 5 different semantic categories (grasshopper, lemonade, museum, colander, lorry) are presented to the patients who are asked to read aloud and learn these words. Encoding is controlled by asking the patients to tell what is the building, the vehicle, the drink, the insect, the cookware when looking at the list of words. Then the list of words is removed, and the patients are asked to recall the 5 words (immediate recall). If one or more words are missing, the examiner provides the cue (e.g. there was a fruit, do your remember it?). If the word is not found, the examiner reminds it to the patients. After a delay, and an interfering task, recalling the words is asked again (delayed free recall), and a cue is provided as well to help recalling the missing words if any (delayed cued recall). The total score is 10 (five for the immediate recall, sum of the free and cued recall, and five for the delayed recall as well). The cut-off for this test is 10 (since it is not very sensitive, but highly specific).

Normal aged subjects displayed good encoding, efficient storage, and consolidation (few forgetting, efficient cued recall),

and intrusions are rare. Patients with the amnestic hippocampal syndrome (like in mild Alzheimer's disease) are characterized by weak encoding of words and severe deficit for storage and consolidation (important forgetting, impaired cued recall), and they make numerous intrusions. On the opposite, subcortical, and frontal dysfunction, like in vascular cognitive impairment, is characterised by low free recall scores, efficient cueing (although less efficient than in controls) and no forgetting between immediate and delayed total recall (i.e. free + cued recall). Recognition id better than recall, and provision of multiple-choice alternatives enhances performance.

4.1.2. Isaacs set test [23]

The Isaacs Set Test shortened at 15 seconds evaluates verbal fluency abilities and speed of verbal production. Subjects have to give a list of words (with a maximum of 10) belonging to a specific semantic category in 15 seconds. Four semantic categories were successively used (cities, fruits, animals, and colours). The score ranges from 0 to 40. It is a good test to measure cognitive changes, since it does not suffer from a floor effect of a ceiling effect.

4.1.3. Frontal Assessment Battery (FAB) [24]

It is a short cognitive and behavioural battery to assess frontal lobe functions. It consists of 6 subtests exploring: 1) conceptualization (similarities: in what way are they alike? Table and chair, tulip rose and daisy); 2) mental flexibility (lexical fluency: say as many words as you can beginning with the letter "S"); 3) motor programming (learning of a gestural sequence, series of Luria: fist-edge-palm); 4) sensitivity to interference (conflicting instructions: tap twice when I tap once); 5) inhibitory control (Go-No-Go: tap once when I tap once; do not tap when I tap twice); and 6) environmental autonomy (prehension behaviour: do not take my hands). It takes approximately 10 minutes to administer. It correlates with other frontal lobe tests. Frontal lobe functions may be especially impaired in vascular subcortical lesions.

4.1.4. Clock Drawing Test [25]

The patient is asked to draw a clock put in all the numbers, and set the hands at ten past eleven. This test provides information about general cognitive functioning, visuo-spatial habilities and constructional praxis

4.2. Neuropsychological tools

To further explore a cognitive decline, a few commonly used tests are presented, generally administrated by neuropsychologists, in a standardized way. Each neuropsychologist is accustomed to using his/her own battery. The most important thing in clinical practice is to use pertinent tools to detect and characterize a dysfunction.

4.2.1. Mattis dementia rating scale (DRS) [26]

It was designed as a screening instrument to detect the presence of brain pathology in impaired geriatric patients. It evaluates a broad array of cognitive functions and includes subtests for attention, initiation-perseveration, construction, conceptualization, verbal and nonverbal memory. Its administration requires 15-30 minutes. It is sensitive to frontal and fronto-subcortical dysfunctions. It is useful in the assessment and progression of dementia including Alzheimer's disease, subcortical dementias such as vascular dementia, Parkinson's disease, and Huntington's disease, and age-related dementia in mental retardation and Down's syndrome.

4.2.2. Free and cued selective reminding test [27]

This test has inspired the 5 words test. But in this long version of the test, there are 16 words to be remembered, presented 4 at a time on a card. There are 4 phases: 1) Encoding and immediate cued recall; 2) Free and cued recall (3 series); 3) Yes-no recognition of the 16 to-be-remembered words among 16 semantic and 16 neutral distractors. 4) Free and cued delayed recall, 20 minutes after the recognition test.

4.2.3. Frontal lobe test

- The Wisconsin Card Sorting test (WCST) measures executive function closely related to the dorsolateral prefrontal cortex. Four stimulus cards and one response card are shown; the cards had geometric designs divided into three categories: colour, form and number of sets. The subjects are asked to decide how to categorise a response card to the four cards, and to search for the correct categorisation by trial-and-error. The achievement scores are related to working memory. Perseverative errors are related to cognitive shifting ability, as the errors are caused by adhering to a former category after the classification category had changed.
- The Stroop test: subjects are tested on naming colours of incompatible words and of control patches (after reading words in black). The interference score is expressed as the difference between the times needed to read each of the two types of cards [28].
- The Trail Making test (part A and B) assesses the mental flexibility. Both parts of the Trail Making Test consist of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1 – 25, and the patient should draw lines to connect the numbers in ascending order. In Part B, the circles include both numbers (1 – 13) and

letters (A – L); as in Part A, the patient draws lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The patient should be instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper.
- Tests of social cognition and theory of mind. Theory of mind is the ability to attribute mental states – beliefs, intents, desires, pretending, knowledge, etc.—to oneself and others and to understand that others have beliefs, desires and intentions that are different from one's own. Test of social cognition may help to explain behavioural changes related to frontotemporal dysfunction: decision-making, recognition of facial emotion and cognition, "faux pas", false belief, etc.

