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Narrative Review Article

# The Gut–Brain Axis and Insulin Resistance: Evaluating Alzheimer's Disease as Type 3 Diabetes

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## ABSTRACT

Alzheimer's disease is a progressive neurodegenerative disorder characterized by memory loss and cognitive decline. While traditionally associated with amyloid-beta plaques and tau protein tangles, recent research suggests that metabolic dysfunction, particularly impaired insulin signaling in the brain, may play a central role in its development. This supports the hypothesis that Alzheimer's disease may represent "Type 3 Diabetes." At the same time, the gut–brain axis has emerged as an important system linking gut microbiota to brain function through immune, metabolic, and neural pathways. This paper examines how gut microbiome dysbiosis may contribute to insulin resistance and Alzheimer's disease. Evidence suggests that dysbiosis promotes inflammation and disrupts insulin signaling, but causality remains unclear.

**Keywords:** Alzheimer's; neurodegenerative disorder; insulin signaling; gut–brain axis; gut microbiome dysbiosis; insulin resistance; inflammation; Type 3 Diabetes

## INTRODUCTION

Alzheimer's disease is a progressive neurodegenerative disorder and one of the leading causes of dementia worldwide (1, 2). It is characterized by memory loss, cognitive decline, and behavioral changes that worsen over time. Traditionally, Alzheimer's disease has been explained by the accumulation of amyloid-beta plaques and tau protein tangles in the brain (1, 3). Amyloid-beta (Aβ) and tau are two proteins in the brain that are strongly associated with Alzheimer's disease when they become abnormally aggregated. While these features are well documented, they do not fully explain why the disease begins or why it progresses differently among individuals (1, 2, 4).

In recent years, researchers have begun to explore alternative explanations that focus on metabolic dysfunction in the brain. One important hypothesis is that brain cells in individuals with Alzheimer's disease become less responsive to insulin, a hormone that regulates glucose uptake. Insulin is secreted by the pancreas to facilitate cellular glucose uptake and convert it to energy (3, 5). Insulin resistance refers to a condition in which cells respond less effectively to insulin, resulting in reduced glucose uptake and impaired energy metabolism.

Because glucose is the brain's primary energy source, reduced insulin responsiveness can lead to broader impairments in neuronal energy utilization. This is closely associated with insulin signaling in the brain, which is essential for maintaining normal neuronal function. Disruptions in this signaling pathway may therefore contribute to impaired brain function. This supports the hypothesis that Alzheimer's disease may represent a form of "Type 3 Diabetes" (1, 3). At the same

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time, growing attention has been given to the gut–brain axis, a bidirectional communication system linking the gastrointestinal tract and the central nervous system through neural, immune, and metabolic pathways (5, 6). Previous work has also explored the relationship between the gut and brain, including the potential role of kefir as a probiotic source (7).

The gut microbiome, composed of trillions of microorganisms, plays a key role in regulating metabolism, immune responses, and neural signaling. Disruptions in this microbial community can lead to chronic inflammation, which has been associated with metabolic disorders and neurological conditions. Dysbiosis refers to an imbalance in the gut microbiome characterized by reduced microbial diversity, loss of beneficial bacteria and overgrowth of harmful bacteria.

Dysbiosis is associated with reduced production of short-chain fatty acids (SCFAs), which are normally produced by beneficial bacteria during fiber digestion and help reduce inflammation and maintain gut barrier integrity. In contrast, harmful bacteria may produce increased levels of lipopolysaccharides (LPS), which can trigger inflammation if they enter the bloodstream. Together, these changes promote a pro-inflammatory state that can affect both metabolic and neurological function (6, 8) (Figure 1). This review examines the potential connection between gut microbiome dysbiosis, insulin resistance in the brain, and Alzheimer's disease. By integrating these areas, it may be possible to better understand disease mechanisms and identify new approaches for treatment. A proposed mechanistic pathway linking gut microbiome dysbiosis to Alzheimer's disease involves inflammation-driven insulin resistance and subsequent neuronal dysfunction, ultimately contributing to amyloid-β and tau pathology (Figure 2).

