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Advances in the Relationship between B-Amyloid Neurotoxicity and Blood-Brain Barrier Dysfunction in Diabetic Encephalopathy

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Abstract: DE is one of them important co-morbidities of DM, which is a disease with cognitive dysfunction as the main manifestation based on DM, and the prevention of DE has become an urgent public health and social problem in China and worldwide. This series of pathological changes of Aβ becomes the dominant link in the pathogenesis of DE. This series of pathological changes in Aβ becomes the dominant link in the pathogenesis of DE. The abnormal aggregation of Aβ depends on the normal function of BBB, and BBB dysfunction will exacerbate the deposition of Aβ. Therefore, understanding the relationship between abnormal Aβ deposition and BBB is crucial for us to understand the pathogenesis of DE and to formulate treatment plans. A brief review of the relationship between the two is presented.

1. Introduction

Diabetic encephalopathy (DE) is one of the serious chronic complications of diabetes mellitus (DM), which is a structural change and dysfunction of the central nervous system triggered by long-term chronic DM, leading to neurophysiological changes in the brain and cognitive dysfunction, with acquired cognitive dysfunction as the The main clinical manifestations are acquired cognitive dysfunction. In recent years, with the sudden increase in the incidence of diabetes and the prolonged survival of diabetic patients, the risk of complications of diabetic encephalopathy has also increased. Modern molecular biology has shown that the main pathological feature of diabetic encephalopathy is the deposition of large amounts of β-amyloid (amybid β-protein, Aβ) in the brain. Normal Aβ trans-BBB clearance function is a factor in the occurrence and development of DE. The neurological damage caused by the abnormal aggregation of Aβ can directly harm the normal function and structural integrity of the blood brainbarrier (BBB), causes abnormal function of BBB. BBB is a critical link in protecting the dynamic equilibrium relationship between Aβ production and clearance, and BBB dysfunction exacerbates Aβ deposition. Based on a review of recent literature, this paper briefly reviews the characteristics of Aβ deposition and normal function of the BBB in the pathogenesis of DE and the relationship between them.

2. The Current Situation of DE

DM is a series of metabolic disorders such as protein, fat, water and electrolytes caused by absolute or relative insufficiency of insulin secretion and abnormal insulin sensitivity of related target tissue cells, clinically characterized by abnormally high blood glucose levels in the body[1]. Diabetes can cause multi-system damage, dysfunction and failure in the body. A close association between DM and cognitive dysfunction was identified as early as the 1920s. Diabetes is an important cause of functional impairment of the central nervous system of the brain, and a growing body of evidence confirms a strong correlation between diabetes and cognitive dysfunction. A growing body of evidence points to an increasing proportion of patients with cognitive dysfunction caused by abnormal blood glucose, as opposed to those with normal blood glucose[2]. Ott A[3] in his study, used the Mini-Mental State Examination and the Geriatric Mental State Schedule a two-year survey of more than 6,000 patients aged 55 and older, the findings showed that the hazards of cognitive dysfunction was doubled in diabetic patients compared to non-diabetic patients. Several studies in recent years have shown[6] that 60-70% of diabetic patients have varying degrees of cognitive dysfunction and that this rate increases to varying degrees as people's standard of living and lifestyles change, making it a serious chronic complication of diabetes, which is why some scholars have suggested that diabetic encephalopathy be referred to as type 3 diabetes. With the increasing number of patients with DM, the incidence of DE is growing rapidly, and,it is critical to understand the pathology of diabetic encephalopathy and the underlying mechanisms of its disease progression.

The pathogenesis of diabetic encephalopathy is complex and no unified conclusion has been reached on its pathogenesis. An increasing number of scholars have tried to understand whether there is some association between DM and cognitive dysfunction from various perspectives [4], mainly including cerebral microvascular alterations, functional and structural abnormalities of BBB, oxidative stress, non-enzymatic protein glycosylation, altered calcium ion steady state, brain cell aging and insulin side effects, causes neurotoxic effects in the brain resulting in functional abnormalities, eventual development of cognitive dysfunction. Modern molecular biology shows that massive deposition of Aβ and blood-brain barrier dysfunction are the main reasons for the formation of diabetic encephalopathy.

Although the pathogenesis of the disease has been understood to a certain extent, the cause and pathogenesis of the disease are very complex, and so far there is still no recognized pathogenesis theory and effective treatment means.

3. Expression of Aβ

3.1 Expression of Aβ in DM State

Studies now suggest that Aβ is the main pathological protein of DE. The rate of intracranial clearance of Aβ across the BBB is one of the important factors concerning the occurrence and development of DE.

Yoneda [5] found that large abnormal deposits of Aβ in the brains of DM patients. Additionally, Takeda [6] confirmed that diabetes accelerates the progression of cognitive dysfunction and analyzed its cause to be due to excessive deposition of Aβ; in another study[7], after injecting Aβ into diabetic mice, the mice showed significant spatial memory learning deficits, confirming that Aβ deposition is the main cause of the formation of cognitive dysfunction in the diabetic state.