5. Other assessment tools

5.1. Functional scales

- Instrumental Activities of Daily Living (IADL) [29] designate the activities often performed by a person who is living independently in a community setting during the course of a normal day, such as managing money, shopping, telephone use, travel in community, housekeeping, preparing meals, and taking medications correctly. Four activities are particularly sensitive to cognitive impairment, and thus a change in them must be especially searched for: 1) Ability to use telephone (from "operates telephone on own initiative, looks up and dials numbers etc" to "does not telephone at all" , with intermediate levels of loss of autonomy: "dials a few well-known numbers" and "answers telephone but does not dial"); 2) Mode of transportation(from "travels independently on public transportation or drives own car" to "does not travel at all" with intermediate levels "arranges own travel by taxi, but does not otherwise use public transportation", "travels on public transportation when accompanied by another", and "travels limited to taxi or automobile with assistance of another"); 3) Responsibility for own medication (from "is responsible for taking medication in correct dosages at correct time" to "is not capable of dispensing own medication" with an intermediate level: "takes responsibility if medication is prepared in advance in separate dosage"); 4) Ability to handle finances (from "manages financial matters independently", i.e. budgets, writes checks, pays rent, bills, goes to bank to "incapable of handling money" with an intermediate level "manages day-to-day purchases but needs help with banking, major purchases etc"). Any change from a higher level of independency, not due to physical problems, is highly suspect of cognitive decline. Loss of autonomy is part of the definition of dementia.
- Much comprehensive scales such as the Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL) [30] may also be used.

5.2. Behavioural scales

- The Neuropsychiatric Inventory Questionnaire (NPI-Q) is a rapidly administered instrument that provides a reliable assessment of mood and behaviours commonly observed in patients with cognitive impairment or dementia. It assesses the severity of the symptom in the patient and the distress the symptom causes in the caregiver [31]. It questions about delusions, hallucinations, agitation or aggression, depression or dysphoria, anxiety, elation or euphoria, apathy or indifference, disinhibition, irritability or lability, motor disturbance (i.e. repetitive activities, or restlessness), night-time behaviours and sleep, appetite and eating.

6. Most frequent neuropsychological profiles (besides acute stroke)

Subcortical cognitive decline is the most expected profile in patients with diabetes, as for cognitive impairment in other metabolic disorders, and subcortical ischemic vascular disorders related to small vessels disease. It is characterized by forgetfulness, i.e. difficulty in retrieving learned material; slowing of mental and motor processes; impaired ability to manipulate acquired knowledge to generate problem solving; impairment of arousal, attention, and motivation and affective changes (depression), and impairment of set-shifting. Neuropsychological test standard protocols have been proposed for assessing vascular cognitive impairment in 5, 30 or 60 minutes [32].

Typical Alzheimer's disease is characterized by episodic memory impairment: poor learning over repeated trials, impaired delayed recall, and few benefit from cueing. The memory profile is different from that of frontal-subcortical dementias [33]. Confrontation naming may be early impaired with semantic paraphasias, as well as visuospatial skills.

Frontotemporal dementia is suspected on the basis of history: personality and behavioural changes precede and remain prominent during the course of the disease. Behavioural changes include self-monitoring dyscontrol (behavioural disinhibition, irritability, food taste changes, hyperorality, restlessness…), self neglect (personal hygiene, clothing…), self-centred behaviour (apathy, stereotyped behaviour, social neglect…), affective disorders (mainly flat affect) [34]. At early stages, scores on global scales may be within the normal range, patients are oriented in time and place, and provide correct current autobiographical information (contrary to patients with Alzheimer's disease). Family members notice a memory impairment but consider it less important than the behavioural disorder and regard it as due to the behavioural changes. Spontaneous speech is usually reduced. Patients have no difficulties in the perceptual recognition of objects and the appropriate use of objects. Executive functions, and must of all social cognition are impaired.

Lewy body dementia is characterized by a subcortical and cortical cognitive profile, with especially severe executive dysfunction and deficits in visuospatial and visuoconstructive abilities. The main features of the disease are fluctuations, visual hallucinations, parkinsonism, and sleep disorders [35]. Lewy bodies and Alzheimer pathology often coexist.

In summary, when patients have a long history of diabetes (especially if they are getting old), have cognitive complaints, unexplained metabolic poor control, or if cognitive and behavioural changes are reported by an informant, it is useful to search for a cognitive decline. The patient may then be referred to a memory clinic for a work-up including brain imaging, to identify the cause of this decline leading to an appropriate medical and medicosocial management.

7. Conflict of interest

In the last 3 years, Florence Pasquier has participated in pharmaceutical trials in dementia and cognitive impairment: Bioprojet, Exonhit, Ipsen, Medivation, Wyeth, BMS, Bayer. She served as a member of a scientific committee for a study for Servier and for Ipsen, and as a member of an advisory board for a radiotracer for Bayer.

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Hypoglycaemia and dementia in diabetic patients

B. Bauduceau [a,*], J. Doucet [b], L. Bordier [a], C. Garcia [a], O. Dupuy [a], H. Mayaudon [a]

[a] *Service d'Endocrinologie, Hôpital d'Instruction des Armées Bégin, 69, avenue de Paris, 94160 Saint-Mandé, France*
[b] *Service de Médecine Interne Gériatrique, CHU de Rouen, 1, rue de Germont, 76031 Rouen cedex, France*

Abstract

Diabetes and dementia, which have a complex relationship between them, are undergoing extensive growth in their fields. The occurrence of hypoglycaemia, the potential severity of which has just been pointed out in some recent studies, must be included in these relationships. In fact, diabetes is the cause of decline in cognitive functions and most certainly is involved in the occurrence of vascular dementia. The brain, which is highly dependent on glucose for its metabolism, is particularly vulnerable to hypoglycaemia in children and the elderly. Animal studies and pathoanatomical observations confirm the clinical impression of the reality of genuine post-hypoglycaemic encephalopathy. The impact of mild hypoglycaemia however is being debated. Lastly, the existence of dementia promotes the occurrence of hypoglycaemia due to disorders related to eating habits or poor treatment management. This hypoglycaemic risk however must not constitute a pretext for exaggerated laxity in achieving the blood glucose objectives.

Keywords: Dementia; Hypoglycaemia; Diabetes; Cognitive deficit; Insulin; Review

Résumé

Hypoglycémies et démence chez le diabétiques

Le diabète et les démences dont les liens sont complexes, connaissent une expansion croissante. La survenue d'hypoglycémies dont certaines études récentes viennent de rappeler la gravité potentielle, doit être intégrée dans ces relations. En effet, le diabète est à l'origine d'un déclin des fonctions cognitives et participe très certainement à l'installation des démences vasculaires. Le cerveau qui dépend étroitement du glucose pour son métabolisme est particulièrement vulnérable aux hypoglycémies chez l'enfant et le vieillard. Les travaux menés chez l'animal et les constatations anatomo-pathologiques confirment l'impression clinique de la réalité de véritables encéphalopathies post-hypoglycémiques. Cependant, le retentissement des hypoglycémies mineures est discuté. Enfin, l'existence d'une démence favorise la survenue des hypoglycémies en raison de troubles du comportement alimentaire ou d'une mauvaise gestion du traitement. Ce risque hypoglycémique ne doit toutefois pas constituer un prétexte pour un laxisme exagéré dans les objectifs glycémiques.

