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Role and mechanisms of glucagon-like peptide-1 receptor agonists in the treatment of diabetes-associated cognitive dysfunction

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Abstract: Diabetes mellitus is closely associated with cognitive dysfunction, and prolonged hyperglycemia significantly increases the risk of dementia in patients by impairing cognitive function through mechanisms such as oxidative stress, accumulation of glycosylation end products, insulin resistance, and neuroinflammation. Glucagon - like peptide - 1 receptor agonists (GLP - 1RAs), as the core therapeutic agents for diabetes mellitus, have been recommended for diabetes mellitus patients with comorbidities of obesity, cardiovascular disease or chronic kidney disease. There are an increasing number of animal experiments and clinical trials on the effects and related mechanisms of cognitive function in patients with diabetes mellitus. This article focuses on exploring the possible mechanisms of GLP-1RAs in treating cognitive dysfunction in patients with diabetes mellitus, and provides suggestions for further research.

Keywords: Glucagon-like peptide-1 receptor agonists; Diabetes mellitus; Cognitive dysfunction; Insulin resistance; Neuroinflammation; Gut microbiota; Oxidative stress

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Diabetes mellitus is a common chronic metabolic disease. In recent years, its incidence has shown a marked upward trend worldwide [1], making it a public health issue of widespread concern. According to data from the International Diabetes Federation, the number of people with diabetes worldwide exceeded 500 million in 2021 and is expected to rise to 700 million by 2045 [2]. The latest epidemiological survey showed that the prevalence of diabetes among adults in China has reached 11.2% [3]. Long-term hyperglycemia not only causes a series of complications, such as cardiovascular disease and kidney disease, but also adversely affects cognitive function [3-4]. Diabetes-associated cognitive dysfunction (DACD) is an increasingly common complication of diabetes. It is a diabetes-induced complication characterized by cognitive impairment and accompanied by structural and pathophysiological changes in the brain. As the disease progresses, patients with diabetes gradually develop declines in multiple domains, including memory, attention, language, executive function, and visuospatial ability. Clinical studies have shown that the risk of DACD is significantly increased in patients with diabetes compared with individuals without diabetes, seriously affecting patients' quality of life [5-6]. In recent years, increasing attention has been paid to the prevention and treatment of DACD. However, therapeutic options for patients with DACD remain limited, and new treatment strategies need to be further explored to improve cognitive function and quality of life. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a novel class of glucose-lowering drugs developed on the basis of glucagon-like peptide-1 (GLP-1), and they have shown unique potential in improving cognitive function. This article reviews the effects of GLP-1RAs on cognitive function in patients with diabetes and their mechanisms of action, aiming to provide more effective strategies and approaches for the clinical treatment of DACD.

1. GLP-1RAs

GLP-1 is an endogenous peptide hormone secreted by intestinal L cells and plays a central role in regulating glucose homeostasis [7]. GLP-1RAs mimic the biological functions of GLP-1 through artificial synthesis or modification. They specifically bind to GLP-1 receptors on the surface of target cells and activate downstream signaling pathways, thereby achieving multidimensional metabolic regulation. When blood glucose levels are elevated, GLP-1RAs bind to GLP-1 receptors on pancreatic β cells, promoting increased insulin secretion, accelerating glucose uptake and utilization, and reducing blood glucose levels. When blood glucose levels are normal or low, their insulinotropic effect is markedly weakened, thereby reducing the risk of hypoglycemia. At the same time, GLP-1RAs can inhibit glucagon secretion by pancreatic α cells, reduce hepatic glycogenolysis and glucose output, and further stabilize blood glucose [8]. In addition, GLP-1RAs can act on the gastrointestinal tract to delay gastric emptying, prolong the retention time of food in the stomach, and reduce the rapid rise in postprandial blood glucose. They can also act on feeding centers in the central nervous system to suppress appetite and reduce food intake, thereby helping control body weight, which is extremely important for the management of obesity-related diabetes. At present, GLP-1RAs have become first-line therapeutic agents for diabetes. Clinically available GLP-1RAs are diverse and can be divided into short-acting and

long-acting preparations according to half-life [9]. Short-acting preparations, such as exenatide, usually require twice-daily injections and are mainly used to reduce postprandial blood glucose. Long-acting preparations include liraglutide, dulaglutide, and semaglutide. Liraglutide is injected once daily, whereas dulaglutide and semaglutide can be injected once weekly, greatly improving medication adherence. These long-acting preparations have sustained effects in vivo and can control blood glucose more steadily, thereby reducing glycemic fluctuations. GLP-1RAs are important drugs for the treatment of diabetes. Compared with traditional glucose-lowering drugs, they not only have good glucose-lowering efficacy but also show unique advantages in cardiovascular protection, weight management, and renal protection [9]. Recent studies have shown that these drugs have unique potential in improving cognitive function, providing a new direction for the treatment of DACD [9].

