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A Review on Metabolic Dysfunction Hypothesis of Alzheimer's Disease

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ABSTRACT:

Alzheimer's disease (AD) remains a formidable challenge in the field of neurodegenerative disorders. This complex disease characterized by progressive cognitive decline and the accumulation of amyloid-beta (Aβ) plaques and neurofibrillary tangles in the brain, leading to progressive cognitive decline and synaptic dysfunction. While the amyloid cascade hypothesis has long dominated the field, emerging evidence suggests a crucial role for metabolic dysfunction in the pathogenesis of AD. The Metabolic Dysfunction Hypothesis posits that disruptions in energy metabolism, including glucose metabolism and mitochondrial function, contribute significantly to the development and progression of AD. This review aims to comprehensively explore the molecular and cellular aspects of the Metabolic Dysfunction Hypothesis, shedding light on the intricate interplay between metabolic disturbances and neurodegeneration in AD.

Keywords: Alzheimer's Disease, Metabolic Dysfunction Hypothesis, Glucose Metabolism, Insulin Signalling, Mitochondrial Dysfunction, Neuroinflammation

Introduction:

Alzheimer's disease (AD), affecting an estimated 50 million people worldwide, stands as a prevalent and formidable neurodegenerative disorder with significant morbidity and mortality rates (World Health Organization, 2021). Global estimates indicate that the prevalence of the disease is expected to triple by 2050. Traditionally, the primary focus of AD research has centred around the pathological hallmarks of the disease, namely the accumulation of amyloid-beta (Aβ) plaques and hyperphosphorylated tau tangles in the brain (Selkoe et al., 2001; Majd et al., 2018).

Theories surrounding the pathogenesis of AD have long revolved around the amyloid cascade hypothesis and the tau hypothesis. The former posits that the accumulation of Aβ plaques is the primary driver of neurodegeneration in AD. Conversely, the tau hypothesis implicates the hyperphosphorylation of tau proteins, leading to the formation of neurofibrillary tangles, as the central event in disease progression (Querfurth et al., 2010; Scheltens et al., 2016). While these theories have significantly shaped our understanding of AD, the "Metabolic Dysfunction Hypothesis" offers a complementary perspective, emphasizing the intricate interplay between metabolic disturbances and traditional neuropathological features (Hardy et al., 1992; Jack et al., 2013).

Metabolic dysfunction, including alterations in glucose metabolism, insulin resistance, and mitochondrial dysfunction, has emerged as a critical player in the initiation and progression of AD (Jack et al., 2018). Impaired glucose metabolism, reflected in reduced cerebral glucose utilization observed through positron emission tomography (PET) imaging, has been consistently identified in AD patients, particularly in brain regions crucial for memory and cognition (Mosconi et al., 2017). Insulin resistance, akin to that seen in type 2 diabetes, has been implicated in AD, influencing not only glucose uptake but also contributing to abnormal tau phosphorylation, a hallmark of neurofibrillary tangles (Talbot et al., 2012).

Furthermore, mitochondrial dysfunction, marked by compromised ATP production and increased oxidative stress, has been identified in the brains of individuals with AD, establishing a link between energy deficits and neurodegeneration (Swerdlow et al., 2018). Understanding the multifaceted nature of metabolic dysfunction in AD provides a novel perspective on disease aetiology.

1. Glucose Metabolism:

The brain, accounting for a small percentage of body weight yet consuming a significant portion of the body's energy. Accounting for approximately 20% of the body's total energy consumption, this organ relies predominantly on glucose as its primary energy source (Cunnane et al., 2020). Disruptions in glucose metabolism, a key element of the "Metabolic Dysfunction Hypothesis", represent early events in AD, occurring even before the manifestation of cognitive symptoms (Cunnane et al., 2020). Positron emission tomography (PET) studies consistently demonstrate reduced glucose metabolism in AD brains, particularly in regions crucial for memory and cognition (Mosconi et al., 2017). This decline in glucose metabolism contributes to synaptic dysfunction and cognitive decline, emphasizing the intricate relationship between energy deficits and neurodegeneration.

