

Pathogenesis and research progress of diabetes and cognitive impairment

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Abstract

With the improvement of quality of life and the acceleration of aging process of population, the prevalence of diabetes in adults in china is increasing, and the group of patients with diabetes combined with cognitive dysfunction is expanding. At present, diabetes combined with cognitive impairment is gradually becoming a hot issue of worldwide concern. In this paper, the pathogenesis of diabetes combined with cognitive dysfunction is described from the following aspects: metabolic abnormalities, cerebrovascular disease, inflammatory mediators, neurotrophic factor deficiency, blood-cerebrospinal fluid barrier dysfunction, hypothalamic-pituitary-adrenal axis hyperfunction, and activation of renin-angiotensin system.

Keywords: Diabetes, Cognitive Impairment, Metabolic Disorders, Cerebrovascular Disease, Inflammatory Reaction.

Introduction

Diabetes Mellitus (DM) is one of the chronic diseases with the largest number of patients in China at present. DM is a group of metabolic diseases characterized by dysglycemia control for a variety of reasons, which are divided into type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM) and special type diabetes mellitus. DM is very harmful to human body. With the progression of the disease and the prolongation of the course of disease, there will appear a variety of acute and chronic complications, such as diabetic ketoacidosis, diabetic nephropathy, diabetic retinopathy, diabetic neuropathy and diabetic foot. These complications not only reduce the quality of life of patients, but also pose serious challenges to the health care system. According to the recent epidemiological data, the overall prevalence of DM in China has increased to 11.2%, and it continues to rise, with the proportion of T2DM accounting for more than 90% [1]. Various causes lead to damage to relevant areas of the brain, causing a decline in directional ability, memory, thinking, understanding and other aspects, known as cognitive dysfunction. According to the degree of damage, cognitive impairment can be divided into Mild cognitive impairment (MCI) and dementia. Since the 20th century, the prevalence of cognitive impairment has increased year by year, and dementia has become one of the ten leading causes of death in the world [2]. In recent years, cognitive impairment has become a hot topic and has been widely studied in the field of diabetic complications. In order

to further understand the related pathogenesis of diabetes and cognitive impairment, we elaborated on this issue in detail from the following aspects.

Metabolic Disorders

Hyperglycemia

Although most of the energy needed by the brain is provided by glucose, high blood glucose concentration will bring adverse effects or even serious harm to the brain. Long-term hyperglycemia decreases the sensitivity of various brain regions to insulin receptors, resulting in insulin resistance [3]. Central insulin resistance promotes the deposition of amyloid β -protein ($A\beta$) and the formation of neurofibrillary tangles (NFT) through various signal transduction pathways, which are the main pathological features of Alzheimer's disease (AD). At present, relevant medical studies have confirmed that chronic hyperglycemia can lead to brain functional and structural abnormalities [4], and this abnormality is progressive to a certain extent, suggesting that chronic hyperglycemia has a toxic effect on the brain. Glycated hemoglobin can not only reflect the blood glucose level of patients in the past two to three months, but also be used to understand whether the blood glucose control is stable in the near future. The research by Maan et al. showed that the increase of glycated hemoglobin could lead to the decline of cognitive function [5], which illustrated from the side that chronic hyperglycemia would damage cognitive function.

Hypoglycemia

Hypoglycemia is one of the possible adverse reactions of patients with diabetes after using insulin and hypoglycemic drugs. Hypoglycemia can cause a series of corresponding changes in the body, such as the secretion of more blood glucose hormones, and severe fluctuations in blood glucose. Cognitive impairment often occurs rapidly in a hypoglycemic state, and normalization of such impairment occurs 40 to 90 minutes after the body's blood glucose returns to its normal range. Frequent hypoglycemia during routine blood glucose monitoring without clinical symptoms of hypoglycemia often suggests that the patient may be in a stage of hypoglycaemic sensory hypofunction. A study in the United States showed that when the body's blood glucose was less than 2.2 mmol/L, it would cause the reduction of cerebral blood flow in relevant areas of the brain, thus reducing the patient's cognitive function [6]. At this time, the degree of blood flow reduction in different regions of the brain is different, and the cognitive function damage in this region is also different. In addition to the adverse developments described above, hypoglycemia can also lead to mood changes, depression and anxiety, and fear of recurrent hypoglycemia, which in turn can further affect blood glucose control and lead to blood glucose disorders. Multiple and long episodes of hypoglycemia cause continuous accumulation of cognitive impairment and eventually lead to the occurrence of cognitive impairment.