2. Mechanisms by Which GLP-1RAs Improve DACD

2.1 Insulin Resistance, Amyloid β-Protein, and Tau Protein

Insulin resistance is an important pathophysiological basis of type 2 diabetes mellitus (T2DM) and an important mechanism leading to DACD. Under normal conditions, insulin binds to insulin receptors and activates downstream signaling pathways, thereby regulating cellular glucose uptake and utilization and maintaining blood glucose stability. In a state of insulin resistance, amyloid formation is accelerated in various parts of the body. Excessive accumulation of amyloid β-protein (Aβ) leads to oligomer formation, and these oligomers exert toxic effects on neurons [10]. Insulin resistance may reduce brain uptake of insulin-like growth factor-1 (IGF-1) and insulin, resulting in Aβ accumulation [11]. In turn, elevated Aβ levels antagonize the binding of insulin and IGF-1 to their receptors, thereby aggravating insulin resistance [12]. In addition, insulin dysfunction, together with inflammation and oxidative stress, further enhances the toxicity and concentration of Aβ. Animal experiments have also shown that diabetes can induce impairment of learning and memory by aggravating Aβ deposition in brain tissue [13]. Tau protein also plays an important role in the peripheral nervous system and in the induction of insulin resistance [14-15]. According to the Tau protein hypothesis, Aβ can activate protein kinases, leading to Tau hyperphosphorylation and conversion of normal Tau protein into paired helical filaments and neurofibrillary tangles (NFTs), thereby contributing to the development of Alzheimer's disease (AD) [16]. The rate of Tau aggregation largely depends on the rate of Tau phosphorylation. Insulin resistance prevents insulin from reducing glycogen synthase kinase-3β (GSK-3β) activity through activation of the phosphatidylinositol 3-kinase (PI3K) signaling pathway. GSK-3β has been shown to be one of the most important kinases responsible for Tau phosphorylation. The accumulation of Aβ and hyperphosphorylation of Tau protein can also aggravate insulin resistance. Aβ accumulation can trigger calcium influx and disturb protein kinases such as protein kinase C and GSK-3β, thereby aggravating insulin resistance and Tau hyperphosphorylation. Aβ can also inhibit phosphorylation of insulin receptor substrate 1, further impairing insulin signaling and forming a vicious cycle. Studies have shown that GLP-1RAs can reduce Tau hyperphosphorylation and Aβ deposition by activating the PI3K/protein kinase B (AKT)/GSK-3β signaling pathway [17]. The PI3K/AKT signaling pathway is a classical insulin signaling pathway. PI3K is a lipid kinase and can be divided into three subtypes according to structural and functional differences [18]. Among them, class IA and class IB PI3Ks are the most common. Class IA PI3K is activated through tyrosine kinase activation, whereas class IB PI3K is activated on the basis of G protein-coupled receptor activation. AKT is a direct downstream effector of PI3K. GSK-3β is an isoform of GSK and a common downstream molecular target of AKT. Activated AKT phosphorylates GSK-3β and inhibits its activity. As a member of the G protein-coupled receptor family, the GLP-1 receptor can activate PI3K after GLP-1RAs activate the GLP-1 receptor, thereby inhibiting GSK-3β activation, alleviating insulin resistance, and reducing Aβ accumulation and Tau hyperphosphorylation. Several studies have shown that when GLP-1RAs are administered to rat models of AD, Aβ deposition is significantly reduced, Tau phosphorylation levels are decreased, and cognitive function is markedly improved [19-21]. In summary, GLP-1RAs can act on the PI3K/AKT/GSK-3β signaling pathway to improve insulin resistance, enhance insulin sensitivity, reduce Aβ accumulation and its neurotoxic effects, inhibit Tau hyperphosphorylation, and reduce the generation of paired helical filaments and NFTs, thereby improving cognitive function.