Critical to proper glucose metabolism in the brain are glucose transporters, with GLUT1 and GLUT3 playing central roles in facilitating glucose entry into neurons (Wang et al., 2019). Recent research has illuminated the dysregulation of these transporters in AD. The compromised expression and function of GLUT1 and GLUT3 impede the efficient delivery of glucose to neurons, contributing to a state of cerebral hypometabolism (Wang et al., 2019). This diminished energy supply sets the stage for synaptic dysfunction, impairing neuronal communication and ultimately contributing to cognitive decline.

1.1. GLUT1 and GLUT3 in Healthy Brain Glucose Uptake:

Glucose transporters GLUT1 and GLUT3 play pivotal roles in ensuring the efficient uptake of glucose by neurons, which is critical for their energy demands in normal physiological conditions (Simpson et al., 1994). GLUT1, abundantly expressed in the endothelial cells of the blood-brain barrier (BBB), facilitates glucose entry into the brain, while GLUT3, predominantly expressed in neurons, ensures efficient glucose transport across neuronal cell membranes. The coordinated action of these transporters maintains the steady supply of glucose to support the energy-intensive functions of the brain. (Dai et al., 2017).

1.2. Altered Expression of GLUT1 in AD:

In AD, dysregulation of GLUT1 expression disrupts the delicate balance of glucose supply to the brain. Studies have shown a downregulation of GLUT1 in the microvasculature of the AD brain, particularly in regions vulnerable to AD pathology, such as the hippocampus and cortex (Winkler et al., 2015). This reduced expression compromises the glucose transport across the BBB, potentially contributing to the cerebral hypometabolism observed in AD. Additionally, compromised GLUT1 function may hinder the delivery of glucose to neurons, exacerbating energy deficits and impacting neuronal health (Sweeney et al., 2019; Baker et al., 2021).

Dysregulation of GLUT1, has been linked to vascular dysfunction in AD. A compromised BBB function, often observed in AD, disrupts the tight regulation of glucose entry into the brain (Montagne et al., 2017). This dysfunction at the vascular level further underscores the complexity of GLUT1 alterations in the context of AD and their impact on overall brain glucose metabolism.

1.3. Implications of GLUT3 Dysregulation:

GLUT3 dysregulation in AD further complicates the scenario. As a key neuronal glucose transporter, GLUT3 is essential for maintaining energy homeostasis in neurons. Recent studies suggest that GLUT3 expression is altered in AD brains, with some reports indicating reduced levels in specific brain regions (Simpson et al., 1994; Ashrafi et al., 2017; Liu et al., 2021). Recent studies have demonstrated reduced expression of GLUT3 in AD brains, particularly in regions vulnerable to neurodegeneration (Simpson et al., 2016). This downregulation could impair glucose uptake by neurons, compromising their ability to meet energy demands and contributing to synaptic dysfunction. The resulting energy deficits may exacerbate neuronal vulnerability, especially in regions crucial for learning and memory.

1.4. Consequences for Energy Metabolism and Cognitive Function:

The dysregulation of GLUT1 and GLUT3 in AD has profound consequences for energy metabolism and cognitive function. Reduced glucose transport across the BBB and compromised neuronal glucose uptake contribute to a state of cerebral hypometabolism, as evidenced by decreased glucose utilization observed in AD brains using imaging techniques (Wang et al., 2019). This energy deficit, coupled with impaired synaptic function due to compromised glucose supply, contributes to cognitive decline in AD patients. The intricate interplay between GLUT1 and GLUT3 dysregulation thus directly links altered glucose metabolism to the cognitive impairments observed in AD. Reduced glucose uptake due to GLUT1 downregulation at the BBB and compromised GLUT3 function in neurons can lead to synaptic dysfunction and impaired neuronal communication. Furthermore, the intricate relationship between GLUT dysregulation and Aβ pathology suggests a potential link between impaired glucose metabolism and the classic hallmarks of AD.