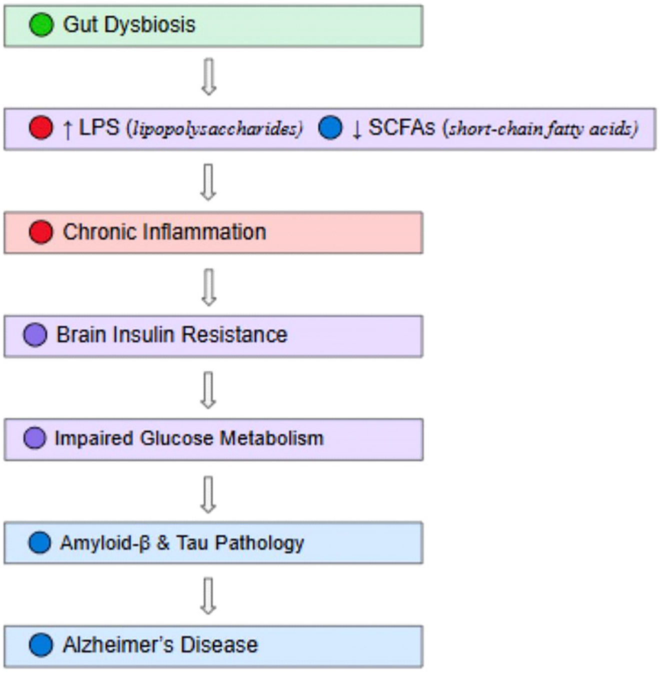

***Figure 2.*** ***Proposed gut–brain–Alzheimer's pathway.*** *Gut microbiome dysbiosis is associated with increased lipopolysaccharide (LPS) levels and reduced short-chain fatty acids (SCFAs), promoting inflammation, brain insulin resistance, impaired glucose metabolism, and Alzheimer's disease–related pathology.*

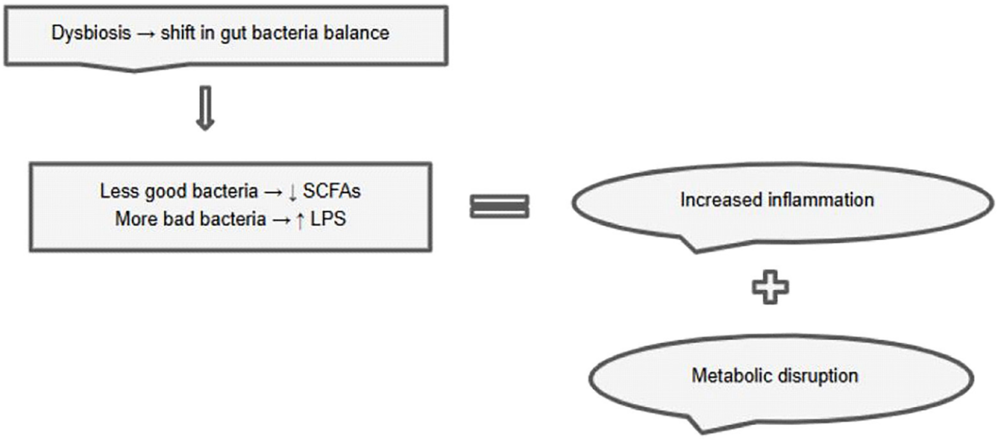

***Figure 1.*** ***Gut dysbiosis-induced metabolic disruption pathway (6, 8).*** *Gut dysbiosis results in a shift in microbial balance, characterized by a reduction in beneficial bacteria and an increase in harmful bacteria. This imbalance leads to decreased production of short-chain fatty acids (SCFAs) and increased levels of lipopolysaccharides (LPS). These changes promote inflammation, which contributes to metabolic disruption.*