2.2 Metabolic Disorders and Oxidative Stress

2.2.1 GLP-1RAs Improve Glucose and Lipid Metabolic Disorders by Promoting Insulin Synthesis and Secretion

Neurodegenerative diseases are characterized by significant metabolic impairment, including reduced glucose uptake or utilization, lipid metabolism disorders, mitochondrial dysfunction, and enhanced oxidative stress responses. Studies have shown that in the early stage of AD, glucose utilization is reduced under pathological conditions. Impaired glucose utilization can also enhance Aβ deposition and reduce its clearance, leading to cognitive dysfunction [22]. Disordered lipid metabolism is also an important factor in diabetes-induced DACD. Abnormal lipid metabolism aggravates arteriosclerosis and leads to insufficient cerebral blood perfusion. As T2DM progresses, long-term hyperglycemia and lipid deposition can cause significant morphological changes in cerebral vessels, including basement membrane thickening, calcium deposition in microvascular walls, and reduced cortical capillary density. These changes are accompanied by regional disruption of blood-brain barrier integrity in

areas such as the midbrain and hippocampus, allowing glucose, sodium, potassium, choline, ketone bodies, insulin, and other substances to enter brain tissue. This causes changes in cerebral microcirculatory hemodynamics, microvascular biochemical substances, and neurotransmitter activity, thereby damaging neurons and glial cells, inducing white matter lesions and neural demyelination, impairing neural signal conduction [23-24], and ultimately leading to DACD. GLP-1RAs specifically bind to GLP-1 receptors on the surface of pancreatic β cells, activate adenylate cyclase, and increase intracellular cyclic adenosine monophosphate (cAMP) levels. cAMP further activates protein kinase A, which subsequently phosphorylates transcription factors and promotes insulin production and release. Insulin promotes glucose uptake, inhibits gluconeogenesis, promotes glycogen synthesis, and inhibits lipolysis, thereby improving glucose and lipid metabolic disorders.

2.2.2 GLP-1RAs Reduce the Generation and Accumulation of Oxidative Stress Products

Mitochondrial dysfunction and excessive production of reactive oxygen species (ROS) also play crucial roles in the development of diabetes [25]. Evidence suggests that insulin resistance in diabetes may be a factor that increases and promotes oxidative stress-induced neurodegeneration in AD [26]. ROS generated by oxidative stress and the resulting damage are highly evident in AD, manifested by reduced ATP production, neuronal degeneration, and the presence of oxidative stress products in NFTs [27]. Aβ can damage mitochondria, leading to energy metabolism disorders and oxidative stress injury. These pathological changes further promote abnormal Aβ accumulation, forming a vicious cycle that leads to neuronal death and disruption of intercellular communication [28]. GLP-1RAs reduce ROS generation and maintain mitochondrial homeostasis through multitarget actions. They activate the adenosine 5′-monophosphate-activated protein kinase (AMPK) signaling pathway, improve mitochondrial oxidative phosphorylation, enhance mitochondrial biogenesis, reduce ROS production, increase mitochondrial quantity and function, further optimize energy metabolism, and reduce ROS accumulation [29].

2.2.3 GLP-1RAs Reduce Advanced Glycation End Product Levels

Advanced glycation end products (AGEs) are generated through nonenzymatic condensation between the carbonyl groups of reducing sugars and the free amino groups of nucleic acids, proteins, or lipids, followed by further rearrangement to form stable and irreversible final products. AGEs accumulate in various cells as products of normal aging, but their accumulation rate is greatly increased in patients with diabetes. AGEs promote the aggregation of amyloid oligomers, leading to neurotoxic effects. After binding to their receptors, AGEs activate a series of signaling pathways, resulting in inflammatory responses, vascular injury, and neuronal dysfunction, which subsequently impair cognitive function [30-31]. A study by Dybjer *et al.* [32] showed that plasma GLP-1 levels and AGEs were negatively correlated with cognitive test results. Some GLP-1RAs, such as semaglutide, have been shown to cross the blood-brain barrier. Therefore, GLP-1RAs may improve cognitive dysfunction by reducing AGE levels in the brain.

In summary, glucose and lipid metabolic disorders can directly or indirectly affect cognitive function. GLP-1RAs improve glucose and lipid metabolic disorders by promoting insulin synthesis and secretion, thereby indirectly improving cognitive function. GLP-1RAs can also reduce the generation and accumulation of oxidative stress products through multiple mechanisms and decrease AGE levels in the brain, thereby improving DACD.