Mots clés : Démence ; Hypoglycémie ; Diabète ; Déficit cognitif ; Insuline ; Revue

1. Introduction

Hypoglycaemia is a phenomenon that is justifiably feared by diabetics, their families and doctors owing to the accidents and complications that it can induce. Recent studies such as ACCORD and VADT have only strengthened these concerns by showing an increased risk of mortality and cardiovascular accidents in groups that receive intensive treatment. At the same time, there is a growing incidence of hypoglycaemia [1, 2]. The cerebral consequences of severe hypoglycaemia have been less extensively explored than the cardiovascular complications of diabetes. The brain, however, is directly and rapidly affected by the decrease in blood glucose since its metabolism relies exclusively on glucose. The majority of diabetologists have already noticed major cognitive changes occurring with repeated and severe hypoglycaemia, constituting the classic "post-hypoglycaemic encephalopathy".

Considering the increased prevalence of dementia and diabetes, the optimal treatment of which is the control of hypoglycaemia, a clarification of relationships between

* Corresponding author.
E-mail address: bernard.bauduceau@wanadoo.fr (B. Bauduceau).

these two entities is required after an analysis of the methodological difficulties and reporting of the experimental and clinical data.

2. Definition and prevalence of hypoglycaemia in diabetics

The definition of hypoglycaemia is based on biochemical and clinical criteria: blood glucose level less than 0.60 g/L with suggestive symptoms. So-called "severe" hypoglycaemia is that which requires help from a third person.

This definition is not quite precise enough since many cases of hypoglycaemia go undetected, especially those that occur at night, so as a result it is difficult to record them and assess the consequences. Mild hypoglycaemia is very common in type 1 diabetics and is not always reported by patients.

The rate of severe hypoglycaemia varies according to the type of diabetes, the blood glucose objectives and the treatment used. It is rarer in type 2 diabetes treated with insulin or sulfonamides. On the other hand, hypoglycaemia induced by insulin secretors is often more serious due to its long duration of action in cases of renal failure, especially in elderly subjects. It is therefore difficult to compare the consequences of repeated hypoglycaemia in young type 1 diabetics with those of fragile elderly subjects with type 2 diabetes.

3. Difficulties in determining the role of hypoglycaemia in the occurrence of cognitive disorders and dementia

The study concerning the relationship between hypoglycaemia and dementia faces several difficulties.

3.1. Heterogeneity of hypoglycaemia

The cerebral consequences of hypoglycaemia probably depend on its intensity, duration and rate of occurrence. As this information is often missing in published studies, it is difficult to determine the role of hypoglycaemia in the occurrence of cognitive disorders.

3.2. The definition of cognitive deficits and dementia

The determination of cognitive deficits and the diagnosis of the type of dementia are not always easy. Thus the boundary between cognitive deficit, early dementia and encephalopathy is difficult to discern. Diabetologists are poorly trained in this practice, which emphasises the worth of collaboration with geriatricians. Moreover, the term "hypoglycaemic encephalopathy" seems to be more appropriate than the term "dementia", which is usually associated with Alzheimer's disease or with vascular dementia in elderly subjects who present different anatomical and histological lesions.

3.3. Responsibility of diabetes in the occurrence of dementia

The relationship between hypoglycaemia and cognitive disorders in diabetics does not appear to be simple, insofar as the influence of the diabetic disease itself, its duration and its degenerative complications interfere to a great extent [3]. Indeed, diabetes itself seems to be responsible for the occurrence of dementia and cognitive deficits, so as a result it is difficult to separate the responsibility of blood glucose control, cardiovascular complications and severe or repeated hypoglycaemia.

At this stage, some epidemiological data on dementia during diabetes should be mentioned. The large epidemiological studies emphasize the joint increase in the prevalence of diabetes and dementia. This phenomenon is largely related to the aging of the population. The projections thus made by WHO show that between 1995 and 2025, the adult population will increase by 11% in developed countries, and the number of type 2 diabetics will increase by 42% [4]. In a parallel manner, over 33% of women and 16% of men over the age of 65 years will develop dementia and have resulting total loss of autonomy [5]. The incidence of Alzheimer's disease, which makes up 70% of dementia cases, has been assessed at 1.17% in France. Alzheimer's disease affects 1.5% of people aged 65 to 70 years and 30% of subjects over the age of 90 years [6].

Although the influence of diabetes on cognitive functions was suggested by Miles over 80 years ago and a large number of studies have been done in this area since then, no consensus has emerged regarding the responsibility of diabetes in the development of dementia or the protector effect of optimal blood glucose control [7]. As a consequence, the exact role of hypoglycaemia therefore seems to be difficult to pinpoint.

3.4. Lack of reference studies

Lastly, a large reference study on this question is missing. The available results up to now have often been contradictory. The recent implementation of the GERODIAB study by the Diabeto-Geriatric francophone group plans on answering some of these questions [8].

4. From experimental data to pathoanatomical observations

Brain structures are very sensitive to hypoglycaemia since they rely almost exclusively on glucose for their metabolism [9]. This explains the significance of neuropsychological signs of acute hypoglycaemic incidents, regardless

of whether they originate from medication or are related to an insulinoma.

The medium to long-term effects of hypoglycaemic episodes have however been less well described due to the lack of a reference study, which would be difficult to conduct. Animal studies done on rats show the high level of fragility of the hippocampus to hypoglycaemia, this being a region that is vital to the function of memorisation. The observed lesions are similar to those induced by chronic ischemia or by acute stress such as hypoxia [10]. Severe hypoglycaemia thus leads to necrosis of the neurons in the hippocampus region but also in the regions of the cortex. On the other hand, rats that underwent repeated and moderate hypoglycaemia seemed to be largely protected from the consequences of severe hypoglycaemia due to cerebral preconditioning to the lack of glucose [11].

Identical lesions have been demonstrated in diabetics who died from hypoglycaemic comas, thus confirming the high sensitivity of these cerebral areas in humans to the lack of glucose [12]. Results obtained in insulin shock therapy show improvement of psychotic states in patients subjected to hypoglycaemic shocks. These results were even used to justify the use of such methods in Soviet-era dissidents who were classified as having "subclinical schizophrenia". It is probable that the observed improvements were actually related to the lesions in cerebral areas sensitive to hypoglycaemia. Fortunately, these methods have now become part of history.