## Gut Microbiome and Brain Function

The gut microbiome consists of bacteria, viruses, and fungi that live in the digestive tract. These microorganisms support digestion, vitamin production, and immune regulation. Importantly, the gut microbiome communicates with the brain through the gut–brain axis via three major pathways. First, gut bacteria produce metabolites such as short-chain fatty acids (SCFAs), including butyrate, acetate, and propionate. These help maintain the blood-brain barrier, which protects the brain from harmful substances. When this barrier is disrupted, inflammation may occur in brain tissue (6). Second, the immune system plays a key role in gut-brain communication. Dysbiosis can activate immune responses and increase the production of inflammatory molecules known as cytokines. These molecules can travel through the bloodstream and affect brain function, contributing to neurodegenerative processes (5, 9). Third, the vagus nerve provides a direct neural connection between the gut and the brain. Signals transmitted through this nerve allow the gut microbiome to influence mood, behavior, and cognitive function (3, 5) (Figure 3). When the gut microbiome becomes imbalanced, these communication pathways may be disrupted. Increased intestinal permeability allows harmful bacterial products, such as lipopolysaccharides (LPS), to enter the bloodstream, contributing to chronic inflammation, a known risk factor for Alzheimer's disease (1).

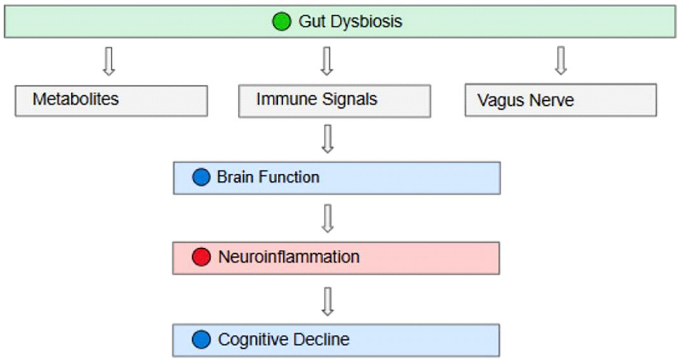

***Figure 3.*** ***Gut–brain axis communication (5, 6, 8, 9).*** *The figure illustrates multiple communication pathways linking gut dysbiosis to changes in brain function and cognition. Gut dysbiosis influences the central nervous system through neural signaling via the vagus nerve, immune-mediated signaling, and circulating microbial metabolites. These pathways alter brain function by disrupting neural activity and physiological regulation. Additionally, gut-derived immune activation and metabolic changes promote neuroinflammation, creating a pro-inflammatory environment in the brain. Over time, the combined effects of altered brain function and sustained neuroinflammation are associated with progressive cognitive decline.*

## Insulin Resistance in the Brain

Insulin regulates glucose metabolism not only in the body but also in the brain (3). Neurons depend on insulin signaling for energy production, synaptic plasticity, and memory formation. Synaptic plasticity, the ability of synapses to strengthen or weaken over time, is essential for learning and memory (2, 3). Impaired insulin signaling reduces energy availability in neurons and disrupts synaptic function. This dysfunction has been associated with increased amyloid-beta accumulation and tau pathology, which contribute to the progressive weakening of synaptic connections and subsequent cognitive decline (3).

When insulin binds to its receptors on brain cells, it activates pathways that regulate glucose utilization and cellular metabolism (3). In individuals with insulin resistance, cells become less responsive to insulin, reducing glucose uptake efficiency. In the brain, this may contribute to an energy deficit, impairing neuronal function. Over time, this reduced metabolic efficiency is associated with cognitive decline and neurodegeneration (2, 3). Insulin resistance leads to impaired insulin signaling, which reduces synaptic plasticity and contributes to memory loss. Insulin resistance → impaired insulin signaling → reduced synaptic plasticity → memory loss (3).

Research has shown that insulin resistance is associated with several key features of Alzheimer's disease. These include increased oxidative stress, mitochondrial dysfunction, and the accumulation of amyloid-beta proteins. Mitochondria are responsible for converting glucose into cellular energy, and mitochondrial dysfunction results in reduced energy availability for neurons. Insulin resistance may also influence tau protein phosphorylation, contributing to the formation of neurofibrillary tangles (3).