2. Insulin Signalling:

Insulin, classically recognized for its peripheral role in glucose homeostasis, has a key function in brain physiology, given the brain's status as an insulin-sensitive organ. Abundant insulin receptors in regions crucial for learning and memory, such as the hippocampus, highlight the relevance of insulin signalling in cognitive processes. Disruptions in insulin signalling pathways have the potential to contribute to the pathogenesis of AD, including the accumulation of Aβ plaques and tau hyperphosphorylation. The observed impaired insulin signalling in AD brains aligns with the "Type 3 diabetes" hypothesis, linking brain insulin resistance to neurodegenerative processes (Talbot et al., 2012). This disruption adversely affects the regulation of cellular processes, contributing to Aβ accumulation and tau pathology, central contributors to AD progression (De La Monte et al., 2021).

2.1. Insulin's Role in Aβ Metabolism:

Expanding beyond its classical role, insulin intricately modulates Aβ metabolism. Dysregulated insulin signalling in AD brains influences the processing of the amyloid precursor protein (APP). Altered activities of key enzymes in the proteolytic cleavage of APP, particularly increased β-secretase cleavage, result in the preferential production of Aβ peptides over non-amyloidogenic pathways (Chen et al., 2020). This dysregulation initiates a cascade of events contributing to the early accumulation of Aβ plaques.

2.2. The Significance of Insulin-Degrading Enzyme (IDE):

Central to the insulin-Aβ interplay is insulin-degrading enzyme (IDE), a critical regulator of Aβ levels. IDE is responsible for the degradation of Aβ peptides, modulating their concentrations in the brain. Impaired insulin signalling in AD compromises IDE efficiency, leading to reduced Aβ clearance (Talbot et al., 2012). This compromised clearance mechanism further contributes to the persistence of Aβ aggregates in the AD brain.

3. Mitochondrial Dysfunction and Aβ Overproduction:

As cellular organelles involved in energy production, mitochondria are linked to glucose metabolism and Aβ dynamics. Dysfunctional glucose metabolism is often associated with impaired mitochondrial function, leading to increased oxidative stress. Mitochondrial dysfunction not only contributes to enhanced Aβ production but also exacerbates the accumulation of Aβ through impaired clearance mechanisms. Oxidative stress promotes the formation of Aβ oligomers and fibrils, further propagating the cycle of Aβ pathology (Swerdlow et al., 2018). The interplay between glucose metabolism and mitochondrial function creates a detrimental feedback loop, amplifying the burden of Aβ in the AD brain.

3.1. Mitochondrial-Related Oxidative Stress and Aβ Accumulation:

Mitochondrial dysfunction initiates a detrimental cycle through elevating oxidative stress, a prominent contributor to Aβ pathology. Impaired mitochondrial function in the context of dysfunctional glucose metabolism leads to an increased generation of reactive oxygen species (ROS). This heightened oxidative stress not only damages cellular components but also triggers the aggregation of Aβ, promoting the formation of toxic oligomers and fibrils. The intricate interplay between mitochondrial dysfunction and Aβ dynamics establishes a feedback loop, amplifying the burden of Aβ in the AD brain (Swerdlow et al., 2018).

3.2. Impaired Aβ Clearance:

Mitochondrial dysfunction's impact extends to Aβ clearance mechanisms, further complicating the scenario. Aβ clearance involves various cellular processes, including enzymatic degradation and cellular uptake. Mitochondrial dysfunction hampers these clearance pathways, compounding the persistence of Aβ aggregates in the extracellular space. The impairment directly affects microglial cells, compromising their ability to efficiently clear Aβ deposits. This impaired clearance mechanism adds another layer to the perpetuation of Aβ pathology in AD (Swerdlow et al., 2018; Cai et al., 2021; Yao et al. 2021).

4. The Feedback Loop:

The intricate relationship between glucose metabolism and mitochondrial function sets the stage for a detrimental feedback loop in AD.

4.1. Dysfunctional Glucose Metabolism and Mitochondrial Impairment:

Dysfunctional glucose metabolism compromises the efficiency of mitochondria in producing energy. The consequent reduced ATP production and increased generation of ROS, further disrupts cellular bioenergetics, impacting neuronal health and function (Cai et al., 2021).