2.3 Neuroinflammation

Neuroinflammation is also one of the important pathological mechanisms of DACD. The development of neuroinflammation involves multiple pathways, including increased inflammatory cytokines and activation of microglia [33]. Microglia initiate the first stage of neuroinflammation by activating nuclear factor kappa-B (NF-κB) [34]. The NF-κB signaling pathway is initiated by proinflammatory molecules such as interleukin (IL)-1, lipopolysaccharide, or tumor necrosis factor (TNF)-α. The resulting products bind to corresponding receptors on cells and induce signal transduction responses [35], ultimately leading to the release and nuclear translocation of NF-κB. After entering the nucleus, NF-κB binds to κB elements in gene promoters, thereby enhancing downstream gene expression of various enzymes, adhesion molecules, chemokines, and cytokines involved in inflammatory responses. Another important process involved in neuroinflammation is Aβ-induced microglial activation, which leads to the release of various inflammatory cytokines, such as IL-1β, IL-6, and TNF-α [36]. The neurotoxic processes mediated by these cytokines may include direct neuronal death caused by enhanced apoptosis, inhibition of synaptic function, and hippocampal neuronal injury [37], thereby resulting in cognitive decline. In addition, inflammatory signals such as TNF-α or IL-1 can activate c-Jun N-terminal kinase (JNK) and p38 protein through the mitogen-activated protein kinase (MAPK) pathway. Activated JNK and p38 phosphorylate transcription factors to form the activator protein-1 (AP-1) complex, promoting the transcription of IL-6 and TNF-α. Meanwhile, p38 can activate the downstream target MAPK-activated protein kinase 2 (MK2), and MK2 activation increases the stability and translation of proinflammatory factor mRNA, jointly amplifying the inflammatory response. GLP-1RAs can inhibit activation of the NF-κB and MAPK pathways [38], reduce the phosphorylation levels of extracellular signal-regulated kinase, JNK, and p38, and decrease AP-1 activity, thereby inhibiting the expression of inflammatory factors [39]. GLP-1RAs also promote the generation of phosphatidylinositol (3,4,5)-trisphosphate (PIP3), activate AKT protein, inhibit caspase-3 activity, promote the expression of antiapoptotic proteins, and reduce neuronal apoptosis [40]. In addition, GLP-1RAs can significantly

increase the expression of nerve growth factor and brain-derived neurotrophic factor, promote the differentiation of neural stem cells into neurons, increase neuronal number, and help repair damaged neural tissue [41]. Neurotransmitters also play key roles in cognitive, emotional, and memory functions of the brain. In patients with DACD, the synthesis, release, and metabolism of neurotransmitters such as acetylcholine, dopamine, and γ-aminobutyric acid are affected, leading to disordered neural signal transmission and impaired cognitive function. Related studies have shown that GLP-1RAs can promote cholinergic neuron activity, increase acetylcholine synthesis and release, regulate levels of dopamine and γ-aminobutyric acid, maintain balance in neurotransmitter systems, promote normal neural signal transmission, and thereby improve cognitive function [42].

2.4 Gut Microbiota

The gut microbiome is a complex microbial community system colonizing the human digestive tract and is characterized by marked diversity. Its core microbiota include major phyla such as Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. This ecosystem plays important roles in regulating host material and energy metabolism and maintaining immune homeostasis. When ecological imbalance occurs in the microbial community, it may induce abnormalities in host metabolic pathways and cause various acute and chronic diseases [43]. Studies have shown that patients with DACD exhibit characteristic structural changes in the gut microbiota compared with patients with diabetes alone [44]. The gut microbiota can communicate bidirectionally with the brain through the gut-brain axis. Dysbiosis of the gut microbiota can induce pathological processes such as disordered glucose metabolism, abnormal insulin signaling regulation, and chronic inflammatory responses, leading to blood-brain barrier impairment, hippocampal neuronal injury, and gliosis. At the same time, reduced neurotransmitters and accumulation of ROS free radicals aggravate cognitive impairment, ultimately leading to DACD. Studies have confirmed that GLP-1RAs can effectively alleviate depression- and anxiety-like behaviors, enhance cognitive function, and exert neuroprotective effects in diabetic mouse models by altering the gut microbiota profile [45]. Therefore, it is extremely important to further investigate the effects of GLP-1RAs on the gut microbiota in patients with DACD.

3. Conclusions and Prospects

In summary, GLP-1RAs have shown significant potential in the treatment of DACD. They can improve cognitive function in patients with diabetes through multiple mechanisms, including regulation of glucose and lipid metabolism, neuroprotection, and antioxidative stress effects. Clinical trials of liraglutide, dulaglutide, and other drugs for the treatment of DACD have been completed, showing favorable efficacy and good safety. Trials investigating the efficacy and safety of other GLP-1RAs, such as semaglutide, in the treatment of DACD are ongoing. In the future, GLP-1RAs have broad application prospects for improving cognitive function in patients with T2DM. Further research should investigate the characteristics and advantages of different GLP-1RAs and develop drugs with higher selectivity and specificity to enhance efficacy and reduce adverse reactions. With continued research, GLP-1RAs are expected to become core drugs for the treatment and prevention of DACD.