3.2 Aβ Production and Clearance

Aβ in the brain is a peptide produced by the cleavage of amyloid precursor protein (APP) by an associated receptor enzyme[8]. Gireud [9] found that the most common Aβ isoforms in the elderly population are $A\beta_{1-40}$ and $A\beta_{1-42}$, of which $A\beta_{1-40}$ has low toxicity and solubility and is widely present in the normal brain, and $A\beta_{1-42}$ is often present in the brains of patients with cognitive impairment[10], is more easily deposited than $A\beta_{1-40}$, and has more toxic effects. Aβ deposition has a strong toxic effect on synapses by blocking proteasome function, altering intracellular calcium levels, and promoting inflammation and neurotoxic effects. Several studies have found that $A\beta_{1-40}$ is usually associated with vascular deposition, while $A\beta_{1-42}$ is mostly observed in parenchymal plaques in patients with diabetic encephalopathy.

In the normal human brain, intracranial Aβ levels are in dynamic and stable variation, but when the neurological function of the brain is impaired, the body's ability to clear Aβ decreases, and the rate of Aβ production is higher than its clearance rate, and the equilibrium is disrupted, resulting in a large accumulation of Aβ in the cerebrospinal fluid, blood and interstitial fluid, synaptic dysfunction, synapse loss, and inflammatory responses. A growing number of studies have confirmed that normal intracranial Aβ production and metabolism is a key component in keeping the nervous system free from damage; an imbalance in the dynamic balance of Aβ is likely to lead to abnormal deposition of Aβ, which in turn leads to neurotoxic effects and cognitive impairment. Abnormal deposition of Aβ can affect the normal structure and function of the BBB. Moreover, the BBB is essential for maintaining normal Aβ metabolism, and BBB dysfunction can exacerbate Aβ deposition. Several studies have confirmed[11] that for DE formed due to abnormal Aβ deposition, abnormal Aβ clearance becomes a more important link than abnormal Aβ production, and that in general the toxic aggregation of Aβ is mainly due to its slowed metabolism rather than to increased production[1] . Furthermore, Mawuenyega et al[12] compared patients suffering from cognitive dysfunction with age-matched controls and showed a 25% to 30% decrease in total Aβ clearance in the brains of cognitively impaired patients. However, the production of Aβ is normal, implying that abnormal metabolism of Aβ may be an important link leading to DE. However, regardless of whether Aβ deposition is the result of its excess production or reduced clearance, it is certain that neurotoxicity due to pathological Aβ deposition is a key component of the mechanism of DE formation. Reduction of neurotoxic effects of Aβ in the brain is currently the main therapeutic strategy for DE, whether targeting Aβ production or clearance[13].

4. Aβ Deposition Interacts with BBB Dysfunction

The BBB is the protective structure in the intracranial capillaries that prevents certain substances (mostly harmful) from entering the brain tissue from the blood. As research continues, it is confirmed that DM leads to functional and structural abnormalities in the BBB, abnormal microcirculatory function in the brain, abnormal neurological tissue function, which in turn leads to the development of DE. Therefore, modulation of BBB function may become a new way and new modality for the treatment of DE.

The pathways of Aβ transport and clearance in the body include the central and peripheral pathways. The most important of these is the peripheral pathway, which refers to the transfer of Aβ to the peripheral circulation via the intracranial BBB clearance mechanism[15]. As related research continues, there is increasing evidence that disruption of the function and structure of the BBB leads to a decrease in the rate of Aβ clearance, allowing for a rapid increase in the prevalence of DM-related cognitive dysfunction [15].

During the development of DE, The neurotoxic effects of Aβ and the structural-functional damage of BBB, both of which together accelerate the process of intracranial nervous system injury.

Structural and functional abnormalities of the BBB lead to a range of pathological reactions, which in turn enhances brain tissue β-secretase1 and γ-secretase1 activities, and finally promotes Aβ overproduction, deposition, and neurotoxic effects. Brain and blood-brain barrier dysfunction may act as a feedback loop leading to cognitive dysfunction and the onset of dementia.

Ridler et al[16] experimentally demonstrated that functional and structural impairment of BBB can directly lead to toxic deposition of Aβ by the specific mechanism of promoting Aβ production and simultaneously inhibiting the rate of Aβ clearance across the BBB. Because Aβ is produced by β-secretase 1 and γ-secretase 1 cleavage. In addition, Montagne et al[17] confirmed by their study that Aβ input impairs the integrity and permeability of the BBB, leading to BBB dysfunction. Further studies [18] showed that excessive Aβ production and deposition exacerbates the extent of BBB impairment, which plays an important link in the pathogenesis of DE.