4.2. Oxidative Stress and Enhanced Aβ Production:

The compromised mitochondrial function and heightened ROS levels contribute to the oxidative modification of cellular components, creating a microenvironment conducive to enhanced Aβ production. Oxidative stress influences the amyloidogenic processing of APP, favouring the generation of Aβ peptides over non-amyloidogenic pathways (Cai et al., 2021; Swerdlow, 2018). This sets the stage for the accumulation of Aβ plaques.

4.3. Aβ-Induced Mitochondrial Impairment:

Aβ, once generated, instigates a second wave of mitochondrial impairment, perpetuating the feedback loop (Majd et al., 2007). Aβ aggregates interact with mitochondrial membranes, disrupting their structural integrity and impairing function (Manczak et al., 2011). Mitochondria become more susceptible to calcium dysregulation, further escalating oxidative stress and impairing ATP production. This exacerbates the cellular energy deficit, contributing to synaptic dysfunction and neurodegeneration.

4.4. Impaired Cellular Bioenergetics:

The self-reinforcing loop creates a state of chronic cellular bioenergetic deficits. Dysfunctional glucose metabolism, mitochondrial impairment, and enhanced Aβ production collectively contribute to an ongoing energy crisis within neurons. The compromised ATP production and energy supply significantly impact cellular processes, impairing neurotransmission, and ultimately leading to synaptic dysfunction and cognitive decline (Cai et al., 2021).

5. Neuroinflammation and Aβ Accumulation:

The intricate relationship between dysfunctional glucose metabolism and neuroinflammation unfolds as a dynamic interplay with profound implications for the accumulation of Aβ in AD. Dysfunctional glucose metabolism not only initiates neuroinflammatory responses but also establishes a self-perpetuating cycle, disrupting the equilibrium between Aβ production and clearance.

5.1. Dysfunctional Glucose Metabolism and Provoked Neuroinflammatory Responses:

The cascade commences with dysfunctional glucose metabolism, a prominent feature in AD pathology. Impaired glucose utilization triggers robust neuroinflammatory responses characterized by the activation of microglia and astrocytes. These immune cells release a spectrum of inflammatory mediators, including cytokines and ROS, creating a pro-inflammatory milieu within the brain microenvironment (Heneka et al., 2015). This chronic inflammation serves as a catalyst for the dysregulation of Aβ dynamics.

5.2. Inflammatory Perturbation of Aβ Homeostasis:

Chronic inflammation disrupts the delicate balance governing Aβ production and clearance. Inflammatory mediators, particularly cytokines, impede the mechanisms responsible for Aβ clearance, hindering the effective removal of Aβ aggregates from the brain. Simultaneously, these inflammatory signals induce the expression of enzymes involved in Aβ production, promoting the amyloidogenic processing of APP and exacerbating the accumulation of Aβ (Heneka et al., 2015). This imbalance tilts the scale towards increased Aβ generation and diminished clearance, assisting creating a pro-amyloidogenic environment.

5.3. Neuroinflammation Driving Aβ Pathology:

The ensuing neuroinflammation establishes a microenvironment that perpetuates a vicious cycle. The sustained inflammatory milieu not only amplifies dysfunctional glucose metabolism but also contributes to the persistence of Aβ pathology. Inflammatory signals sustain the activation of microglia and astrocytes, ensuring the continuous release of cytokines and ROS, further intensifying the pro-inflammatory state. This sustained inflammation reinforces the dysregulation of Aβ dynamics, creating a self-reinforcing loop that drives the relentless progression of AD (Heneka et al., 2015).

6. Therapeutic Implications:

Understanding the metabolic dysfunction hypothesis opens avenues for therapeutic interventions in AD. Lifestyle modifications, including diet and exercise, have shown promise in mitigating metabolic dysfunction and improving cognitive outcomes. Targeting insulin signalling pathways and promoting glucose metabolism through pharmacological agents represent potential therapeutic strategies. Additionally, compounds with anti-inflammatory properties may attenuate the neuroinflammatory responses associated with metabolic dysfunction. Recent research highlights the potential of strategies aimed at restoring normal glucose metabolism, including interventions to promote the expression and function of glucose transporters (Cunnane et al., 2020). These approaches may hold the key to mitigating the early metabolic disturbances observed in AD and, consequently, slowing the progression of cognitive decline.