Conflict of Interest: None

Reference

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· 研究进展 ·

胰高血糖素样肽-1受体激动剂治疗糖尿病相关认知功能障碍的作用及机制

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摘要：糖尿病与认知功能障碍密切相关，长期高血糖通过氧化应激、糖基化终产物蓄积、胰岛素抵抗及神经炎症等机制损害认知功能，显著增加患者痴呆风险。胰高血糖素样肽-1受体激动剂（GLP-1RAs）作为治疗糖尿病核心药物，已被推荐用于合并肥胖、心血管疾病或慢性肾病的糖尿病患者。目前关于糖尿病患者认知功能的影响和相关机制的动物实验和临床研究越来越多，本文综述了GLP-1RAs治疗糖尿病患者认知功能障碍的可能机制，并为后续研究提出建议。

关键词：胰高血糖素样肽-1受体激动剂；糖尿病；认知功能障碍；胰岛素抵抗；神经炎症；肠道微生态；氧化应激

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Abstract: Diabetes mellitus is closely associated with cognitive dysfunction, and prolonged hyperglycemia significantly increases the risk of dementia in patients by impairing cognitive function through mechanisms such as oxidative stress, accumulation of glycosylation end products, insulin resistance, and neuroinflammation. Glucagon-like peptide-1 receptor agonists (GLP-1RAs), as the core therapeutic agents for diabetes mellitus, have been recommended for diabetes mellitus patients with comorbidities of obesity, cardiovascular disease or chronic kidney disease. There are an increasing number of animal experiments and clinical trials on the effects and related mechanisms of cognitive function in patients with diabetes mellitus. This article focuses on exploring the possible mechanisms of GLP-1RAs in treating cognitive dysfunction in patients with diabetes mellitus, and provides suggestions for further research.

Keywords: Glucagon-like peptide-1 receptor agonists; Diabetes mellitus; Cognitive dysfunction; Insulin resistance; Neuroinflammation; Gut microbiota; Oxidative stress

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糖尿病是一种常见的慢性代谢性疾病，近年来其发病率在全球范围内呈显著上升趋势[1]，已成为受广泛关注的公共卫生问题。据国际糖尿病联盟数据显示，2021年全球糖尿病患者人数已超5亿，预计到2045年将攀升至7亿[2]。最新流行病学调查显示，我国成年人糖尿病患病率达11.2%[3]。而长期高血糖状态不仅会引发一系列并发症如心血管疾病、肾脏疾病等，还会对认知功能产生不良影响[3-4]。糖尿病相关认知功能障碍（diabetes-associated cognitive dysfunction，DACD）是一种越来越普遍的糖尿病并发症，它是由糖尿病引起的以认知功能障碍为表现、伴有脑内结构及病理生理改变的并发症。

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随着病程的进展，糖尿病患者逐渐出现记忆、注意力、语言、执行功能、视空间能力等多个方面的减退。临床研究表明，糖尿病患者发生DACD的风险相较于非糖尿病患者明显增加，严重影响患者的生活质量[5-6]。近年来，针对DACD的预防及治疗的研究愈来愈多，但对DACD患者的治疗手段仍较有限，需进一步探索新的治疗方式，从而改善患者的认知功能，提高其生活质量。胰高血糖素样肽-1受体激动剂（glucagon-like peptide-1 receptor agonists，GLP-1RAs）是一类基于胰高血糖素样肽-1（glucagon-like peptide-1，GLP-1）研发的新型降糖药物，在改善认知功能方面展现出独特潜力，本文综述GLP-1RAs对糖尿病患者认知功能的影响及其作用机制，旨在为临床治疗DACD提供更为有效的策略和方法。

1　GLP-1RAs

GLP-1是由肠道L细胞分泌的内源性肽类激素，在调节血糖稳态中发挥核心作用[7]。GLP-1RAs通过人工合成或修饰来模拟GLP-1的生物学功能，与靶细胞表面的GLP-1受体特异性结合，激活下游信号通路，实现多维度代谢调控。当血糖增高时，GLP-1RAs与胰岛β细胞表面的GLP-1受体结合，促使胰岛β细胞分泌更多的胰岛素，加速葡萄糖的摄取和利用，降低血糖水平；当血糖处于正常或较低水平时，其刺激胰岛素分泌的作用则明显减弱，降低低血糖发生的风险。同时，它还能抑制胰岛α细胞分泌胰高血糖素，减少肝糖原的分解和输出，进一步稳定血糖[8]。此外，GLP-1RAs还可以作用于胃肠道，延缓胃排空，延长食物在胃内的停留时间，减少餐后血糖的快速上升，并且通过作用于中枢神经系统的摄食中枢，抑制食欲，减少食物摄入，从而有助于控制体质量，这对于肥胖型糖尿病的管理也极为重要。目前，GLP-1RAs已成为糖尿病的一线治疗药物。临床上常见的GLP-1RAs种类丰富，按照半衰期长短可分为短效和长效制剂[9]。短效制剂，如艾塞那肽，通常需要每日注射两次，主要用于降低餐后血糖；长效制剂包括利拉鲁肽、度拉糖肽、司美格鲁肽等，利拉鲁肽每日注射一次，而度拉糖肽和司美格鲁肽则可以每周注射一次，大大提高了患者的用药依从性。这些长效制剂在体内的作用时间持久，能够更平稳地控制血糖，减少血糖波动。GLP-1RAs是治疗糖尿病的重要药物，与传统降糖药物相比，它不仅具有良好的降糖效果，还在心血管保护、体重管理、肾脏保护等方面展现出独特优势[9]。近年来研究显示，该类药物在改善认知功能方面展现出独特潜力，为治疗DACD提供了新方向[9]。