5. Related Receptors on BBB and Metabolism of Aβ

The normal structure and function of the BBB is a key process in maintaining a stable production and clearance of Aβ in the brain, which is generally in a dynamic equilibrium in the cranium. there are numerous mechanisms by which BBB dysfunction leads to toxic deposition of Aβ triggering DE, the most important of which is alteration of BBB receptors. Numerous receptors at the BBB act together to regulate Aβ transport across the BBB. Affected by DE pathology, the number and distribution of these receptors are altered to varying degrees, which in turn affects Aβ transport across the BBB, leading to its massive deposition.

Various Aβ transporter receptor proteins located on the BBB regulate the inflow and outflow of Aβ. The expression of these transporter receptor proteins is altered during the pathogenesis of diabetic encephalopathy. There is growing evidence that low density lipoprotein receptor-related protein-1 (LRP-1) has a positive effect on Aβ transport and may contribute to Aβ clearance from the brain. A study in which receptor proteins on the BBB of diabetic rats with cognitive deficits were examined showed that decreased expression levels of LRP-1 and increased expression of late glycosylation end products caused a lack of energy supply in the brain, leads to toxic deposition of Aβ in the brain, which in turn leads to cognitive decline.

LRP-1 is a receptor on the surface of cell membranes involved in various pathophysiological processes, is highly expressed in the cerebral nervous system, binds Aβ specifically, and has reduced protein levels in the brain of patients with cognitive impairment with age [19]. It has also been shown that reduced levels of LRP-1 protein expression lead to a decrease in the rate of Aβ clearance in the brain, which ultimately leads to Aβ aggregation. And $Aβ_{1-42}$ is central to the formation of Aβ deposition mechanism, which corroborates from another perspective that LRP-1 has a specific role for Aβ transport. Osgood[20] found that Aβ can be exported from the brain through the blood-brain barrier via LRP-1 as a carrier and found that LRP-1 in brain microvessels of patients with diabetic cognitive impairment levels were downregulated. Later experiments by Gali [19] confirmed this finding and proposed the neurovascular hypothesis of diabetic cognitive dysfunction. This hypothesis suggests that decreased levels of LRP-1 expression lead to impaired Aβ efflux, blocking its passage through the BBB leads to abnormal deposition of Aβ, which produces neurotoxic effects and ultimately promotes the progression of DE. LRP-1 expression decreases with age [21] and in patients with diabetic cognitive dysfunction, manifesting itself throughout the brain and in brain capillaries. Several studies have found [22] that reducing LRP-1 expression leads to abnormal toxic aggregation of Aβ, which in turn improves the cognitive function of animals, suggesting on the other hand that LRP-1 is closely involved in the translocation clearance of Aβ.

The protein tyrosine kinase 2 beta (PTK2B) gene may be a significant gene for cognitive

dysfunction in late-onset diabetes [22]. The PTK2B gene encodes the PTK2B protein, a non-receptor tyrosine protein kinase that is directly or indirectly related to central nervous system messaging[23]. Studies have shown that PTK2B protein may reduce the efflux of $A\beta_{1-42}$ from brain tissue to the bloodstream by downregulating LRP-1, which leads to the aggregation of $A\beta_{1-42}$ in brain tissue and consequently its behavioral function.

Several studies have demonstrated that Pyk2, the expression product of the PTK2B gene, plays an important role together with LRP-1 in the development of certain cardiovascular and cerebrovascular activities[24]. It has also been shown that PTK2B interacts with LRP-1 in the development of Alzheimer's disease (AD)[25] and that stimulation by factors such as stress or aging can activate PTK2B, a susceptibility gene for cognitive dysfunction in diabetes, to increase the level of its expression product PTK2B [26]. decreases the level of LRP-1 protein phosphorylation and thus downregulates LRP-1 expression levels. Meanwhile, several studies in animal models of diabetic encephalopathy found [27] that due to pathological changes in BBB function, its LRP-1 levels were downregulated, leading to increased Aβ levels in brain tissue, which further upregulated PTK2B, thus positively regulating the development of diabetic encephalopathy. This suggests, on the other hand, that PTK2B protein increases Aβ clearance and thus reduces Aβ aggregation through upregulation of LRP-1.

6. Conclusion

The etiology of DE is complex, and current research has not yet clarified what the underlying mechanisms are. With the increasing enrichment of social life and the expanding population of DM patients, the incidence of DE will continue to rise, and the economic burden caused by this disease will have an unpredictable impact on society if there is still no specific and feasible treatment or mitigation plan for DE. Currently, the hot spots of DE research are the Aβ neurotoxicity hypothesis and the relationship between Aβ and BBB functional structure, but there is no unified conclusion on the specific mechanism, the BBB functional structure dysfunction will cause the toxic deposition of Aβ, and the neurotoxic effect of Aβ will in turn aggravate the BBB functional structure damage, and the two are related, thus accelerating the pathogenesis of DE. In summary, the neurotoxic effect of Aβ and the impaired functional structure of BBB are the key links affecting the pathogenesis of DE. Therefore, it is of great scientific value to investigate and elucidate the causes and cellular-molecular mechanisms of DE pathogenesis, and then to identify valuable new therapeutic targets, which is the key to finally overcome the disease.

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