

# *Research Progress of Central Insulin Resistance and Cognitive Impairment*

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**Abstract:** With the acceleration of the aging of the world's population, the number of patients with cognitive dysfunction has increased significantly, resulting in more and more serious social problems, economic problems, family problems and public health problems, how to better prevention and treatment of cognitive dysfunction is also a hot spot of clinical research. Studies have shown that insulin resistance and compensatory hyperinsulinemia (HI) exist in many patients with cognitive dysfunction, which also provides new ideas for the prevention and treatment of dysfunction. At present, more attention has been paid to peripheral insulin resistance, but there is little discussion on cognitive dysfunction caused by central insulin resistance. Insulin receptors (InsRs) are widely distributed in the brain region, especially in the hippocampus. Insulin can be through the blood - brain barrier to enter the central nervous system, adjust the structure of cerebral glucose metabolism and brain plasticity, protect nerve cells, improve memory, in order to protect the nervous system and cognitive function, while type 2 diabetes mellitus (T2DM) patients with insulin resistance, in turn, cause central insulin resistance can cause cognitive dysfunction [1]. Therefore, the effects of central insulin resistance on cognitive function and related mechanisms have gradually become a research hotspot. This paper summarizes the current research situation.

## **1. Effects of insulin resistance on cognitive function**

Insulin resistance is a common pathophysiological mechanism of metabolic diseases such as obesity, type 2 diabetes mellitus and metabolic syndrome, and is closely related to Alzheimer's disease and depression. Cognitive impairment, also known as cognitive deficit, is a pathological process of abnormal processing of advanced intelligence in the brain related to learning, memory and thinking judgment, resulting in learning and memory disorders, accompanied by changes such as aphasia, apraxia and agnosia. It can be caused by craniocerebral trauma, cerebrovascular diseases, brain aging, chronic systemic diseases, environmental, mental and psychological abnormalities and other factors. [14] Studies have shown that the occurrence of mild cognitive impairment (MCI) is related to insulin resistance and the degree of resistance. The more severe the insulin resistance, the higher the incidence of MCI, and insulin resistance has an impact on all

aspects of cognitive function. Insulin resistance affects cognitive function, and insulin resistance and high insulin level are independent risk factors for MCI. [15]

Insulin resistance is an important risk factor for cognitive dysfunction. First of all, when insulin resistance occurs, the efficiency of glucose uptake and utilization decreases. At this time, the body will experience compensatory excessive insulin secretion and produce hyperinsulinemia to maintain the stability of blood glucose. So this is a problem of a metabolic defect with hyperinsulinemia. In the central nervous system, long-term hyperinsulinism can impair the function of the blood-brain barrier and insulin activity [16]. Insulin resistance can lead to long-term exposure of neurons to high levels of insulin, leading to neuronal degeneration and irreversible memory impairment [17]. Secondly, insulin resistance changes the main energy (glucose) source required by the brain: insulin stimulates abnormal glucose metabolism and glycogen synthesis in neurons, and insulin bound to the hippocampus reduces glucose utilization, leading to cognitive decline. Third, under the effect of insulin resistance, the tyrosine phosphorylation level of insulin receptor substrate protein decreases, which further affects insulin signal transmission, thereby causing the loss of insulin-mediated neurotrophic effect, and making neurons more susceptible to neurotoxic stimulation, resulting in neuronal dysfunction and neurological diseases [2].

## **2. Mechanism of insulin resistance leading to cognitive dysfunction**

Typical pathological features of AD include the formation of neurofibrillary tangles and senile plaques due to increased A $\beta$  aggregation in the brain and neuronal loss due to abnormal tau phosphorylation. Insulin can reduce A $\beta$  generation and aggregation, and insulin degrading enzyme (IDE) can degrade A $\beta$  [3]. It has been suggested that insulin resistance may be the initial factor of cognitive dysfunction, but the underlying mechanism remains unclear. This paper suggests that the mechanism of insulin resistance leading to cognitive dysfunction may be related to the following factors: A $\beta$  deposition, Tau phosphorylation, central nervous system inflammation, oxidative stress, hippocampal synaptic plasticity.