5. Contributions of clinical studies

Few follow-up studies of sufficient duration have been specifically interested in the cognitive consequences of repeated and severe hypoglycaemia in humans, whereas glucose is essential to proper neuron functioning. Admittedly, the assessment of cognitive function, which is routinely practiced by geriatricians, has still not become part of the normal diabetology work-up. The ENTRED study in particular does not contribute much in this domain [13].

5.1. Influence of diabetes and hypoglycaemia on cognitive decline

Epidemiological data show a correlation between the main cardiovascular risk factors and the decline of cognitive functions, although this does not include dementia. This is particularly true of arterial hypertension [14,15].

Brain performance appears to be sensitive to acute variations in blood glucose levels [16]. However, the role of chronic hypoglycaemia in cognitive functioning is still the subject of controversy, although it appears to be a real phenomenon [17]. The deterioration of cognitive functions in diabetics is correlated to the time since the diagnosis of the diabetes and blood glucose control [18,19]. Deterioration of cognitive function can appear very early, from the glucose intolerance stage, even before the diagnosis of diabetes is made [7,20]. Not everyone however accepts the idea of diabetes as a risk factor of cognitive decline. Other studies have not observed any significant differences in cognitive functioning between controls, subjects with glucose intolerance and those with diabetes after adjustment for confounding factors [21,22]. Lastly, improvement of blood glucose control improved cognitive functioning in a small series of elderly type 2 diabetics [23].

The influence of hypoglycaemia must therefore be assessed by taking into consideration these complex and controversial data, in which some studies conclude that hypoglycaemia is responsible for cognitive deficits [24] and others rule it out [25, 26].

Large studies published in 2008 showed excessive mortality of cardiovascular origin in the intensive arms of the ACCORD and VADT trials. This fact appears to be related to an increase of severe hypoglycaemia [1,2,27]. On the other hand, although this is without a doubt due to the methodology and the limited duration of these studies, not enough emphasis has been put on the psychological consequences of hypoglycaemia. In the ADVANCE study however, the hypoglycaemic risk was low and there were no differences in cognitive changes between the two arms (intensive and conventional). Nevertheless, subjects that presented with cognitive disorders had an increased risk of death and cardiovascular accidents [28]. An ancillary study of ACCORD provided us with additional information, although it met with difficulties, since the glycaemic objectives in both arms were now identical. The specific aim of the ACCORD-MIND trial was to assess the influence of blood glucose control on cognitive functions. This transversal study shows that the increase of HbA_{1c} is significantly related to decreased cognitive functioning as assessed by four validated tests [29]. It should be pointed out however that these results do not take into considerations the post-prandial blood glucose levels, which might contribute in the deterioration of cognitive functioning [30]. The ACCORD-MIND follow-up study, which is still underway, will provide data on the long-term consequences of blood glucose levels on cerebral performance.

This relative lack of scientific data contrasts with the fact that everyone is aware of the negative role of severe and repeated hypoglycaemia, particularly in type 1 diabetes, occurring in childhood.

5.2. Influence of diabetes and hypoglycaemia on dementia

Dementia is defined as the decline of memory and other cognitive functions over a given time period compared with the former state of the patient. Large post-mortem studies of elderly subjects with dementia showed that the dementia occurred in relation with Alzheimer's disease in 80% of cases; the diagnosis of "pure" vascular dementia was present in 7 to 10% of cases; and a "mixed" dementia occurred in 3 to 5%, combining the lesions of Alzheimer's disease and vascular

dementia. The role of hypoglycaemia turns out to be very modest in the usual aetiologies of dementia and its role in the appearance or worsening of dementia is difficult to clarify.

5.2.1. Alzheimer's disease

Alzheimer's disease is a degenerative disease of the central nervous system characterised by progressive and sustained weakening of all cognitive functions. Histologically it presents with specific neuropathological lesions. Hypercholesterolemia and systolic arterial hypertension seem to constitute independent risk factors of Alzheimer's disease [31,32]. Diabetes might also be a risk factor for Alzheimer's dementia, which would then place it in the vascular disease category rather than neurodegenerative [33]. This data is not only of theoretical interest, since the prevention and management of Alzheimer's disease might be conditioned by those of cardiovascular risk factors [34]. Nevertheless, the type of treatment does not seem to influence the occurrence of Alzheimer's disease [35]. The most recent studies agree that insulin resistance bears some responsibility for the occurrence of Alzheimer's disease [36]. However, not all authors agree on the role of diabetes [37,38]. This fact was confirmed by a recent post-mortem study, which showed even that the lesions of Alzheimer's disease are less frequent than in non-diabetics [39]. The role of hypoglycaemia thus seems to be very uncertain in early Alzheimer's disease, the histological lesions of which are very distinctive. On the other hand, severe hypoglycaemia might worsen the cognitive disorders of Alzheimer's disease.

5.2.2. Vascular dementia

Vascular dementia is characterised by a sudden deterioration of cognitive functions or by the occurrence of dementia within three months following a cerebral vascular episode [40]. In addition to this symptomatology, there must be focal neurological signs that are compatible with a cerebral vascular accident and anomalies on the medical imagery of multiple infarctions or hemorrhagic accidents. Diabetes increases the risk of occurrence of cerebral vascular accidents and could therefore promote the development of vascular dementia. In the study by Hassing, diabetes doubled the risk of vascular dementia but not Alzheimer's disease [38]. The conclusions of the Rotterdam Study point in this direction: the presence of diabetes doubled the risk of the appearance of vascular dementia in 6370 elderly subjects who were initially free of dementia [41]. In a study of more than 1700 subjects over the age of 60 years, the combination of type 2 diabetes and cerebral vascular accident increased the risk of dementia by 8-fold [42]. Lastly, the combination of arterial hypertension and diabetes increased the risk of vascular dementia by 6-fold in a cohort of 1259 subjects who had been followed for seven years and were free of cognitive function alterations at the inclusion [43].

The results of these studies are thus often divergent, the role of hypoglycaemia is only rarely suggested and its responsibility in the occurrence of dementia becomes secondary.

