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# *Adiponectin and Its Receptor Agonist (AdipoRon) in the Treatment of Diabetes-Associated Cognitive Dysfunction: Research Progress*

**Lei Shi[1,a], Qiyang Ding[1,b], Ji Xia[2,c], Nisha Wang[2,d], Xiaohong Lu[3,e,*]**

*[1]Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712046, China*
*[2]Xi'an Jiaotong University, Xi'an, Shaanxi, 710049, China*
*[3]Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712000, China*
*[a]1591155727@qq.com, [b]dingqy2022@163.com, [c]1121466196@qq.com, [d]wnisha@126.com, [e]673089930@qq.com*
*[*]Corresponding author*

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***Abstract:*** China stands out as a nation with a particularly high prevalence of diabetes, making it one of the global leaders in the number of individuals living with this condition. A significant and debilitating complication of diabetes is Diabetic Associated Cognitive Dysfunction (DACD), which in its most advanced form, dementia, becomes the primary cause of mortality among diabetics, second only to cancer. Despite the gravity of this issue, existing treatments for DACD have fallen short in their effectiveness, underscoring the pressing need for the identification of novel therapeutic targets. In this context, AdipoRon, a small molecule that activates adiponectin receptors AdipoR1 and AdipoR2, emerges as a promising candidate for addressing both diabetes and the associated cognitive decline. This comprehensive review delves into the latest research advancements regarding AdipoRon, highlighting the challenges and future research avenues that must be pursued to facilitate its transition from bench to bedside. The aim is to equip healthcare professionals with the knowledge necessary for the effective prevention and management of DACD.

## 1. Introduction

Cognitive impairments encompass a range of issues or deficits in cognitive domains such as attention, memory, reasoning, judgment, and language. These impairments can stem from diverse causes, including age-related decline, neurological conditions (like diabetic brain disease, Alzheimer's), head injuries, or substance misuse. With China's progression towards an aging population, there is a growing focus on diseases associated with diabetes. Statistics from the International Diabetes Federation indicate that the global prevalence of diabetes was 540 million in 2021 and is expected to rise by 46% to 780 million by 2045 [1], China holds the position as the country with the highest number of diabetes patients, with 140 million individuals affected in 2021, accounting for 26.2% of the global diabetes patient population [2]. Ninety percent of these cases are Type 2 diabetes, and the risks of dementia and mild cognitive impairment for these patients are 1.5

times and 1.6 times higher, respectively, compared to healthy controls [3]. The spectrum of cognitive impairments associated with diabetes spans from subtle reductions in cognitive abilities to mild cognitive impairment and, at the most severe end, dementia [4]. Patients with Diabetes-Associated Cognitive Dysfunction (DACD) are at a significantly higher risk for hypoglycemia (double the risk), major cardiovascular incidents (increased by 27%), and mortality (33% higher) when compared to diabetic patients who do not have cognitive impairments [5-7]. Dementia, marking the advanced stage of DACD, has exhibited a stark rise in fatality rates for individuals with diabetes. As documented in The Lancet Diabetes & Endocrinology in 2021, the mortality rate associated with dementia in diabetic populations climbed from 0.9‰ in 2001 to 5.1‰ in 2018, positioning it as the second most frequent cause of death for diabetics, following cancer [8]. Nevertheless, the prevailing strategies for managing DACD center around the early detection of cognitive deficits, followed by interventions that include behavioral and medicinal approaches. These methods are capable of reducing the symptoms of cognitive impairment but do not address the underlying DACD that has already developed [9-12]. The neuroprotective role of adiponectin is well-documented, and its agonist, AdipoRon, has been implemented in diabetes management, demonstrating significant promise in addressing diabetic brain disease.

