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Cognitive impairment in diabetes and poor glucose utilization in the intracellular neural milieu

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ABSTRACT

The main characteristic of diabetes is hyperglycemia. Depending on whether diabetes is type-1 or type-2, it is characterized by deficiencies in insulin secretion, insulin receptor sensitivity, hexokinase activity, and glucose transport. Current drug treatments are able to lower circulating glucose but do not address the problem of glucose utilization in the intracellular milieu, the consequence of which is tissue damage. In the long-term, such changes can produce structural damage in many cortical and subcortical brain areas that are related to cognitive function. Many epidemiological reports consider anxiety and depression as clinical entities that accompany diabetes. However, anxiety and depression in diabetes appear to occur in parallel and do not follow a causal relationship. From a behavioral perspective, anxiety may be considered adaptive, whereas depression can be considered reactive in response to changes in lifestyle and ailments that are caused by the disease. Therefore, the main alteration in diabetes seems to be cognitive function. We hypothesized that in type-2 diabetes, hypoglycemic medications do not restore the function of glucose in the intracellular compartment, which may have deleterious effects on neural tissue with behavioral consequences. In such a case, it is important to develop pharmacological interventions that directly restore plasma insulin levels, insulin receptor function, and hexokinase activity, thereby avoiding damage to neural tissue that is associated with cognitive deficits in diabetic patients, particularly patients with type-2 diabetes. The better management of such alterations in diabetes should be directed toward improving glucose utilization by neural tissue.

Introduction

Diabetes comprises two main clinical entities. Type-1 diabetes results from chronically low insulin secretion. Type-2 diabetes is a heterogeneous group of disorders that are characterized by varying degrees of insulin resistance, a decrease in insulin secretion, and an increase in glucose production. Diabetes is a complex syndrome that is associated with excess extracellular glucose and deficient intracellular glucose disposition. Three neurological and psychiatric entities are often observed in diabetes: anxiety, depression, and cognitive impairment [1–3]. A low level of anxiety may be a useful adaptive response [4] that helps the individual cope with ailments that are associated with diabetes. When the level of anxiety surpasses a certain threshold, it can be considered a disease that is frequently associated with the course of diabetes. Depression in diabetes negatively influences quality of life. Individuals who suffer from diabetes must cope with managing their disease, especially in the presence of complications and stress associated with their work life [5]. Although anxiety and depression might not be considered to be a direct consequence of diabetes *per se*, diabetes is associated with cognitive deficits and a higher risk of dementia [3] that is likely related to neural tissue damage.

The hypothesis

Type-1 and type-2 diabetes present substantial differences, ranging from pathophysiology to therapeutic management. Their similarities usually consist of clinical manifestations that commonly occur with different timing. In both cases, hyperglycemia causes endothelial and tissue damage. In type-1 diabetes, the restoration of plasma insulin levels can reduce some tissue

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damage. In type-2 diabetes, hypoglycemic medications do not restore the function of glucose in the intracellular compartment, which may have deleterious effects on neural tissue with behavioral consequences. From a behavioral perspective, cognitive alterations in diabetes may result from neural tissue damage because of poor glucose utilization in the intracellular milieu. Therefore, it is important to develop pharmacological interventions that control plasma hyperglycemia and correct disruptions of intracellular glucose utilization.

Supporting arguments

Course of diabetes and daily stress

Any chronic disease may constitute a strong stressor that disrupts homeostasis. Allostasis is an adaptive response and essential component of maintaining homeostasis. Allostasis allows the organism to effectively cope with challenges and survive. When allostatic systems are overstimulated or do not perform normally, allostatic load can occur [6]. In many cases, allostatic load can result in a disease state [7], with the participation of glucocorticoids (e.g., cortisol), and lead to mood disorders [8]. Cortisol in humans (corticosterone in other mammals) plays an essential role in maintaining physiological homeostasis through its receptors [9]. Cortisol is considered a marker of stress. Before a disease state is fully expressed, the body is subjected to strong and chronic stress in parallel with glucose intolerance and insulin resistance [10]. Allostatic load may cause a worsening of diabetes, and diabetes itself may represent an allostatic load, in which energy sources for intracellular function become inefficient with a consequent risk of cellular damage. In animal models of diabetes, daily restraint stress or daily cortisol administration causes the retraction and/or simplification of hippocampal apical dendrites of CA3 pyramidal neurons and the depletion of synaptic vesicles of mossy fibers that form excitatory synaptic contacts with proximal CA3 apical dendrites [11]. The ventral hippocampus and amygdala are involved in emotional control [12,13], and the presence of emotional changes can be expected during the course of diabetes.