2　GLP-1RAs改善DACD的机制

2.1　胰岛素抵抗与β-淀粉样蛋白（amyloid β-protein，Aβ）及Tau蛋白　胰岛素抵抗是2型糖尿病（type 2 diabetes mellitus，T2DM）的重要病理生理基础，也是导致DACD的重要机制。在正常情况下，胰岛素可以通过与胰岛素受体结合，激活下游信号通路，调节细胞对葡萄糖的摄取和利用，维持血糖的稳定。在胰岛素抵抗状态下会加速身体各个部位淀粉样蛋白的形成，其中Aβ的过度积累会形成寡聚体，寡聚体会对神经细胞产生毒性作用[10]。而胰岛素抵抗可能导致胰岛素样生长因子（insulin-like growth factor，IGF）-1和胰岛素脑摄取减少，从而导致Aβ积累[11]，而Aβ水平升高又会拮抗胰岛素和IGF-1受体结合，进而加重胰岛素抵抗的发生[12]。此外，胰岛素功能障碍和炎症与氧化应激相结合，进一步增强了Aβ的毒性和浓度。动物实验也表明，糖尿病能通过加重脑组织Aβ沉积进而引起学习和记忆功能减退[13]。Tau蛋白在外周神经系统以及诱导胰岛素抵抗中也起着重要作用[14-15]。Tau蛋白假说认为：Aβ能通过激活蛋白激酶，导致Tau蛋白过度磷酸化，使正常Tau蛋白转化为成对螺旋纤维和神经原纤维缠结（neurofibrillary tangle，NFT），从而导致阿尔茨海默病（Alzheimer's disease，AD）的发生[16]。而Tau蛋白聚集的速率在很大程度上取决于Tau蛋白磷酸化的速率，胰岛素抵抗的发生会导致胰岛素无法通过激活磷脂酰肌醇3激酶（phosphatidylinositol 3 kinase，PI3K）信号通路来降低糖原合成酶激酶（glycogen synthase kinase，GSK）-3β活性，而GSK-3β目前已被证明是导致Tau蛋白磷酸化最重要的激酶。而Aβ的积聚和Tau蛋白的过度磷酸化也能加重胰岛素抵抗。Aβ的累积能引发钙离子内流进而扰乱蛋白激酶C和GSK-3β等蛋白激酶，加重胰岛素抵抗和Tau蛋白过度磷酸化；Aβ也能阻碍胰岛素受体底物1的磷酸化而加重胰岛素信号通路受损，形成恶性循环。有研究表明，GLP-1RAs可以通过激活PI3K/蛋白激酶B（protein kinase B，AKT）/GSK-3β信号通路降低Tau蛋白的过度磷酸化以及降低Aβ沉积[17]。PI3K/AKT信号通路是一条经典的胰岛素信号通路，PI3K属于脂质激酶，根据结构和功能差异，可分为3种亚型[18]，其中ⅠA和ⅠB两种类型最为常见，ⅠA类PI3K通过激活酪氨酸激酶激活PI3K，ⅠB类PI3K则是在激活G蛋白偶联受体的基础上激活PI3K。AKT是PI3K下游的直接效应子，GSK-3β是GSK的亚型，也是AKT常见的下游分子靶点，活化的AKT使GSK-3β磷酸化以抑制其活性。而GLP-1受体作为G蛋白偶联受体家族的一员，GLP-1RAs可以在激活GLP-1受体的基础上激活PI3K，抑制GSK-3β的激活，减轻胰岛素抵抗以及Aβ的积累与Tau蛋白过度磷酸化。几项研究显示，将GLP-1RAs用于AD大鼠模型，实验组Aβ沉积明显减少，Tau蛋白磷酸化水平降低，大鼠认知功能明显改善[19-21]。综上所述，GLP-1RAs能够作用于PI3K/AKT/GSK-3β信号通路改善胰岛素抵抗、增强胰岛素敏感性与减轻Aβ的积累，减少其对神经细胞的毒性作用以及抑制Tau蛋白过度磷酸化，减少成对螺旋纤维和NFT的产生，从而改善认知功能。