6. Consequences of hypoglycaemia according to age and type of diabetes

The consequences of hypoglycaemia vary according to the type of diabetes and thus the treatment but also according to the individual characteristics. Indeed, the fragility of cerebral structures seems to be increased in children and elderly subjects.

6.1. Young subjects and type 1 diabetes

Type 1 diabetics, whose HbA_{1c} target is below 7%, generally present with hypoglycaemia. As a result, there was a 3-fold increase in the risk of severe hypoglycaemia in the intensive arm of the Diabetes Control and Complications Trial (DCCT) [44]. The impact of these hypoglycaemic events must be assessed according to their severity, as well as their duration and frequency. The cerebral consequences have been well established and are a justifiable threat in children and in elderly subjects after deep and prolonged hypoglycaemic coma [45]. Severe and recurrent hypoglycaemia has an acknowledged negative effect on the cognitive abilities of diabetics, which can lead to hypoglycaemic encephalopathy [46]. This clinical picture is due to lesions of the frontal cortex and includes decreased cognitive functioning, particularly with regard to memory and attention, especially in children. Early-onset diabetes results in more significant disturbances of some cognitive and functional MRI tests [47]. In the DCCT study however, severe hypoglycaemia was not associated with decreased cognitive functioning, whereas some anomalies were observed in subjects with poor blood glucose control [48].

This hypoglycaemic encephalopathy therefore seems to mainly concern patients with early-onset (in childhood) type 1 diabetes that have presented with severe and recurrent hypoglycaemia. This clinical picture thus differs very considerably from signs of dementia both in its symptomatology and its cerebral lesions. The improvement of techniques and the quality of patient management of patients has most certainly limited the occurrence of these serious complications.

6.2. Elderly subjects and type 2 diabetes

The consequences of severe hypoglycaemia appear to be more significant in elderly subjects who generally present type 2 diabetes. Prevention of these metabolic incidents must therefore be included in a more comprehensive management of elderly diabetic patients, particularly with the aim of decreasing the frequency of falls, malnutrition and depression [49]. The incidence of hypoglycaemia induced by sulfonylureas is less common than those caused by insulin therapy, but they can

be longer lasting and therefore more serious, especially with pre-existing renal failure [50].

The medium and long-term consequences of hypoglycaemia are still being debated. Severe hypoglycaemia occurring between 55 and 65 years clearly seems to be a risk factor for the occurrence of dementia after 20 years of progression. In a large retrospective study on 16,667 elderly diabetic patients, the risk of occurrence of dementia increased by 26% in diabetics that had presented with one severe episode of hypoglycaemia, by 80% for two episodes of hypoglycaemia and by 94% for three or more episodes of hypoglycaemia [51]. The attributable risk of dementia between the subjects with or without a history of hypoglycaemia is 2.39% per year. Although this annual increase appears modest, the cumulative effect must not be neglected. On the other hand, the consequences of mild hypoglycaemia are not known [51]. This hypoglycaemic risk, especially in elderly subjects, must not however constitute an argument for laxity in the blood glucose objectives, which must be set individually according to the individual characteristics and the fragility of the patient [52].

7. Dementia promotes hypoglycaemic incidents in diabetics

Dementia alone is a significant risk factor for the occurrence of severe hypoglycaemia due to these patients' random eating habits and errors in the management of their treatment [53]. In the ADVANCE study, an increase in the frequency of severe hypoglycaemia was observed in subjects presenting with significant cognitive disorders [28].

In the "Fremantle Diabetes Study" performed on 302 elderly diabetics aged over 70 years, there was a correlation between the history of severe hypoglycaemia and cognitive status. The existence of dementia was a very significant risk factor for the occurrence of severe hypoglycaemia in the 5 years following the study. On the other hand, there was no evidence of hypoglycaemia requiring the help of a third person in the appearance of cognitive deficits [53].

The recognition of the clinical manifestations of hypoglycaemia is difficult in patients presenting with dementia. In fact, agitation, increased confusion or other behavioural disorders may be associated with the dementia and lead to the initiation of inappropriate psychotropic drug treatment. For this reason, findings of a particularly low HbA1c level should cause suspicion of unobserved past hypoglycaemic episodes.

8. Conclusion

Severe hypoglycaemia has an impact on the function of the brain, which is highly dependent on glucose. Experimental data and post-mortem studies demonstrate significant alterations in brain tissue following severe hypoglycaemia. In daily practice, these severe hypoglycaemic events can induce genuine encephalopathy, especially in children or elderly subjects. The cerebral consequences however that might result from mild hypoglycaemia are not known. This missing information is due to the lack of fine assessment of cognitive functions in the therapeutic trials and the strong interference of the diabetic disease itself. The rate of severe hypoglycaemia has declined due to the improvement of techniques and therapeutic strategies, and the improvement of insulin and materials. Specific studies however on the relationships between diabetic hypoglycaemia and cognitive disorders must be conducted due to the growing prevalence of diabetes and dementia. Indeed, the risk of hypoglycaemia must not be an insurmountable obstacle to the optimisation of blood glucose control. The follow-up of the elderly diabetic cohort (GERODIAB study) implemented by the SFD-SFGG Diabetic-Geriatric francophone intergroup should be able to provide some responses to certain questions [8].

9. Conflict of interest

The authors have not declared any conflicts of interest

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Hyperglycaemia, microangiopathy, diabetes and dementia risk

I. Bourdel-Marchasson [a, b*], A. Mouries [a], C. Helmer [c]

[a] *CHU of Bordeaux, Department of Gerontology, Bordeaux, France UMR 5536 CNRS/University Victor Segalen Bordeaux 2, Bordeaux, France*
[b] *UMR 5536 CNRS/University Victor Segalen Bordeaux 2, Bordeaux, France*
[c] *INSERM, U987, F-33076 Bordeaux, France; Université Victor Segalen Bordeaux 2, F-33076 Bordeaux, France*

Abstract

Brain microangiopathy increases in frequency and severity with older age, with the presence of hypertension and to a lesser extent with diabetes. Magnetic resonance imaging is used to provide anatomical descriptions, but at this time only clinical examination and neuropsychological testing can assess white matter functioning. Clinical correlates of microangiopathy appear as subcortical cognitive alterations, but data are controversial about dementia risk. Brain microangiopathy seems to be however a complication of chronic hyperglycaemia, probably due to similar mechanisms occurring in retinopathy and other microvascular complications. To date, many questions have been raised: How can brain microangiopathy progression be monitored? Is there a reversible stage of brain microangiopathy? Which preventive actions should be implemented in aging patients with diabetes? Finally, what type of care should be provided for people with diabetes and mild cognitive impairment or overt dementia to slow down cognitive worsening?