Anxiety and diabetes

In type-2 diabetes, a tenuous relationship between anxiety and general functioning has been reported, independent of the presence of depression [14]. Anxiety has the potential to interfere with routine daily functioning and impact the management of diabetes. The presence of anxiety influences the development of diabetes. In fact, a recent diagnosis of almost any chronic disease can be assumed to produce some degree of anxiety.

Individuals who are older or drug users and suffer from hypertension and hyperlipidemia are at risk of developing anxiety during the course of diabetes [15]. Hypertension and hyperlipidemia are two of the three components of metabolic syndrome. The third component is diabetes, which may cause some confusion when looking for strict relationships. The use of questionnaires to screen for anxiety symptoms and semi-structured clinical interviews to diagnose anxiety disorders have failed to demonstrate an association between anxiety and glycemic control [16]. However, when diabetes is well established, higher state anxiety is associated with poor clinical control [17,18], which is corroborated by higher glycosylated A1c hemoglobin levels [18].

In animal models of oxidative stress, increases in blood pressure and insulin resistance, anxiety-like behavior, and neuronal damage in the amygdala and hippocampus have been reported [19]. Notably, in animal models of diabetes, the dose of an anxiolytic drug that is necessary to produce an anxiolytic-like effect is higher than the dose that is required in control animals [20]. Hyperglycemia may reduce the sensitivity of benzodiazepine receptors [21]. Animals with experimental diabetes exhibit a reduction of interneuronal dendritic arborization in the medial prefrontal cortex (mPFC) and lower expression of the enzyme that is responsible for the synthesis of the inhibitory neurotransmitter γ-aminobutyric acid [22], a primary target of anxiolytic drugs.

In summary, diabetes can result in anxiety. In the initial stages of the disease, a certain level of anxiety may be useful in an adaptive sense but may result in poor adherence to treatment in the long-term. Any conclusions that are drawn concerning a direct relationship between anxiety and diabetes are not necessarily definitive. A greater likelihood is that diabetes produces anxiety because of associated changes in an individual's expectations about their future quality of life, dietary limitations, and other lifestyle changes that are usually recommended as part of managing their disease.

Depression and diabetes

The frequent comorbidity between depression, anxiety, and type-1 diabetes can compromise diabetes management and glycemic control [23]. Studies of experimental diabetes have reported decreases in hippocampal neurogenesis and neuroplasticity, which may contribute to cognitive decline and depressive symptoms [24]. In these models, clear deficiencies are observed in neuroplasticity in the PFC, hippocampus, and amygdala [25], structures that are related to emotional memory processes [12,13].

In experimental animal models of diabetes, lower sensitivity to conventional antidepressant treatment is observed, and insulin can reverse some of the behavioral effects of hyperglycemia [26]. After 6 weeks of fluoxetine or venlafaxine treatment, pancreatic β-cell secretory function (homeostatic model assessment-β) significantly increased, suggesting that antidepressants might affect insulin secretion independently of the therapeutic effects on concurrent major depression [27]. Moreover, antidepressants that reduce signs of despair also favorably affect insulin receptor phosphorylation [28]. Insulin may produce anti-despair actions that are comparable to the antidepressant sertraline [29].

The effectiveness of medications that are used to treat depressed mood is unclear in patients with comorbid diabetes and depression [24]. Antidepressant-like effects that are mediated by serotonin 5-hydroxytryptamine-1A (5-HT_{1A}) receptors may be attenuated by diabetes [30]. Psychological interventions and antidepressant drug treatment, specifically treatment with selective serotonin reuptake inhibitors (SSRIs), were shown to exert a moderate beneficial effect on depression and the control of hyperglycemia after several weeks of treatment [31,32]. Such beneficial effects are seen only with SSRIs; noradrenergic and tricyclic antidepressants may cause the metabolic syndrome to deteriorate [33,34].

Anxiety and depression appear to play important and complex adaptive and reactive roles, respectively, in diabetes, but any relationship with the metabolic process is far from clear [35]. A bidirectional relationship has been reported between depressive symptoms and diabetes distress [5], particularly in middle-aged patients and not in patients who are >65 years old [36]. Depression and diabetes reciprocally influence each other [37].

Cognition and diabetes

Approximately two-thirds of patients who are admitted to educational hospitalization for type-2 diabetes can be categorized into a frontal lobe dysfunction group, delayed recall group, or mixed-type group [38]. Imaging studies have revealed various types of neurological damage that is caused by diabetes, depending on whether it is type-1 or type-2. Type-1 diabetes is characterized by thalamic damage. Type-2 diabetes is characterized by more