Importantly, brain insulin resistance can occur even in individuals without systemic diabetes, suggesting that central insulin signaling may be regulated independently from peripheral insulin function. Factors such as inflammation, oxidative stress, or alterations in insulin receptor signaling in brain cells may selectively impair insulin signaling in the brain (3, 10).

### Molecular Mechanisms of Insulin Signaling

Insulin signaling in the brain involves a series of molecular events that allow neurons to use glucose efficiently. When insulin binds to its receptor on the surface of a neuron, it activates a signaling cascade beginning with insulin receptor substrate proteins (IRS). These proteins activate downstream pathways such as phosphoinositide 3-kinase (PI3K) and protein kinase B (Akt), which regulate glucose metabolism, cell survival, and synaptic plasticity (3).

In Alzheimer's disease, this signaling pathway is disrupted. One key problem is the abnormal phosphorylation of IRS-1, which reduces its ability to transmit signals. As a result, the downstream PI3K/Akt pathway is impaired, leading to reduced glucose uptake and energy production in neurons (3). This disruption has several consequences. First, decreased Akt activity may lead to increased activity of glycogen synthase kinase-3 beta (GSK-3β), an enzyme that promotes tau protein hyperphosphorylation. This contributes to the formation of neurofibrillary tangles, a hallmark of Alzheimer's disease. Second, impaired insulin signaling reduces the clearance of amyloid-beta, allowing plaques to accumulate in the brain (1). Together, these molecular changes link insulin resistance directly to the key pathological features of Alzheimer's disease. This provides strong support for the "Type 3 Diabetes" hypothesis and highlights the importance of metabolic dysfunction in neurodegeneration.

### Gut Microbiome–Insulin Resistance Connection

The gut microbiome plays a significant role in metabolic regulation, including the modulation of insulin sensitivity. Dysbiosis has been associated with the development of systemic insulin resistance through multiple mechanisms, particularly those involving inflammation.

One key mechanism involves the production of lipopolysaccharides (LPS) by certain bacteria. When intestinal barrier integrity is compromised, LPS can enter the bloodstream and activate immune responses. Chronic exposure to LPS promotes low-grade systemic inflammation, which interferes with insulin signaling pathways and contributes to systemic insulin resistance (9). In addition to its role in inflammation, the gut microbiome influences hormonal regulation and energy balance. Alterations in microbial composition can affect the secretion of hormones involved in appetite regulation and glucose metabolism, including insulin and glucagon-like peptide-1 (GLP-1) (6). These metabolic alterations may extend to the central nervous system, where inflammation and impaired insulin signaling can disrupt neuronal function. Collectively, these observations support the hypothesis that gut dysbiosis may contribute to both systemic insulin resistance and brain-specific (central) insulin resistance (3, 6).

### Evidence from Human and Animal Studies

Several studies support a link between the gut microbiome and Alzheimer's disease. For example, Vogt *et al*. (2017) found that individuals with Alzheimer's disease had reduced microbial diversity and differences in specific bacterial groups compared to healthy controls. These changes were associated with increased markers of inflammation (4).

Animal studies further support this relationship. In mouse models, altering the gut microbiome has been shown to influence amyloid-beta accumulation and cognitive performance. For instance, germ-free mice or mice treated with antibiotics showed reduced plaque formation, suggesting that gut bacteria may play a role in disease progression. However, findings remain inconsistent due to differences in diet, geography, and methodology. This variability highlights the need for standardized and large-scale human studies. Despite these limitations, evidence supports an association between gut microbiome alterations, inflammation, and Alzheimer's disease. Observations from *C. elegans* models provide preliminary insight into potential metabolic and microbiome-related pathways (11) (Figure 4).

## CONCLUSION

The connection between the gut microbiome, insulin resistance, and Alzheimer's disease represents an emerging and promising area of research. Current evidence supports significant associations among gut dysbiosis, inflammation, and impaired insulin signaling in the brain; however, causal relationships have not yet been definitively established (6, 7, 9). Within this context, the "Type 3 Diabetes" hypothesis provides a useful conceptual framework for understanding the role of metabolic dysfunction in Alzheimer's disease, while also emphasizing that neurodegeneration likely arises from complex interactions among metabolic, genetic, and environmental factors (1–3).