## 2. The current state of adiponectin research

The neuroprotective action of adiponectin is mediated through the activation of its corresponding receptors. Adiponectin, also known as ADPN, is a plasma protein released by fat tissue, present in the bloodstream at levels of 2-30 μg/mL, constituting 0.01% of the total serum proteins, with a half-life ranging from 2.5 to 6 hours, and its central nervous system concentration is approximately one-thousandth of that found in the plasma. This protein exists in four distinct active configurations: trimers, hexamers, high molecular weight (HMW) multimers, and globular adiponectin (gAD). Primarily found in the periphery as trimers, the HMW multimers exhibit the most potent activity, yet they are incapable of crossing the blood-brain barrier (BBB). In contrast, the other three forms are able to traverse the BBB through receptor-mediated transport and engage with receptors that are extensively present throughout the central nervous system (see Figure 1). The abundance of adiponectin receptors on neuronal surfaces indicates the potential for adiponectin to function as a naturally occurring hormone that protects neural functions [15]. Adiponectin, recognized for its anti-diabetic properties, engages with AdipoR1 and AdipoR2 receptors, triggering the AMPK and PPAR-α signaling pathways. Through these interactions, it promotes insulin sensitivity, combats inflammation, prevents fibrosis, and hinders atherosclerosis in the body's peripheral tissues [16]. Over the recent years, the neuroprotective capabilities of adiponectin have garnered significant global interest, with a surge in studies highlighting its role in neuronal protection and cognitive enhancement [17-18]. Adiponectin mitigates the accumulation of Aβ proteins in microglia via the autophagy-lysosome pathway, thus enhancing cognitive functions in Alzheimer's disease mouse models [19]; following the induction of a cerebral infarction model, intravenous administration of 5mg/kg adiponectin at 6, 24, and 48 hours post-modeling elevated HIF-1α protein levels and transcriptional activity, which in turn increased EPO and VEGF expression, reducing apoptosis and oxidative stress, fostering angiogenesis, alleviating cerebral ischemia-reperfusion injury, and decreasing infarct and atrophy sizes [20]; in sepsis models, intracerebroventricular injection of 0.1 μg/g adiponectin protected neurons and improved cognitive functions by suppressing oxidative stress and apoptosis associated with mitochondrial damage [21], low doses of alcohol increased hippocampal adiponectin levels, activated Nrf2, enhanced antioxidant enzyme expression, curbed oxidative stress, lessened hippocampal damage in mice, and improved cognitive deficits and anxiety-related behaviors induced by high-fat diets [22]; adiponectin also protected ischemic

neurons and improved vascular cognitive impairment and dementia by upregulating PPARγ expression and dampening pro-inflammatory microglial responses [23]. Consequently, adiponectin holds promise as a novel therapeutic target and treatment for cognitive dysfunction, offering dual benefits in diabetic patients by enhancing insulin sensitivity and providing neuroprotection to ameliorate and prevent DACD.

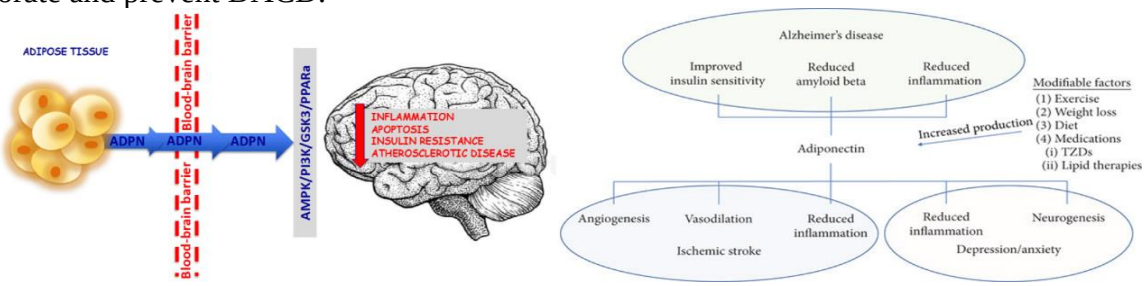


Figure 1: Adiponectin crosses the blood-brain barrier to play a beneficial role in the nervous system [13, 14]

