JOURNAL OF MULTIDISCIPLINARY SCIENCES AND INNOVATIONS
VOLUME 5, ISSUE 02
MOPNTHLY JOURNALS
ISSN NUMBER: 2751-4390
IMPACT FACTOR: 9,08

TYPE 3 DIABETES MELLITUS: BIOLOGICAL MECHANISMS AND ITS RELATIONSHIP WITH ALZHEIMER'S DISEASE

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Abstract

Type 3 diabetes mellitus is an emerging conceptual framework that links metabolic dysfunction with neurodegenerative processes, particularly Alzheimer's disease. Unlike classical diabetes types that primarily affect peripheral glucose regulation, type 3 diabetes describes insulin resistance and relative insulin deficiency localized within the brain. This impairment disrupts neuronal glucose metabolism, leading to cellular energy deficits, oxidative stress, neuroinflammation, and progressive synaptic dysfunction. Central to this pathology is altered insulin signaling through the PI3K/Akt pathway, which contributes to amyloid-β accumulation, tau hyperphosphorylation, mitochondrial dysfunction, and neuronal loss. Epidemiological evidence indicates that individuals with type 2 diabetes have a significantly elevated risk of developing Alzheimer's disease, supporting the hypothesis that metabolic and neurodegenerative pathways are closely interconnected. Understanding these mechanisms highlights the importance of insulin sensitivity, metabolic regulation, and anti-inflammatory strategies in preserving cognitive function. Although type 3 diabetes is not yet formally recognized as a clinical diagnosis, growing experimental and clinical data underscore its relevance in explaining Alzheimer's pathophysiology and guiding future therapeutic approaches. Continued research may open new preventive and treatment strategies aimed at protecting brain health through metabolic intervention.

Introduction

Diabetes mellitus is among the most widespread chronic disorders globally and affects hundreds of millions of individuals. Traditionally, diabetes is categorized into type 1 diabetes, which involves autoimmune destruction of pancreatic beta cells; type 2 diabetes, characterized by insulin resistance and gradual beta-cell failure; gestational diabetes; and several less common specific forms. In recent years, however, researchers have increasingly discussed a conceptual entity known as "type 3 diabetes."

Type 3 diabetes is not yet an official clinical diagnosis. The term is most often used to describe insulin resistance that occurs specifically within the brain and is believed to contribute to the onset and progression of Alzheimer's disease. Some scientists even refer to Alzheimer's disease as "brain diabetes," emphasizing that impaired insulin signaling in the central nervous system may drive neurodegenerative processes.

It is important to distinguish this concept from type 3c diabetes (pancreatogenic diabetes), which results from structural damage to the pancreas such as chronic pancreatitis or pancreatic tumors. The present discussion focuses on the brain-centered form linked to Alzheimer's disease.

Definition of Type 3 Diabetes

Type 3 diabetes describes a pathological condition in which insulin resistance and relative insulin deficiency develop within neural tissue, even when systemic glucose levels are normal or

only mildly elevated. This disturbance compromises cerebral glucose utilization, leading to neuronal energy deficiency, accumulation of toxic proteins, inflammatory responses, and progressive neuronal injury.

The concept gained prominence in the mid-2000s and has since been reinforced by findings from postmortem brain analyses, experimental animal models, and epidemiological research. These studies consistently show that individuals with type 2 diabetes have a markedly increased risk—approximately two to four times higher—of developing Alzheimer's disease.

Core Mechanisms Underlying Type 3 Diabetes

The central feature of this condition is disruption of insulin signaling within the brain. Several interrelated biological pathways contribute to this dysfunction.

Brain Insulin Resistance

Under physiological conditions, insulin binds to neuronal and glial insulin receptors, activating the PI3K/Akt signaling cascade. This pathway supports glucose uptake, cellular survival, synaptic plasticity, and protection against programmed cell death.

In type 3 diabetes, persistent peripheral hyperinsulinemia—often associated with type 2 diabetes or metabolic syndrome—reduces receptor sensitivity in the brain. As Akt signaling weakens, downstream protective mechanisms fail. Inflammatory mediators, oxidative stress, and vascular injury affecting the blood–brain barrier further aggravate central insulin resistance.

Disrupted Glucose Transport and Energy Production

Neurons depend heavily on glucose to meet their metabolic demands. When insulin signaling is impaired, the activity of glucose transporters—including GLUT1, GLUT3, and insulin-responsive GLUT4—declines. The result is cerebral glucose hypometabolism, a phenomenon consistently observed in early Alzheimer's disease using neuroimaging techniques.

This metabolic shortfall produces a neuronal energy crisis. Although alternative substrates such as ketone bodies may partially compensate, they cannot fully sustain long-term neuronal function.

Amyloid-β Accumulation and Clearance Failure

The insulin-degrading enzyme (IDE) normally metabolizes both insulin and amyloid-β peptides. In states of chronic hyperinsulinemia, IDE preferentially processes excess insulin, reducing amyloid-β breakdown. Consequently, amyloid deposition increases, promoting plaque formation. Impaired insulin signaling also disrupts amyloid clearance across the blood–brain barrier and perivascular drainage systems.

Tau Protein Hyperphosphorylation

Akt signaling ordinarily restrains glycogen synthase kinase-3β (GSK-3β), an enzyme that phosphorylates tau protein. Reduced Akt activity removes this inhibition, allowing excessive tau phosphorylation. Abnormal tau aggregates form neurofibrillary tangles, interfering with neuronal structure and contributing to cell death.

Oxidative Stress and Mitochondrial Injury

Defective insulin signaling compromises mitochondrial efficiency and elevates production of reactive oxygen species. This oxidative burden damages lipids, proteins, and DNA, accelerating neuronal degeneration.

Neuroinflammatory Processes

Insulin resistance stimulates activation of microglia and astrocytes, leading to sustained release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. Advanced glycation end-products and their receptors amplify this inflammatory environment, creating a feedback loop that further weakens insulin signaling.

Synaptic Failure and Neuronal Loss

The combined metabolic, inflammatory, and structural disturbances ultimately impair synaptic integrity, reduce neurogenesis—particularly within the hippocampus—and drive progressive cognitive decline characteristic of Alzheimer's disease.

Comparison of Peripheral and Brain-Centered Insulin Resistance

Type 2 diabetes primarily affects peripheral tissues such as muscle, liver, and adipose tissue, producing systemic insulin resistance and metabolic complications. In contrast, type 3 diabetes is centered within neural tissue, where disrupted insulin pathways contribute directly to neurodegeneration, amyloid accumulation, tau pathology, and cerebral hypometabolism.

Clinical Implications and Preventive Considerations

Individuals with type 2 diabetes or prediabetes face a substantially elevated risk of Alzheimer's disease. Strategies that enhance insulin sensitivity—including regular physical activity, Mediterranean-style dietary patterns, weight control, and effective glycemic management—may reduce this risk. Ongoing research is evaluating therapies capable of crossing the blood–brain barrier, such as insulin sensitizers, GLP-1 receptor agonists, and anti-inflammatory agents, as potential neuroprotective treatments.

Conclusion

Type 3 diabetes provides a valuable framework linking metabolic dysfunction with neurodegenerative disease. Although not formally classified as a diagnostic entity, substantial evidence indicates that impaired brain insulin signaling plays a pivotal role in many Alzheimer's cases. Continued investigation into these mechanisms may guide preventive strategies and innovative therapies aimed at preserving cognitive health through metabolic regulation.

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