Keywords: Dementia; Cerebral microangiopathy; Hypertension; Hyperglycaemia; Magnetic resonance imaging; Review

Résumé

Hyperglycémie microangiopathie cérébrale, diabète et démence

La micro-angiopathie cérébrale augmente en fréquence et en sévérité avec l'âge, l'hypertension artérielle et plus discrètement avec le diabète. L'imagerie de résonnance magnétique fournit une description anatomique, mais pour l'heure, seule la clinique et la psychométrie permet d'évaluer le fonctionnement de la substance blanche. Les manifestations cliniques de la micro-angiopathie apparaissent comme des altérations sous corticales, mais les données disponibles sont contradictoires pour le risque de démence. Cependant, la micro-angiopathie cérébrale semble secondaire à l'hyperglycémie, probablement selon des mécanismes similaires à ceux de la rétinopathie et des autres complications microvasculaires. À ce jour, de nombreuses questions attendent une réponse : Comment suivre cliniquement la progression de la micro-angiopathie cérébrale ? Existe-t-il un stade réversible de la micro-angiopathie ? Quelles mesures préventives proposer au patient diabétique âgé ? Enfin, quel traitement proposer aux personnes atteintes de diabète et qui présentent un déficit cognitif léger ou une démence pour ralentir le déclin cognitif ?

Mots clés : Démence ; Microangiopathie cérébrale ; Imagerie de résonance magnétique ; Hypertension ; Hyperglycémie chronique ; Revue

1. Introduction

Many efforts have been made to describe the links between diabetes and dementia due to the importance of any means for decreasing the incidence of dementia, and thus targets for prevention [1]. There is an increasing body of evidence supporting the role of diabetes in vascular dementia (VD) or mixed dementia (MD), rather than in Alzheimer's disease (AD).

Diabetes is a major cause of microangiopathy, related to hyperglycaemia and hypertension, and leads to renal insufficiency, retinal damage and polyneuropathy. The brain is thus likely a site for microangiopathy, whether or not in association with large-vessel brain pathology. However, the brain is not an easy organ to access, and few non-invasive tools are able to provide an accurate description of its anatomy and functioning. For these purposes, magnetic resonance imaging (MRI) and neuropsychological testing were used, sometimes

* Corresponding author.
E-mail address: isabelle.bourdel-marchasson@chu-bordeaux.fr (I. Bourdel-Marchasson).

supplemented by neuropathological autopsy studies. These MRI and neuropsychological investigations are however difficult to conduct due to high costs and scarcity of magnetic resonance imaging equipment.

We aim here to review the consequences of brain microangiopathy on cognitive functioning and dementia risk, as well as the role of diabetes and hyperglycaemia with respect to other risk factors.

2. Dementia and diabetes

We previously reviewed the role of insulin resistance and diabetes as risk factors for dementia, AD, VD and dementia of any type [1]. The complexity of the dementia risk factor spectrum makes it difficult to isolate the role of diabetes to the exclusion of other vascular risk factors, mainly the ApoE-ε-4 allele. An increased risk of any dementia type and not only AD or VD seems possible in people with diabetes, but the means of causality remain clinically uncertain [2].

The predominant cognitive deficits in vascular cognitive impairment are subcortical, i.e., frontal and executive functioning alterations [3]. In vascular dementia, diabetes is equally represented in the risk factor profile of small and large vessel diseases [4]. After a stroke, dementia risk increases [5-7] and recovery of cognitive function is less frequent [8] in patients with diabetes.

The effects of diabetes on accelerated cognitive decline may decrease with older age, as it had no effect on cognition in subjects older than 85 years in the Leiden 85-plus study [9]. Another longitudinal community-based study in people older than 75 years showed an increased risk for vascular dementia in subjects with diabetes but no effect on Alzheimer's disease risk [10]. However, the authors found an increased risk of Alzheimer's disease in subjects with undiagnosed diabetes and with high blood glucose values; they concluded that there was a hyperglycaemic effect independent of vascular complications, which was involved in the neurodegenerative process. During a 5-6 year follow-up, a population-based study confirmed an increased risk for developing dementia only in subjects with undiagnosed diabetes and with an $HbA_{1c} > 7\%$ [11].

3. MRI findings in relation to cognition

White matter lesions, also known as leukoariosisiosis or brain microangiopathy, were first described from brain imaging with some uncertainty about their clinical expression. Extrapyramidal symptoms [12-14], gait disturbance [15,16], falls [13,16] and bladder incontinence [16] are reputed to be clinical features of brain leukoariosis. However, these latter studies had some difficulties showing correlations between these symptoms and MRI signs of leukoaraiosis. Microangiopathy in MRI appeared as white matter hyperintensities (WMH) in FLAIR or T2 sequence; lacunae, which are ischemic lesions, appeared as hypointensities in FLAIR sequence and hyperintensities in T2; microbleeds were only seen with gradient-echo T2* MRI due to the paramagnetic effect of hemosiderin.

Subjects with WMH may be either non-symptomatic, have cognitive impairment or be severely demented. It is agreed that the prevalence and severity of lesions increases with age [17]. Hypertension in older people has been shown to be a major risk factor for brain microangiopathy and brain atrophy, which progress independently over time [18]. A cross-sectional study showed that there were significant relationships between WMH and blood pressure, hypertension, and plasma cholesterol in subjects aged 65 to 74 years. After this age, the relationship weakened [19]. In this study, WMH tended to be associated with lower scores on cognitive function tests and were significantly associated with subjective mental decline [19]. Indeed, the influence of older age seems very important. Leukoaraiosis is very common in older subjects [14]. Correlations between the severity of cognitive impairment associated with aging, such as slowed psychomotor speed, alteration of episodic memory and executive dysfunctions with severity of frontal and temporal WMH, have been shown [20]. Another cross-sectional study found a relationship between WMH and cognitive deficits and an association with brain atrophy [21].