Abnormal Lipid Metabolism

Normal lipid metabolism helps maintain the structure and function of brain neurons, while most patients with diabetes suffer from lipid metabolism disorders, the most common of which are increased triglycerides, increased low-density lipoprotein and decreased high-density lipoprotein. Since the neurons in the brain are highly sensitive to fatty acids, the disorders of lipid metabolism can induce related neurodegenerative diseases such as AD. Studies have found that fatty acids can affect the energy metabolism balance of neurons, because they can promote the production of hypothalamic ceramide, resulting in the destroyed energy balance of the body and disrupted the endocrine system. The metabolic disorder will trigger a chain reaction of the body, including abnormalities in all aspects such as blood glucose and blood lipid, which to some extent accelerated the development of cognitive dysfunction in diabetes [7]. Other studies have shown that the increase in blood cholesterol concentration in the elderly is related to the cognitive decline in different fields, while lipid-lowering drugs (statins) and low-cholesterol diet have great individual differences in the reduction of cognitive function [8].

Hyperhomocysteinemia

Homocysteine(Hcy) was previously considered to be related to liver diseases more often. However, with the deepening of research on homocysteine, it has been found that obesity, cardiovascular events, and even cognitive decline have a certain relationship with Hcy [9]. A population survey based on magnetic resonance imaging showed that hyperhomocysteinemia was associated with atrophy of cerebral cortex and hippocampus [10], which is one of

the imaging features of AD. Researchers also found through the mouse test that Hcy aggravated the pathological process of AD. In the mouse model, Hcy accelerated the formation and deposition of A β . Another important point is that Hcy reacts to neurotoxicity through oxidative stress, which may interfere with neuronal proliferation and affect neuronal differentiation [11], which is also one of the possible causes of decreased cognitive ability.

Blood Insulin Disorder

The onset of diabetes is accompanied by insulin resistance and inadequate insulin secretion, which are manifestations of insulin disorders. Insulin plays an important role in regulating the body's blood glucose. In addition, it also has the function of regulating neurons in the brain, including synaptogenesis, synaptic remodeling and the regulation of neurotransmitter levels. Insulin receptors are also distributed in different regions of the central nervous system [12]. The regions with high insulin receptor levels include the olfactory bulb, the cerebral cortex, and the hypothalamus, but they are less abundant in the pituitary gland and cerebellum [13]. Therefore, functional insulin deficiency in the brain also belongs to one of abnormal insulin regulation. A previous study found that the obvious degeneration of nerve cells in the intensive insulin receptor area of the brain was related to the cognitive impairment of patients. From the perspective of insulin-degrading enzymes(IDE), abnormal insulin regulation may damage the clearance of A β in the brain and lead to plaque formation by regulating and competing with the expression of IDE, which not only destroys insulin but also reduces the degradation of A β [14]. The deposited amyloid β -protein accelerated the phosphorylation of Tau protein, causing a slowdown in brain energy metabolism and a decrease in acetylcholine synthesis, a process similar to that in AD, supporting the view that insulin dysregulation might accelerate cognitive impairment.

Advanced Glycation End Products

Advanced glycation end products (AGEs) is a compound formed by the reaction between lipids or nucleic acids and reducing sugars (such as glucose). In a hyperglycemic environment, tissues contain high levels of AGEs and AGE receptors(RAGE). Hyperglycemia is an important feature of diabetes. The hyperglycemic environment in the tissues of patients with diabetes directly promotes the production of plenty of AGEs. AGEs can promote the development of atherosclerosis. Studies have found that, in addition to causing vascular disease accidents, AGEs is also found in the amyloid plate and neurofibrillary tangles in Alzheimer's patients [15], suggesting that AGEs is involved in the pathogenesis of AD. Some studies have found that AGEs is involved in the chronic inflammatory response of the central system, and RAGE may provide certain clinical value for cognitive decline after the rain [16].

Neurotransmitter Disorders

Cognitive impairment is one of the typical characteristics of nervous system degeneration. Changes in the concentration and function of various neurotransmitters and their receptors, such as dopamine and glutamic acid, play an important role in the

occurrence and development of cognitive impairment. Dopamine is the main catecholamine in mammalian brain, which affects a variety of functions, including motor activity, cognitive, emotional and endocrine regulation. Glutamic acid is a major excitatory neurotransmitter involved in the regulation of the development, learning and memory of neuronal circuits [17]. In addition, it has been proved in animal experiments that the cholinergic system plays an important role in learning and memory [18].

Diabetic Cerebrovascular Disease

Microvascular and macrovascular lesions occur in most patients with diabetes at a later stage of disease progression because increased platelet aggregation in patients with diabetes increases plasma viscosity, resulting in decreased cerebral blood flow and slower flow rate. In addition, microvessels in the brain will also be involved. Once cerebral ischemia occurs, the damage of neurons in the brain will be very obvious. For example, some areas related to learning and memory function appear ischemic condition, cognitive dysfunction will also appear. Previous studies have found that cerebral ischemia can lead to different degrees of neuronal apoptosis and even brain tissue necrosis due to insufficient oxygen and energy supply to various brain tissues, and the degree of cognitive dysfunction of patients is positively correlated with the degree and duration of ischemia [19]. The decrease of cerebral blood flow in DM patients can damage brain function, thus reducing the brain's ability to recognize, process and integrate information, resulting in the body not being able to identify the external environment and make the corresponding treatment. In addition, elevated blood glucose also increases nitric oxide (NO) levels in the body. Animal experiments showed that the cognitive function of rats with neuronal nitric oxide synthase knockout was significantly decreased [20], suggesting that NO played a positive role in the retention of cognitive function.