## 3. Adiponectin Substitutes Research Status

The high cost of adiponectin extraction is compounded by the fact that elevated adiponectin levels over time are linked to numerous unfavorable health outcomes, a phenomenon referred to as the "adiponectin paradox". Such high levels are associated with an increased catabolic state and resistance to adiponectin, raising the risks of liver fibrosis in chronic hepatitis and estrogen receptor-positive breast cancer. Individuals with elevated adiponectin levels also face a 1.63-fold and 1.87-fold higher risk of developing dementia and Alzheimer's disease, respectively, compared to those with lower levels. This heightened risk may stem from adiponectin's dual role in regulating amyloid protein expression, which can be beneficial during reproductive years but detrimental in the context of aging. In chronic kidney disease patients, reduced clearance of adiponectin leads to higher levels, and the exogenous administration of adiponectin can further strain the kidneys [24]. Consequently, the search for alternative therapies to adiponectin is an emerging field, focusing on the synthesis of structural analogs and the stimulation of upstream or downstream pathways. Synthetic structural analogs: These are peptides containing adiponectin's active sites, with molecular weights between 500 and 26,000 Da, including ADP355, Osmotin , Os-pep, rCTRP9 [25], peptide P17, peptide 27, BHD-1028, Pep70, Arctiin [26], and recombinant adiponectin [27]. They are produced through bacterial fermentation and are cost-effective for mass production, but their structural differences from mammalian sources and lower activity can be limiting, with excessive modifications potentially reducing receptor affinity. Mammalian-derived structural analogs face challenges such as low expression levels, lengthy production cycles, and high production costs due to cell strain instability. Activating upstream pathways: Medications like etanercept, honghua acid, and rimonabant, which target TNFα, 5-HT, and CB1, respectively, to increase adiponectin levels, have shown limited efficacy and are primarily used for conditions such as rheumatoid arthritis, hair loss, and weight management, rather than for diabetes and related complications. Activating downstream pathways: AdipoRon [28], GTDF, Tiliroside, and others function as adiponectin receptor agonists, while AICAR, metformin, and aspirin act as AMPK activators, and rosiglitazone, telmisartan, and pioglitazone serve as PPAR-γ agonists. Given that AMPK activators and PPAR-γ agonists only partially replicate the effects of adiponectin, AdipoRon stands out among adiponectin receptor agonists for its well-substantiated efficacy in improving diabetes and related conditions. It boasts several advantages, including a small molecular size, low cost, stability, and the ability to cross the blood-brain barrier, making it a highly promising candidate as an adiponectin receptor agonist.