These mechanistic insights carry important implications for prevention and therapeutic intervention. If gut microbiome alterations contribute to disease

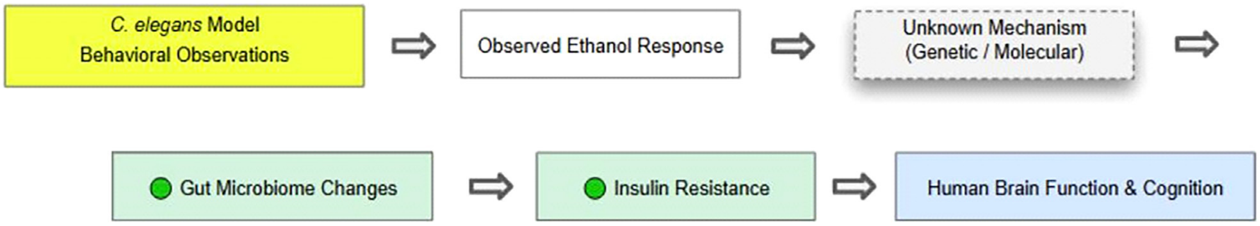

***Figure 4.*** ***From observation to mechanism (11).*** *The figure presents a conceptual framework linking findings from a C. elegans model to potential human outcomes. In the model organism, behavioral responses following ethanol exposure are observed, although the underlying genetic and molecular mechanisms remain unclear. These experimental observations are associated with alterations in gut microbiome composition, which are further linked to the development of insulin resistance. This metabolic disruption is proposed to influence broader physiological processes, providing a potential mechanistic bridge between gut-related changes and systemic effects. In humans, these pathways are associated with altered brain function and cognition, suggesting a potential gut–brain axis influencing cognitive outcomes.*

progression, strategies aimed at modulating the microbiome—such as dietary changes, probiotics (e.g., kefir), and other microbiome-targeted approaches—may help reduce disease risk. For instance, diets rich in fiber can promote the production of short-chain fatty acids (SCFAs), which are associated with reduced inflammation and improved metabolic regulation (6). In addition, the variability of the human microbiome highlights the potential importance of personalized medicine, in which interventions are tailored to individual microbial profiles. Advances in sequencing and bioinformatics technologies may facilitate such approaches in the future.

Building on these implications, further research is needed to clarify the underlying mechanisms and strengthen the evidence base. In particular, longitudinal human studies are essential to determine how changes in the gut microbiome influence the onset and progression of Alzheimer’s disease over time (4). Integrating microbiome research with studies of the gut–brain axis may enable the development of more effective prevention and treatment strategies. Potential therapeutic approaches—including dietary interventions, probiotics, and microbiome modulation—warrant further investigation for their ability to improve insulin sensitivity, reduce inflammation, and support cognitive function (6, 9).

Despite these promising directions, several important limitations must be considered. Much of the current evidence is derived from animal models and observational human studies, which limits the ability to establish causality (4, 7). Human studies are often constrained by small sample sizes and confounding variables such as diet, lifestyle, and genetics (2). Additionally, translating findings from animal models to human disease remains challenging. While the “Type 3 Diabetes” hypothesis offers valuable insight, it does not fully account for all aspects of Alzheimer’s disease pathology (1, 2). Furthermore, the complexity and variability of the gut microbiome present additional challenges for research and clinical application. Differences in microbial composition across individuals make it difficult to identify consistent patterns or universal mechanisms (4, 7).

In summary, these findings highlight both the potential and the current limitations of microbiome-based approaches in Alzheimer’s disease. Continued research integrating metabolic, neurological, and microbiome perspectives will be essential to clarify causality and to translate these insights into effective clinical strategies.

## CONFLICT OF INTEREST

The author declares that there are no conflicts of interest related to this work.

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