Conclusion:

The “Metabolic Dysfunction Hypothesis” of AD represents an innovative departure from the traditional understanding of the disease's aetiology and offering a more comprehensive and integrative framework that acknowledges the multifaceted nature of AD’s origins. In the conventional model, the focus predominantly centred on the pathological hallmarks of Aβ plaques and tau tangles. However, the Metabolic Dysfunction Hypothesis urges a broader perspective, recognizing AD as not solely a brain-centric disorder but one with systemic underpinnings to metabolism (Figure 1.)

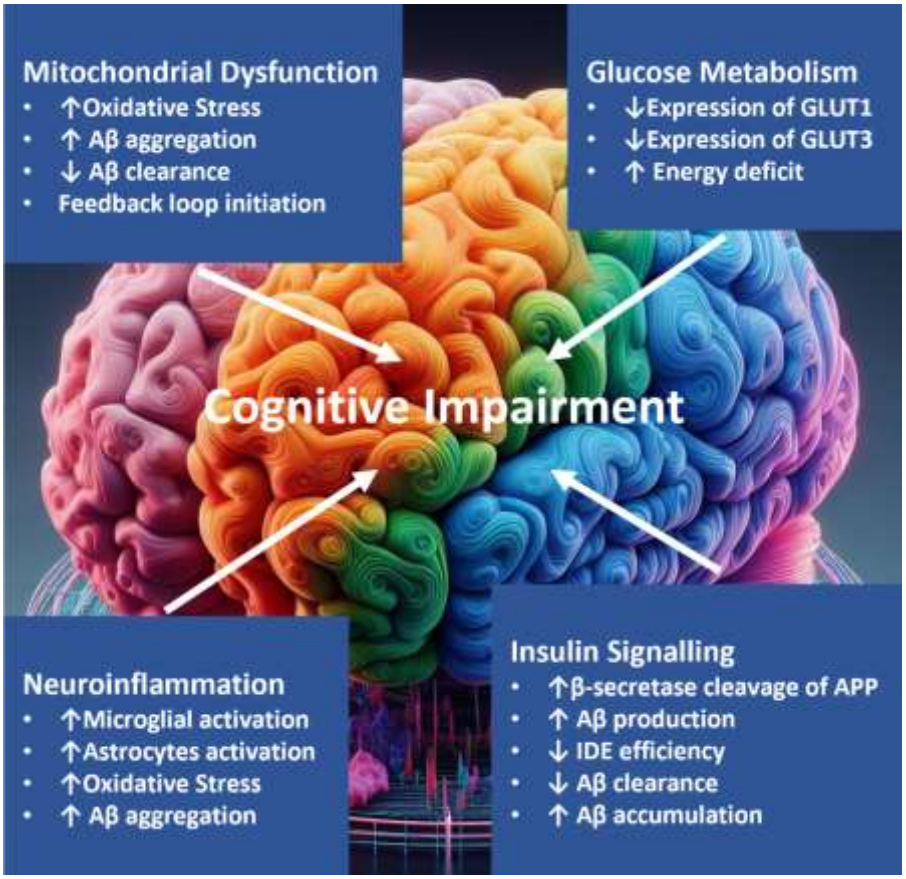

Figure 1: Simplified Schematic Illustration of the Metabolic Dysfunction Hypothesis of Alzheimer's Disease. Aβ: Beta- Amyloid; APP: Amyloid Precursor Protein; IDE: Insulin-Degrading Enzyme

The "Metabolic Dysfunction Hypothesis" explain the intricate connections between systemic factors involved in energy production and neurodegeneration. It contends that disturbances in glucose metabolism, insulin resistance, and mitochondrial dysfunction are not mere consequences of the disease but integral contributors to its initiation and progression. This paradigm shift prompts a re-evaluation of therapeutic approaches, advocating for interventions that address both the neurological and metabolic facets of AD. Therapeutic interventions designed to target both neurological and metabolic factors may hold greater promise in halting or slowing the progression of the disease. This paradigm shift also necessitates a transformation in research methodologies, encouraging interdisciplinary collaboration between neuroscientists, endocrinologists, and metabolism researchers to unravel the complex interplay between metabolic dysregulation and neurodegeneration.

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