### **2.1. A $\beta$ deposition**

Amyloid protein (A $\beta$ ) produced by the hydrolysis of amyloid precursor protein (APP) has obvious neurotoxic effects, which can induce apoptosis and oxidation of cells, cause intracellular calcium overload, affect synaptic plasticity, and damage the function of cholinergic nervous system. Insulin can enhance a secretase activity, promote the generation of soluble APP and reduce the production of A $\beta$ , insulin can accelerate the APP/A $\beta$  transport at the same time, reduce A $\beta$  cell deposition [2], so central insulin resistance can lead to a lack of insulin in the brain, makes the increase in the number of generated A $\beta$ , and transport and degradation is restrained, promote neuron degeneration. Some studies have shown that when A $\beta$  is injected into the cerebral cortex of rats or monkeys, tissue necrosis, loss of peripheral neurons and proliferation of nerve keratin at the injection site are found, and premature apoptosis of nerve cells is induced. As one of the most important nerve cells in the brain, neurons play an important role in the maintenance of physiological functions such as learning, cognition, memory formation and information integration [4]. Therefore, central insulin resistance leads to A $\beta$  deposition, which in turn leads to cognitive dysfunction.

### **2.2. Phosphorylation of Tau**

Microtubule system is a component of neural cytoskeleton and can be involved in many cellular functions. Microtubules are composed of tubulin and microtubule-associated proteins. Tau is the

microtubule-associated protein with the highest content, which plays an important role in the synthesis and stabilization of microtubules and the maintenance of normal nerve function in normal nerve cells. It has been found that there is excessive phosphorylation of Tau protein in brain tissue with cognitive dysfunction [5]. The binding force of Tau protein with tubulin after abnormal hyperphosphorylation is only 1/10 of that of normal Tau protein, which makes it lose its biological function of promoting microtubule assembly and maintaining microtubule stability, leading to the decline of axonal transport and synaptic function, and then causing neuronal degeneration.

### **2.3. Central nervous system inflammation, oxidative stress**

Decreased insulin action is closely related to the process of inflammation and oxidative stress in the central nervous system [6]. The physiological concentrations of IL-1 $\beta$ , IL-6 and TNF- $\alpha$  in the central nervous system play an important role in the process of learning and memory, but overexpression can lead to the impairment of learning and memory function. Studies have found that mild hyperinsulinemia can increase the levels of inflammatory factors in plasma and cerebrospinal fluid [2]. Serum IL-2 level in patients with vascular dementia (VD) is significantly higher than that in normal elderly people, and is related to the severity of dementia. In addition, IL-2 attenuates the long-term potentiation of hippocampal neurons and may affect hippocampal learning and memory processes in this way. Therefore, the effect of inflammatory factors may be an important factor linking insulin resistance and cognitive impairment.

### **2.4. Hippocampal synaptic plasticity**

Synaptic plasticity mainly includes short-term synaptic plasticity and long-term synaptic plasticity, which have been recognized as the biological basis of learning and memory activities at the cellular level. Insulin resistance can affect hippocampal synaptic plasticity and thus affect cognitive function. It is characterized by structural and functional plasticity of hippocampal synapses. In terms of structure, synaptic degeneration, the number of synapses, the thickness of synaptic vesicles and postsynaptic dense decreased, and the synaptic cleft widened. In terms of function, long-term enhancement (LTP) effect is reduced or long-term inhibition (LDP) effect is facilitated [7]. Insulin induces LTP by acting on NMDA receptors, thereby enhancing learning and memory. In insulin resistance, the biological efficacy of insulin decreases, and this pathway dysfunction will lead to the decline of learning and memory function [8].

