Research Progress on Brain Insulin Resistance and Obesity-Related Neurological Disorders

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Abstract This article systematically reviews the molecular mechanisms of brain insulin resistance (BIR) and its role in Alzheimer's disease, Parkinson's disease, depression, anxiety disorders, and ischemic stroke. Research demonstrates that obesity triggers BIR by inducing chronic inflammation and metabolic dysregulation, which subsequently drives neurodegeneration through dysfunction in insulin signaling pathways. Current research still faces limitations such as inconsistent evaluation systems and unclear temporal causality. This review aims to provide a theoretical reference for the early prevention, control, and precision treatment of obesity-related neurological disorders.

Key words Brain insulin resistance, Obesity, Neurological disorders

0 Introduction

Obesity has become a global public health crisis and shows significant comorbidity rates with neurological disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), and depression. The core mechanism underlying this "metabolic-neurological" comorbidity has been confirmed to be closely linked to brain insulin resistance (BIR). As a core feature of obesity and metabolic diseases, BIR has been demonstrated to drive neurodegeneration through specific mechanisms; simultaneously, obesity can induce BIR by disrupting peripheral metabolism, allowing its effects to cross the blood-brain barrier, thereby forming a "metabolic-neurodegenerative" vicious cycle. This article reviews the latest research progress and analyzes the association mechanisms between BIR and obesity-related neurological disorders, aiming to provide more theoretical foundations for the prevention and treatment of these diseases.

1 Research progress on brain insulin resistance

BIR refers to a state of diminished neuronal responsiveness to insulin signaling[1-2]. Research indicates that BIR primarily manifests as the failure of bioactive insulin to function normally within the central nervous system, involving reduced surface expression of insulin receptors, imbalance in isoform expression, or weakened downstream signal transduction[3], as well as abnormal serine phosphorylation of insulin receptor substrate-1 (IRS-1), inhibition of the PI3K/Akt pathway, and overexpression of downstream GSK-3β[4-5]. Consequently, this leads to impaired energy metabolism, exacerbated oxidative stress, and increased neuroinflammation[6-7]. Although the brain primarily relies on insulin-independent glucose transporters like GLUT1 and GLUT3 for glucose uptake, the insulin receptor (INSR) is highly expressed in crucial brain regions such as the hypothalamus, hippocampus, cerebral cortex, and cerebellum, indicating its indispensable roles in synaptic plasticity, memory consolidation, mood regulation, and neurotransmitter balance[1,8-9].

2 Research progress on brain insulin resistance and obesity-related neurological disorders

2.1 Brain insulin resistance and obesity Obesity is not only a significant risk factor for chronic diseases such as cardiovascular disease and diabetes, but also a major modifiable risk factor for conditions like cognitive impairment and neurodegenerative diseases. Its essence lies in inducing chronic low-grade inflammation, which exerts detrimental effects on the central nervous system[10-11]. In the state of obesity, adipose tissue expands and remodels, leading to the infiltration and activation of pro-inflammatory immune cells, disruption of immune homeostasis, increased secretion of pro-inflammatory adipokines, and reduced levels of anti-inflammatory factors; simultaneously, excess lipids elevate ceramide levels. These bioactive molecules, upon entering the bloodstream, can act directly on the brain, triggering neuroinflammatory responses, impairing synaptic plasticity, inducing cerebral oxidative stress, and disrupting insulin signaling pathways, thereby contributing to neuronal loss, brain atrophy, and the development of neurodegenerative disorders[12-14]. Relevant animal experiments have shown that mice fed a high-fat diet exhibit more severe pathological symptoms and behavioral deficits in models of AD and PD[15]. Therefore, obesity is not merely an accumulation of fat; rather, it represents a persistent, low-grade, systemic inflammatory state that can significantly accelerate the onset and progression of various neurological diseases.

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2.2 Brain insulin resistance and AD BIR is regarded as the link connecting type 2 diabetes mellitus (T2DM) and AD, forming the basis of the "type 3 diabetes" hypothesis. Arnold *et al.* [1] proposed that chronic hyperinsulinemia in T2DM impairs blood-brain barrier function, reducing insulin entry into the brain and consequently leading to dysfunction in brain insulin signaling pathways. Rhea *et al.* [16], who introduced the concept of BIR, discovered a selective loss of the long-chain isoform of the insulin receptor in the brain microvasculature of AD patients. Studies have identified features of insulin resistance in the brains of AD patients; notably, over 64% of non-diabetic AD patients exhibit an abnormal TyG index, further implicating BIR in the pathogenesis of AD[1, 17]. BIR accelerates the pathological progression of AD through multiple mechanisms: it inhibits the activity of insulin-degrading enzyme (IDE), hindering the clearance of amyloid-beta protein (Aβ); it activates GSK-3β kinase, catalyzing the hyperphosphorylation of tau protein and leading to the formation of neurofibrillary tangles[16-18]. Aβ oligomers competitively inhibit insulin receptor activity, thereby exacerbating BIR[19]. Furthermore, BIR can epigenetically upregulate the expression of relevant genes, enhancing the modification of proteins like BACE1, which subsequently accelerates Aβ deposition and cognitive decline[20-21]. Therefore, viewing AD as a metabolic disorder stemming from dysregulation in brain insulin and IGF-1 signaling systems offers a perspective for developing novel disease-modifying therapeutics[19].