Hypertension is well-recognised as a major risk factor for stroke. In the SCOPE trial comparing hypertensive subjects with candesartan or placebo and normotensive subjects, MRI exams explored the rate of brain atrophy and the change in WMH over a 3-year period [18]. The WMH fraction correlated with baseline diastolic blood pressure, and changes were related to baseline MRI WMH, baseline systolic blood pressure and inter-exam diastolic blood pressure. The rate in brain atrophy was independent of WMH fraction or changes. Brain atrophy was related to baseline systolic blood pressure. The comparison between the 3 groups showed that non-hypertensive subjects had a lower rate of brain atrophy compared with subjects treated with candesartan, and that those receiving the drug had a lower rate than those receiving placebo [18].

There is an ongoing debate about the respective role of periventricular leukoaraiosis (PVLA) compared to deep white matter leukoaraiosis (DWMLA) in cognitive impairment. In a small sample of cognitively intact elderly subjects, worsening of non-dementia cognitive impairments were shown to be related to PVLA worsening rather than to baseline PVLA severity [22]. Furthermore, in the Rotterdam study, the 5-year dementia risk increased with the higher severity of PVLA, while the relationship with baseline DWMLA was less significant [23]. PVLA seems to be correlated with age, while DWMLA does not [3].

In a large autopsy study, the presence of subcortical infarcts in Alzheimer's disease incrementally increased the risk of dementia [24]. However, the brains of demented patients from the Baltimore Longitudinal Aging Study did not exhibit more frequent subcortical infarcts (lacunae) in the autopsy study [3]. On the other side, lacunae and cerebral atrophy were both found to be predictors of mild cognitive impairment in the longitudinal Cardiovascular Health Study [25].

Microbleeds are mainly associated with small vessel lipohyalinose degeneration related to hypertension but are also present in cerebral amyloid angiopathy. Cross-sectional studies, although not all, have shown associations of microbleeds with cognitive alterations [26]. Microbleeds occurred more frequently in Alzheimer's patients compared to controls; they were predominantly found in the occipital region, were associated with severity of leukoaraiosis, and were not associated with a history of hypertension, suggesting that they might represent amyloid vasculopathy [27].

4. Association of brain vascular pathology with diabetes

In patients with peripheral arterial pathology, type 2 diabetes was associated with more global and subcortical brain atrophy and more lacunar infarcts [28]. In this cross-sectional study in patients with diabetes, high glucose levels and diabetes duration were associated with global brain atrophy.

In the LADIS study, which included non-disabled subjects, 14.4% of them with diabetes, significant mild cognitive deficits were seen only in those with combined medial temporal lobe atrophy and severe WMH on MRI exams [29]. Severity of age-related microangiopathy was correlated with severity of cognitive alterations (general functioning, memory, verbal fluency, executive functions and attention). Patients with diabetes performed worse in these neuropsychological tests independent of age, education and previous stroke [30]. During the 3-year follow-up for 639 patients, white matter changes and diabetes, both together and independently, predicted cognitive decline (including dementia). Diabetes however did not specifically predict VD or AD in this study [31].

The cohort of men in the Honolulu-Asia Aging Study underwent MRI investigation at a single visit. The proportion of men with diabetes in the cohort was high (38%), and more than one in two were undiagnosed. Men with diabetes had a higher rate of lacunae and hippocampal atrophy. Furthermore, those with longer diabetes duration (> 20 years compared to < 5 years) had more lacunae, hippocampal atrophy, infarcts, and WMHs [32]. An increased frequency of lacunae has also been shown to be associated with diabetes elsewhere but in an unadjusted model with a small size population [33]. Another study found a trend for increased frequency of white matter disease with diabetes, but in multivariate analysis the association disappeared and only age, stroke history and the presence of the ApoE-ε-4 allele carriage were found to be predictors [34].

Other cross-sectional studies have shown that type 2 diabetes was associated with hippocampal atrophy specifically [35, 36] or with cortical atrophy [37] but not with white matter lesions.

Neuropathological studies however, which are scarce, had difficulty finding systematic differences in the brains of older patients with type 2 diabetes and others. In non-demented subjects, Nelson et al. showed increased cerebrovascular disease in patients with a history of diabetes, involving both small and large vessels, and less Alzheimer-type pathology compared to controls [38]. A Finnish prospective study in the very elderly found an increased risk of dementia with diabetes, both VD and AD, in fully adjusted analysis including the APO E phenotype [39]. However, the brain of the individuals with diabetes showed more vascular pathology and less Alzheimer's [39]. Insulin resistance was shown to be negatively associated with right hippocampal volume and with global cognitive functioning in a group of middle-aged women without diabetes [40]. In a longitudinal population-based study, insulin resistance measured in the 5 previous years before death was not associated with significant increases in Alzheimer's neuropathology in the absence of the ApoE-ε-4 phenotype, but was enhanced in the opposite case [41].

5. Diabetes and the blood brain barrier

One other consequence of brain microangiopathy could be a less effective blood brain barrier (BBB). The CSF albumin/serum albumin ratio increases with the severity of BBB dysfunction. It has been consistently shown that this ratio increases with age in the cognitively intact elderly but also in demented patients. However there were no differences between VD and AD shown in this ratio, nor any relationship with dementia severity [42]. It is likely that these changes were due to associated microangiopathy. Indeed, it has recently been found in a MRI study that older age, hypertension, diabetes and aspirin use were related to increased BBB permeability [43]. In a streptozotocin-induced diabetes rat model, an increase of BBB permeability has been shown via a loss of tight junction proteins dependent on increased matrix metalloproteinase activity. In this animal model the increased BBB permeability in diabetes did not result from hyperglycaemia alone, and the intervention of other metabolic abnormalities (insulin defect, dyslipidaemia) seemed likely [44]. In a similar model, the time consequences of diabetes on BBB were not equal in all brain regions. The midbrain was the first place exhibiting this functional damage, followed by the hippocampus, cortex and basal ganglia [45]. The consequences of permeability aberration of small brain vessels on brain functions remain to be explored.

6. Brain microangiopathy and diabetes-related complications

The severity of WMH was associated with arterial stiffness, arterial thickness and markers of endothelial dysfunction independent of common cardiovascular risk factors in a sample of elderly subjects with memory complaints [46]. Indeed, an MRI study in the general population showed a correlation between WMH or lacunae presence and retinal arterial narrowing and sclerosis [47]. Several reports have described an association between hypertensive retinopathy

and lacunae. In hypertensive subjects free of stroke, age and severity of retinopathy were independent risk factors for lacunae [48].