### **2.5. Glial cell - neuron energy metabolism coupling**

Normal physiological activities of the brain require normal energy metabolism channels to provide physiological energy, and the energy metabolism of brain tissue plays an important role in maintaining the normal morphology, structure and function of brain tissue cells. Energy metabolism in brain tissue is mainly the transport of nutrients and metabolites between neurons and glial cells, namely glial cell-neuron energy metabolism coupling [9]. Share the experiment through improved "sandwich" training method to establish neurons, astrocytes co-culture system, and establish the system of central insulin resistance model, the following conclusion: central insulin resistance can affect the morphology of neurons and synapses tangibility, accelerate the apoptosis of neurons and the aging process, in turn, affect cognitive function [10].

### 3. Prospects of improving insulin resistance in the treatment of cognitive dysfunction

#### 3.1. Prospect of Western medicine treatment

In recent years, a lot of literature has shown that insulin and insulin sensitizers can improve cognitive dysfunction. It has been reported that intranasal insulin administration can improve cognitive function and neurodegenerative diseases in mice with cognitive dysfunction by reversing cerebral insulin resistance. After intranasal insulin treatment, learning and memory function of mice were significantly recovered, and hippocampal neurogenesis was improved [28]. Studies have shown that hypoglycemic drugs can change the morphology, structure, function, apoptosis and aging process of brain tissue cells by regulating astrocyt-neuron metabolic coupling, thereby affecting spatial memory impairment in central insulin resistant mice [9]. In addition to the intervention of related drugs, IR can also be improved by improving living habits. Jennifer et al. reported that A relatively simplified diet can increase the concentration of insulin in cerebrospinal fluid and down-regulate the levels of A $\beta$ 42 and lipoprotein, so as to delay or even prevent the development of AD [5].

#### 3.2. Prospect of TCM treatment

Traditional Chinese medicine has a certain effect on improving central insulin resistance and treating cognitive disorders. Studies have concluded that by animal experiments that Buyanghuanwu Decoction with lowering blood sugar, blood lipid, serum CRP level, increase the IRS - 1 and IRS 2 mRNA expression of the function, may be through the above link, Yang also five soup through anti-inflammatory mechanisms, relieve central insulin resistance play a role of the intervention of cognitive dysfunction in MS and [11]. Related experiments have confirmed that rhizophorus granulosa (APL), honeysuckle (LJT) and cinnamon (CCB) can effectively prevent cognitive dysfunction caused by amyloid beta deposition by reducing neuroinflammation and enhancing insulin signaling. APL showed the greatest effectiveness in improving cognitive function [12]. Studies of insulin resistance by establishing a central in the rat model with Alzheimer's disease, a preliminary discussion of berberine on Alzheimer's disease model in rats and its possible mechanism of the improvement of cognitive function and its, concluded, berberine by increasing the hippocampus of rats and protein expression of reduced protein deposition, reduce loss, improve the pyramidal neurons cell morphology, To improve the cognitive function of model rats [13].

### 4. Conclusion

With the emergence and onset of type 2 diabetes mellitus and abnormal glucose tolerance, the incidence of cognitive dysfunction caused by central insulin resistance is also increasing, which seriously affects people's work and life. Therefore, it is urgent to study the pathogenesis of cognitive dysfunction caused by central insulin resistance and establish effective prevention and treatment measures. In conclusion, there are several possible mechanisms by which insulin resistance leads to cognitive dysfunction: Such as A $\beta$  deposition, Tau phosphorylation, central nervous system inflammation, oxidative stress, hippocampal synaptic plasticity, glial cell-neuron energy metabolism coupling, etc., clinically, most diabetic patients with central insulin resistance can develop cognitive dysfunction in the late stage of the disease. The main clinical manifestations are as follows: Memory function, language, understanding and judgment ability decline, learning ability decline, can be accompanied by dull expression, apathy, slow reaction, severe cases can be further developed into Alzheimer's disease or dementia. Central insulin resistance is closely related to the occurrence of cognitive dysfunction. Therefore, more attention should be paid to insulin

resistance in clinical work, timely detection and early intervention. At the same time, it is necessary to strengthen the management of patients with metabolic syndrome, hypertension and diabetes, and timely evaluate their cognitive function to prevent the occurrence of cognitive function and the development of Alzheimer's disease.

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