2.3 Brain insulin resistance and PD The role of insulin resistance in PD is receiving increasing attention. Theodora Ntetsika *et al.* [22] contend that individuals with T2DM face an elevated risk of developing PD, and that dysfunction in brain insulin signaling pathways impairs neuronal energy metabolism and proteostasis, promoting the accumulation of alpha-synuclein. Even in non-diabetic PD patients, the prevalence of peripheral insulin resistance (IR) reaches approximately 58.4% and is associated with more severe non-motor symptoms[23]. Alise Zagare *et al.* discovered that midbrain organoids derived from patients with GBA1 mutation-associated PD (GBA-PD) exhibit dysregulation in the expression of key insulin signaling pathway genes, even in the absence of systemic diabetes, with FOXO1 identified as a central node. This suggests that central insulin resistance can occur independently and precede the onset of typical motor symptoms[24]. Raed AlRuwaili *et al.* [25] argue that the PI3K/AKT/GSK3β pathway plays a significant role in PD, and its imbalance promotes the aggregation of alpha-synuclein and impairs mitochondrial function; furthermore, abnormalities in insulin receptors dependent on the peripheral nervous system are present in the brains of PD patients, including loss of insulin receptor mRNA in the substantia nigra and reduced activation of downstream signaling molecules IRS-1 and AKT, ultimately compromising neuronal survival[23]. Consequently, a growing number of researchers view Parkinson's disease as a form of "diabetes of the brain", offering novel insights for modifying its disease course.

2.4 Brain insulin resistance and depression, anxiety disorders The comorbidity between obesity and depression is well-established, with chronic low-grade inflammation serving as a key intermediary linking the two. During overweight/obesity, adipose tissue releases numerous inflammatory mediators, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). These substances not only induce insulin resistance and metabolic syndrome but can also breach the blood-brain barrier via the bloodstream and vagus nerve pathways. Once in the central nervous system, they activate microglia and astrocytes, triggering neuroinflammation. This cascade ultimately damages the function of critical brain regions involved in mood regulation, such as the hippocampus[26].

Roger S. McIntyre *et al.* [27] found that metabolic indices such as the triglyceride-to-HDL ratio and elevated fasting blood glucose can predict the risk of developing new-onset major depressive disorder over the subsequent nine years. This finding aligns with the theoretical model of a "metabolic shift to the brain". Research utilizing brain-enriched exosome technology has revealed elevated concentrations of L1CAM + exosomal IRS-1 in patients with major depressive disorder (MDD), indicating a state of central nervous system insulin resistance. Furthermore, this alteration is associated with suicidal ideation and anhedonia[28].

F. A. Monsalve *et al.* [26] propose that chronic low-grade inflammation, HPA axis dysregulation, and the gut microbiota-gut-brain axis collectively constitute the "patho-toxicological" relationship between obesity and depression. Long-term high-fat diets induce obesity, insulin resistance, and concurrently trigger a cascade of issues including chronic mild inflammation, disruption of intestinal barrier function, and disturbance of gut microbiota homeostasis. These, in turn, affect central nervous system function and contribute to the development of anxiety-like behaviors. Caloric restriction, however, can reverse both peripheral and central insulin resistance induced by long-term high-fat feeding, thereby effectively alleviating anxiety behaviors[29-30].

2.5 Brain insulin resistance and ischemic stroke The role of insulin resistance in ischemic stroke (IS) is also garnering increasing attention. Patients with ischemic stroke frequently exhibit insulin resistance and elevated blood glucose. This not only exacerbates secondary brain tissue damage but also significantly increases the risks of infection, mortality, and poor functional outcomes. Therefore, alongside active treatment of the primary disease, effectively managing metabolic disturbances has become a crucial approach to improving patient prognosis[31].

Xu Liwa *et al.* [31] discovered a significant association between insulin resistance and carotid atherosclerosis, proposing insulin resistance as an independent risk factor for atherosclerosis. Studies indicate that over 50% of non-diabetic stroke patients exhibit significant IR. Prior to stroke occurrence, insulin resistance can increase the risk of stroke through mechanisms such as promo-

ting thrombosis and accelerating atherosclerosis; following stroke onset, it further inhibits neuronal survival and synaptic plasticity, thereby impeding neurological recovery[32]. Consequently, enhancing central insulin sensitivity is regarded as a potential neuroprotective strategy. Intranasal administration can bypass the blood-brain barrier, directly augmenting brain insulin signaling, activating the AKT pathway, and consequently mitigating ischemia-reperfusion injury[32].

During acute stroke, Zhang Xin *et al.* [33] found that the use of diabetes-specific enteral nutritional formulas significantly improves glycemic stability and insulin resistance status, reducing HOMA-IR and daily blood glucose fluctuations. This study posits that nutritional intervention serves not merely as a means of caloric provision but also as a pathway for metabolic regulation. Collectively, these studies demonstrate that insulin resistance represents a common pathway linking metabolic dysregulation to various neurological disorders.

3 Conclusions

In recent years, the research focus in this field has shifted from epidemiological associations between simple obesity and neurological disorders towards elucidating the molecular mechanisms by which BIR acts as a central pathological hub. However, the temporal causality between BIR and neurodegeneration remains unclear, and whether it acts as a primary factor or a secondary consequence is still unresolved. Major limitations of current research include: the lack of standardized BIR evaluation metrics, over-reliance on small-sample observational data, scarcity of large-scale prospective cohort studies, and insufficient attention to the potential feedback effects whereby obesity-related neurological disorders may reciprocally modulate BIR. Future research should focus on establishing a standardized system for measuring BIR, conducting longitudinal studies to clarify temporal causality, and delving deeper into the specific mechanisms by which insulin signaling pathways influence neuronal survival, regulate tau protein phosphorylation, and modulate microglial activation.

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