## 4. AdipoRon Targets Diabetes and Cognitive Pathways

The small molecule AdipoRon, an agonist for adiponectin receptors, was first described in Nature in 2013, showing potential in targeting AdipoR1 and AdipoR2, and demonstrating benefits in diabetes models by improving glycolipid metabolism, insulin resistance, glucose intolerance, and lifespan extension (*Okada-Iwabu, M. et al.2013*). AdipoRon has since been the subject of extensive research, with evidence supporting its positive impact on a range of diabetes-related conditions, including metabolic disorders, insulin and adiponectin resistance, osteoporosis, nephropathy, pancreatic cancer, and neurocognitive impairments [29] (see Figure 2). In metabolic disorders, AdipoRon activates the AdipoR1-AMPK pathway, leading to the phosphorylation of ACC, which enhances fatty acid oxidation and glucose uptake in the liver, muscle, and adipose tissue, thereby improving lipid and glucose metabolism [30]; it also activates the AdipoR2-PPARα pathway to boost fatty acid oxidation in the liver and reduce oxidative stress. Regarding insulin and adiponectin resistance, AdipoRon inhibits mTOR-p70S6K and IRS-1 serine phosphorylation through the AdipoR1-AMPK pathway (*Amatya, R. et al.2022*), activates the docking protein APPL1, and facilitates the binding of IRS-1/2 to the insulin receptor, enhancing insulin sensitivity. In hepatocytes and pancreatic β-cells, AdipoRon enhances ceramidease activity related to AdipoR, increases the metabolism of ceramide, and promotes the formation of the anti-apoptotic metabolite S1P, mitigating the lipotoxic effects of ceramide and its metabolites, improving pancreatic β-cell function, reducing apoptosis, and ameliorating insulin resistance[31]. AdipoRon also upregulates AdipoR in rats [32], ameliorating adiponectin resistance [33]. In osteoporosis, AdipoRon inhibits osteoclast differentiation and reduces bone loss, alleviating periodontitis associated with type 2 diabetes [34]. In nephropathy, AdipoRon upregulates AdipoR1 and AdipoR2 expression and activates the AMPK/PPARα pathway, decreasing lipid peroxidation damage in podocytes of diabetic mice [35]. Against pancreatic cancer, AdipoRon inhibits angiogenesis and tumor-associated macrophage infiltration through the AdipoR1-AMPK pathway, exhibiting anti-pancreatic cancer effects [36]. For neurocognitive damage, AdipoRon, being a hydrophobic small molecule, crosses the BBB and improves mitochondrial homeostasis and reduces oxidative stress/neuroinflammation through the AdipoR pathway, promoting neurogenesis and synaptic plasticity in the hippocampus. Intraperitoneal injection of AdipoRon in an acute coronary syndrome model inhibits pro-inflammatory responses in microglia, enhances neuronal survival, increases axonal integrity, and improves learning and memory [37]. In Alzheimer's disease models, intracerebroventricular injection and long-term oral administration of AdipoRon activate the AdipoR1-AMPK pathway, downregulate β-secretase levels, upregulate LDLR, APOE, and neprilysin, facilitate Aβ clearance in the brain, inhibit microglia and astrocyte activation, reduce inflammatory factors, decrease neuronal loss in the cortex and hippocampus, increase synaptic proteins, and promote hippocampal neural stem cell proliferation, improving cognitive dysfunction in Alzheimer's disease model spatial memory functions [38]. AdipoRon also promotes GLUT4 translocation to the plasma membrane, enhancing glucose uptake and insulin signaling, and increasing insulin sensitivity, which is one of the mechanisms by which Alzheimer's disease progresses based on diabetes pathology [39]. In the treatment of intracerebral hemorrhage models, AdipoRon through the AdipoR1-AMPK-PGC-1α axis can promote the generation of neuronal mitochondrial DNA and ATP, reduce the production of mitochondrial reactive oxygen species (ROS), inhibit the collapse of neuronal mitochondrial membrane potential (△Ψm), thereby reducing neuronal damage [40]; it also activates the transition of microglia/macrophages from a pro-inflammatory M1 state to an anti-inflammatory M2 state, reducing neuroinflammation and ROS levels through the Sirt3-SOD2 pathway, thus improving brain damage induced by intracerebral hemorrhage (*Zheng, J. et al.2019*). In 2021, a study reported that streptozotocin injection for 7 days to damage pancreatic cells, selecting hyperglycemic mice as

a type 1 diabetes model, and using 20 mg/kg AdipoRon intraperitoneal injection for 14 days, preliminarily verified that it could increase dendritic branching and spine density through the AMPK-PGC-1α-BDNF signaling pathway, restore synaptic plasticity in diabetic mice, reduce hippocampal atrophy, and improve cognitive impairment [41].