Inflammatory Reaction

Diabetic patients are often accompanied by chronic inflammation [21], and chronic neuroinflammation is also an important cause of cognitive impairment. Inflammatory indicators such as tumor necrosis factor- α (TNF- α), Interleukin (IL) and C-reactive protein (CRP) have been found to be related to the decline of cognitive function. Studies have shown that TNF- α is involved in the regulation of central insulin resistance and blood glucose in the high glucose state. Long-term small-dose application of TNF- α inhibitors has the potential for early prevention of AD [22]. CRP not only causes endothelial dysfunction, but also its pro-inflammatory response may cause toxic effects on central nervous cells, thus increasing the risk of cognitive impairment in patients [23]. In addition to the formation of beta-amyloid plaques and NFT, the brain of AD patients also shows a persistent chronic low-grade inflammatory response. The formation of such neuroinflammation is due to the activation of microglia, which then secrete many inflammatory cytokines similar to IL-6, and finally cause neuronal degeneration [24].

Neurotrophic Factor Deficiency

Brain-derived neurotrophic factors (BDNF) are members of the neurotrophic family of nerve growth factors. Studies have shown that BDNF plays an important role in the regulation of hippocampal memory-related neural plasticity. T2DM is associated with damages in many cognitive functions, which may be the decrease of BDNF in T2DM patients, leading to cognitive decline, especially in the aspect of memory delay [25]. It can be deduced that BDNF not only has the function of nourishing nerves and accelerating the growth of nerve cells, but also directly affects cognitive function. The mechanism of BDNF affecting cognitive function may be related to the hippocampus. BDNF can improve cognitive function by increasing the hippocampal synaptic density [26].

Blood Brain Barrier Dysfunction

Various biomolecules enter and exit the central nervous system through the blood brain barrier (BBB). Once the function there is impaired, immune cells and immune mediators will move into the brain to produce a series of inflammatory changes and directly participate in neurodegeneration, leading to AD or vascular dementia [27]. Microvascular injury caused by DM will lead to a variety of cardiovascular and cerebrovascular events, and BBB plays an important role in the pathological process of DM patients with AD. Some scholars have found that the central insulin concentration is decreased in AD patients or white matter high signal patients, which may be directly related to the changes of BBB function [28].

Hypothalamic Pituitary Adrenal Axis Hyperfunction

Hypothalamic pituitary adrenal (HPA) axis hyperfunction may independently or synergistically destroy neuronal homeostasis and cause diabetes-related cognitive decline [29]. There has also been a previous view that HPA axis disorders are associated with hippocampal atrophy and increased risk of MCI and AD. High plasma cortisol may affect the overall cognitive, situational memory and executive function decline, which may be explained by cortisol through promoting oxidative stress response in brain tissue caused by oxidative damage in the hippocampus, leading to neuronal apoptosis. In addition, increased glucocorticoid concentration will increase the toxicity of A β and phosphorylation of Tau protein, which will also lead to the decline of cognitive function [30].

Renin Angiotensin System Activation

The decreased islet function in DM patients may be related to the activation of the renin angiotensin system (RAS), and the activation of islet RAS may drive the synthesis of reactive oxygen species, leading to oxidative stress-induced β -cell dysfunction and apoptosis [31]. Recent studies have shown that there is also a RAS system in the brain tissue, which may be related to cognitive functions such as neural plasticity and learning and memory, among which angiotensin II (Ang II) plays a major role. AngII can cause or aggravate insulin resistance in the body, including central insulin resistance; At the same time, as a pro-inflammatory factor,

AngII can increase the expression of various inflammatory factors in the nervous system, promote the differentiation and aggregation of other inflammatory cells, aggravate the neuroinflammation in the brain, and thus accelerate the process of cognitive impairment in DM patients [32].

Discussion

DM has an increasingly prominent impact on cognitive function. However, the pathogenesis of cognitive impairment in DM patients has not been fully clarified. The main diagnostic means is neuropsychological evaluation, and the sensitivity and specificity of diagnosis still need to be improved. In addition, patients and their families themselves easily ignore the relationship between the two diseases, resulting in delay in diagnosis and treatment as well as lack of effective treatment. Early diagnosis and targeted treatment can be achieved only when the pathogenesis is clarified, and the social burden as well as the psychological and economic burden of patients and their families can be reduced. This has become an important task in endocrine field.

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