2.2　代谢紊乱与氧化应激

2.2.1　GLP-1RAs通过促进胰岛素的合成与分泌改善糖脂代谢紊乱　神经退行性疾病均表现出显著的代谢损害，包括葡萄糖摄取或利用减少，脂代谢紊乱、线粒体功能障碍以及氧化应激反应的增强等。研究表明AD的早期，病理状态下葡萄糖利用率降低，葡萄糖利用不良也会增强Aβ沉积，并降低其清除率导致认知功能障碍[22]。脂代谢紊乱也是糖尿病引发DACD的重要因素，脂代谢异常会加剧动脉硬化，导致脑血流灌注不足。T2DM随着病程的延长，长期高血糖状态以及脂质

沉积可导致脑部血管出现基膜增厚、微血管壁钙沉积、皮质毛细血管密度减少等显著的形态学变化，并发生中脑、海马等区域性血脑屏障完整性破坏，使葡萄糖、钠、钾、胆碱、酮体和胰岛素等物质进入脑组织，引起脑微循环的血流动力学、微血管生化物质以及神经递质活性改变，进而损伤神经元、神经胶质细胞等，诱发脑白质病变及神经脱髓鞘，阻碍神经信号传导[23-24]，引起DACD的发生。而GLP-1RAs通过与胰岛β细胞表面的GLP-1受体特异性结合，激活腺苷酸环化酶，促使细胞内环磷酸腺苷（cyclic adenosine monophosphate，cAMP）水平升高。cAMP可以进一步激活蛋白激酶A，随后蛋白激酶A磷酸化转录因子，促进胰岛素的生成与释放。胰岛素可以促进葡萄糖摄取，抑制糖异生、促进糖原合成、抑制脂肪分解，进而改善糖脂代谢紊乱。

2.2.2 GLP-1RAs减少氧化应激产物的生成与积累 线粒体功能障碍和活性氧（reactive oxygen species，ROS）的过量产生在糖尿病的发展中也起着至关重要的作用[25]。有证据表明，糖尿病中的胰岛素抵抗可能是增加和促进氧化应激导致AD神经退化的因素[26]。氧化应激产生的ROS及其由此产生的损伤在AD中极为明显，表现为ATP产生的减弱、神经元变性以及NFT中存在氧化应激产物[27]。Aβ能破坏线粒体导致能量代谢障碍，引起氧化应激损伤等。这些病理改变又促进Aβ的异常积聚而形成恶性循环，从而引起神经元死亡以及细胞间通讯中断[28]。GLP-1RAs通过多靶点作用，减少ROS生成并维持线粒体稳态，其激活单磷酸腺苷活化蛋白激酶（adenosine 5′-monophosphate-activated protein kinase，AMPK）信号通路、改善线粒体氧化磷酸化、增强线粒体生物合成，减少ROS产生，提升线粒体数量与功能，进一步优化能量代谢并降低ROS累积[29]。

2.2.3 GLP-1RAs降低晚期糖基化终产物（advanced glycation end products，AGEs）水平 AGEs是通过还原糖的羰基与核酸、蛋白质或脂质的游离胺基团之间的非酶缩合产生的，然后进一步重排产生稳定、不可逆的最终产物。AGEs作为正常衰老过程的产物在各种细胞中积累，但在糖尿病患者中，其积累速度会大幅增加。AGEs会促进淀粉样蛋白寡聚体的聚集，从而导致神经毒性作用。AGEs与受体结合后激活一系列信号通路，导致炎症反应、血管损伤和神经细胞功能障碍，进而损伤认知功能[30-31]。Dybjer等[32]研究显示，血浆GLP-1水平和AGEs与认知测试结果呈负相关，而部分GLP-1RAs（如司美格鲁肽）已被证实能够通过血脑屏障，因此，GLP-1RAs可能通过降低脑内AGEs水平，进而改善认知功能障碍。

综上所述，糖脂代谢紊乱能够以直接或间接的方式影响认知功能，而GLP-1RAs通过促进胰岛素的合成与分泌，改善糖脂代谢紊乱，并间接改善认知功能；GLP-1RAs还可通过多种方式减少氧化应激产物的生成与积累，降低脑内AGEs水平，从而改善DACD。