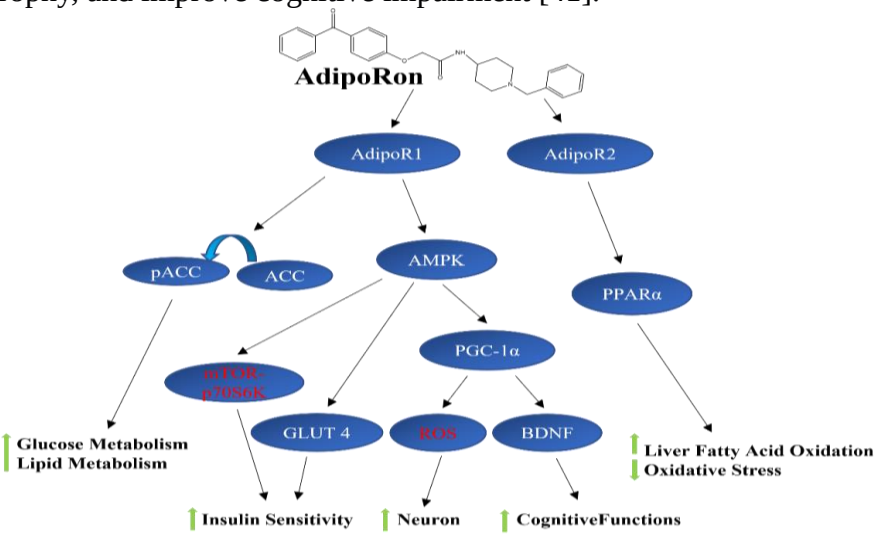


Figure 2: The mechanism of action of AdipoRon

## 5. Conclusions

AdipoRon's strong hydrophobicity and low aqueous solubility, at only 9 mg/L(*Onodera, T. et al.2021*), necessitate the use of DMSO as a solvent for administration via oral, intraperitoneal, or subcutaneous routes [42, 43], which poses a significant risk of embolism if administered intravenously. The use of DMSO as a solvent is not ideal for clinical settings, and the injection methods mentioned are not suitable for long-term administration due to poor patient compliance. When wild-type mice are given a 50 mg/kg oral dose of AdipoRon, they reach a peak blood concentration of 11.8 μM within an hour, with the maximum plasma drug amount being a mere 0.45% of the dose. In Alzheimer's disease models, the same dose results in a peak blood concentration of 16μg/ml after two hours, with the maximum plasma drug amount at only 1.44% of the dose, and a brain drug concentration of 1.9 μg/g after two hours, which is approximately 12.5% of the plasma drug amount, or 1.8‰ of the dose (*Ng, R. C. et al.2021*). This indicates that AdipoRon has low BBB penetration efficiency and poor bioavailability. AdipoRonPEG5, reported in 2021, is a polyethylene glycol-conjugated derivative that increases water solubility by approximately 100 times and peak blood concentration by 3 times. Although its half-life is doubled, it is still only 40 minutes, indicating significant room for improvement (*Onodera, T. et al.2021*). A single carotid artery injection of AdipoRon (5mg/kg) has been shown to not improve brain function (*Clain, J. et al.2022*), but intracerebroventricular injection of 1μg/day for 9 days can reduce Aβ deposition, promote neural stem cell proliferation in the hippocampal dentate gyrus, and ameliorate cognitive impairments in Alzheimer's disease models (*Liu, B . et al.2020*). AdipoRon must act on neuroblastoma cell lines for 24 hours to stimulate neuronal proliferation, and on neural stem cells for 48 hours to promote their proliferation (*Lee, T. H. et al.2021*). Thus, AdipoRon requires an extended period to act on neurons to achieve its maximum effect. In summary, the direct application of AdipoRon is hampered by its poor water solubility, low utilization, short duration of action, and difficulty in targeting the brain. With advancements in modern medicine and the maturation of targeted drug delivery technologies, AdipoRon, with its small molecular size and stability, can be hydrophilic-modified and incorporated into a targeted, sustained-release delivery system. This

system can efficiently penetrate the BBB and selectively release the drug around damaged neurons in DACD over an extended period, enhancing therapeutic effects and reducing adverse effects, thereby improving DACD treatment outcomes.

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