A meta-analysis reported lower cognitive abilities in patients with type 1 diabetes compared to a control group and an association between lower cognitive functions and the presence of retinopathy, although without relationships with blood glucose or blood pressure control [49].

Advanced retinopathy was used as a marker of microvascular disease and chronic hyperglycaemia in a case-control study for type 1 diabetes. Here MRI was not suitable for the study of white matter changes but showed a relationship between the severity of retinopathy and cortical atrophy [50]. However, in another group of patients with type 1 diabetes younger than 40 years old, no relationship was found between the presence of retinopathy or the quality of the blood glucose control with WMH severity [51]. In subjects with type 2 diabetes (mean age 65 years), multivariate analysis showed that older age increased the risk of any brain MRI changes, and in particular, cortical atrophy increased with the presence of retinopathy and cortical infarcts but decreased with the use of statins. DWMLA was more frequent in subjects with higher insulin levels, and PVLA was more frequent with the presence of brain infarcts and less so with the use of statins [52]. The HbA1c value and the measured blood pressure were not related to any of the MRI or cognitive alterations. However, the proportion of subjects with uncontrolled glycaemia or blood pressure was very low in this group. Gold SM et al. found a specific relationship between HbA1c values and hippocampal atrophy in a group of younger subjects with diabetes but no relationship with alterations of cognitive performance [35].

7. The hyperglycaemia hypothesis

Hyperglycaemia has been found to be a risk factor for cognitive decline. Mild cognitive impairment risk increased after 4 years in subjects with HbA1c > 7% in a large female cohort in the general population [53]. Both low and high fasting blood glucose concentrations in middle-aged men with diabetes were associated with lower cognitive functioning in an observational study [54]. An improvement in working memory but not in other cognitive functions in non-demented subjects with diabetes (45-75 years old) was reported after 24 weeks of either rosiglitazone or gliburide and was correlated with better fasting blood glucose control [55]. A randomized controlled trial compared glibenclamide to repaglinide in older people with diabetes (mean age 75 years) for one-year cognitive decline. Executive functions and attention declined in the glibenclamide group but not in the repaglinide one; the difference was attributed to the higher reduction of post-prandial blood glucose [56]. Larger daily blood glucose fluctuations were related to lower levels of cognitive functions in older people with diabetes, independent of fasting and post-prandial blood glucose and HbA1c [57]. Better cognitive performances were consistently seen after taking a low glycaemic index food in elderly subjects with type 2 diabetes [58].

The mechanisms of hyperglycaemia toxicity have been extensively investigated in the pathogenesis of microvascular complications of diabetes [59]. Briefly, hyperglycaemia enhances four interrelated pathways including through increased polyol pathway flux, increased production of advanced glycation end-products, activation of protein kinase C, and increased flux through the hexosamine pathway in endothelial cells. This induces an alteration in blood flow, small and large vessel occlusion, angiogenesis and permeability abnormality due to increased VEGF production, inflammation due to increased NF-κB production, and increased ROS production due to increased level of quinone reduction. Increased production of ROS and NF-κB in endothelial cells also occurs with aging [60], and thus brain microangiopathy could be due to similar mechanisms in diabetes or senescence. The metabolic alterations related to hyperglycaemia seem enhanced in cases of glycaemic fluctuations rather than with constant elevated blood glucose levels. Indeed, transient peaks of hyperglycaemia were shown to induce activation of NF-κB production and epigenetic changes in the promoter of the NF-κB, themselves due to increased ROS production [61]. This could be the basis of what is called “hyperglycaemia memory”, resulting in persistent activation of inflammation even after normalization of blood glucose concentrations.

8. The patient with dementia and diabetes

In a cohort of patients with Alzheimer’s disease (REAL-FR) and with similar dementia severity at baseline, those with diabetes had slower cognitive decline than the others independent of other characteristics of the subjects [62]. The authors hypothesized that subjects with diabetes received drugs more often for vascular protection. However, it has been shown in a randomized controlled trial that an intervention for optimal vascular care compared to usual care did not modify the course of cognitive decline in patients with mixed dementia [63]. Assuming that the rate of cognitive decline in mixed dementia is slower than in Alzheimer’s disease [64], patients with diabetes in the REAL-FR cohort may have been more likely to present the course of mixed dementia. A 12-month longitudinal study in demented subjects with diabetes has shown that cognitive decline was slower among those with insulin therapy compared to those with only hypoglycaemic oral agents [65]. The authors suggested that increased levels of insulin could be beneficial. However, baseline data showed that patients on insulin were older, had longer diabetes duration and had higher levels of fasting glycaemia and lower fasting insulin blood levels than those with oral agents. It is also notable that the rate of complications and hypertension was also higher in patients with insulin. Thus, it seems unlikely that intensification of risk factor control for diabetes and other vascular conditions could modify the course of dementia in people with diabetes.

9. Insights from interventional studies

Indeed, most interventional studies have brought disappointing results. One of the secondary endpoints in the ADVANCE study was the prevention of a 3-point decrease in the Mini-Mental State Examination (MMSE), or lowering the rate of incident dementia in patients with type 2 diabetes. The interventions, either intensive blood glucose control using glycazide [66] or lowering blood pressure with an angiotensin converting inhibitor-diuretic combination [67], had no effect on cognition or incident dementia after a 5-year follow-up. The mean diabetes duration was 8 years before inclusion in the trial, and thus these patients may have suffered from the hyperglycaemia memory phenomenon.

Statins, such as pravastatin, may preserve endothelial function in the presence of hyperglycaemia in patients with diabetes and thus prevent the occurrence of microangiopathy due to decreased activation of NF-κB [68]. However, in the PROSPER (PROspective Study of Pravastatin in the Elderly at Risk) trial, WMH severity increased equally in both groups over time [69]. Furthermore, the long-term brain volume reduction was equivalent in both groups, as was the decline in cerebral blood flow [70].

10. Conclusion

There have been few investigations on brain microangiopathy related to diabetes, probably due to methodological and technical difficulties. Furthermore, its role in dementia risk is still not completely known. However, brain microangiopathy seems to be a diabetes-related complication. Currently, many questions have been raised, namely with regard to monitoring brain microangiopathy progression; whether there is a reversible stage of brain microangiopathy; the preventive actions that should be implemented in aging patients with diabetes; and finally, the best care for people with diabetes and mild cognitive impairment or overt dementia.

11. Conflicts of interest

None of the authors have any conflict of interest concerning this paper

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