2.3 神经炎症 神经炎症也是DACD的重要病理机制之一。神经炎症的产生涉及多种通路，包括炎性细胞因子的增加和小胶质细胞的激活[33]，小胶质细胞通过激活核因子κB（nuclear factor kappa-B，NF-κB）启动神经炎症的第一阶段[34]，NF-κB信号通路由促炎分子如白细胞介素（interleukin，IL）-1、脂多糖或肿瘤坏死因子（tumor necrosis factor，TNF）-α启动，形成的产物与细胞上的相应受体结合，诱导信号转导反应[35]，最终导致NF-κB被释放并进行核转位。进入细胞核后，NF-κB与基因启动子上的κB原件结合，从而增强各种酶、黏附分子、趋化因子和参与炎症反应的细胞因子的下游基因表达。神经炎症涉及的另一项重要过程是Aβ诱导的小胶质细胞激活，导致各种炎性细胞因子的释放，如IL-1β、IL-6和TNF-α等[36]。这些细胞因子介导的神经毒性过程可能包括通过增强细胞凋亡导致的直接神经元死亡、通过抑制突触功能与海马神经来完成[37]，从而导致认知功能下降。另外，炎症信号如TNF-α或IL-1能够通过丝裂原活化蛋白激酶（mitogen activated protein kinase，MAPK）通路激活c-Jun氨基末端激酶（c-Jun N-terminal kinase，JNK）和p38蛋白，激活后的JNK和p38能磷酸化转录因子，形成激活蛋白-1（activator protein-1，AP-1）复合物，促进IL-6、TNF-α的转录；同时，p38能够激活下游靶点MAPK活化蛋白激酶2（MAPK activated protein，MK2），MK2的激活增加了促炎因子mRNA的稳定性和翻译，共同放大炎症反应。而GLP-1RAs可以抑制NF-κB及MAPK通路的激活[38]，降低细胞外调节蛋白激酶、JNK和p38的磷酸化水平，减少AP-1的活性，从而抑制炎症因子的表达[39]。GLP-1RAs还通过促进磷脂酰肌醇（3，4，5）-三磷酸（phosphatidylinositol 3，4，5-trisphosphate，PIP3）生成，激活AKT蛋白，抑制半胱氨酸天冬氨酸蛋白酶-3（cysteinyl aspartate specific proteinase-3，caspase-3）活性，促进抗凋亡蛋白表达，减少神经元凋亡[40]。此外，GLP-1RAs可显著增加神经生长因子和脑源性神经营养因子的表达，促进神经干细胞向神经元方向分化，增加神经元数量，帮助受损神经组织修复[41]。神经递质在大脑的认知、情感、记忆等功能中也起着关键作用。在DACD患者中，神经递质如乙酰胆碱、多巴胺、γ-氨基丁酸等的合成、释放和代谢均受到影响，导致神经信号传递紊乱，影响认知功能。相关研究表明，GLP-1RAs通过促进胆碱能神经元的活性，增加乙酰胆碱的合成和释放，调节多巴胺和γ-氨基丁酸等水平，维持神经递质系统的平衡，促进神经信号的正常传递，进而改善认知功能[42]。

2.4 肠道微生态 肠道微生物组是定植于人体消化道的复杂微生物群落系统，其多样性特征显著，核心菌群包括厚壁菌门、拟杆菌门、放线菌门及变形杆菌门等主要类群。该生态系统在宿主物质能量代谢调节及免疫稳态维持方面发挥重要作用。当微生物群落发生生态失调时，可能诱发宿主代谢途径异常并引发多种急慢性疾病[43]。研究表明，DACD患者相较于单纯糖尿病患者，其肠道菌群呈现特征性结构改变[44]。肠道菌群可通过肠-脑轴途径与大脑实现双向信息交流，肠道菌群紊乱会诱发糖代谢紊乱、胰岛素信号调节系统异常以及慢性炎症反应等病理过程，使血脑屏障受损，导致海马神经元损伤和胶质细胞增生；同时，神经递质的减少和ROS自由基的聚集加重了认知功能的损伤，从而导致DACD的发生。有研究证实，GLP-1RAs能通过改变肠道微生物群谱，有效缓解糖尿病小鼠模型抑郁和焦虑样行为、增强认知功能、发挥神经保护

作用[45]。因此，进一步探讨GLP-1RAs对DACD患者肠道菌群的作用是极其重要的。

3　结论与展望

综上所述，GLP-1RAs在治疗DACD方面展现出了显著的潜力。其能够通过多种机制如糖脂代谢调控、神经保护、抗氧化应激等改善糖尿病患者的认知功能。目前使用利拉鲁肽或度拉糖肽等药物治疗DACD的临床实验已经完成，其展现出了较好的效果与良好的安全性。其他GLP-1RAs如司美格鲁肽治疗DACD的疗效及安全性的试验正在进行中。未来，GLP-1RAs在改善T2DM患者认知功能方面的应用前景极为广阔，深入研究各种GLP-1RAs的作用特点和优势，开发具有更高选择性和特异性的药物，以增强其疗效及减少不良反应。随着研究深入，GLP-1RAs有望成为DACD治疗及预防的核心药物。

利益冲突　无

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