Review Article

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Aberrant energy metabolism in Alzheimer's disease

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ABSTRACT

To maintain energy supply to the brain, a direct energy source called adenosine triphosphate (ATP) is produced by oxidative phosphorylation and aerobic glycolysis of glucose in the mitochondria and cytoplasm. Brain glucose metabolism is reduced in many neurodegenerative diseases, including Alzheimer's disease (AD), where it appears presymptomatically in a progressive and region-specific manner. Following dysregulation of energy metabolism in AD, many cellular repair/regenerative processes are activated to conserve the energy required for cell viability. Glucose metabolism plays an important role in the pathology of AD and is closely associated with the tricarboxylic acid cycle, type 2 diabetes mellitus, and insulin resistance. The glucose intake in neurons is from endothelial cells, astrocytes, and microglia. Damage to neurocentric glucose also damages the energy transport systems in AD. Gut microbiota is necessary to modulate bidirectional communication between the gastrointestinal tract and brain. Gut microbiota may influence the process of AD by regulating the immune system and maintaining the integrity of the intestinal barrier. Furthermore, some therapeutic strategies have shown promising therapeutic effects in the treatment of AD at different stages, including the use of antidiabetic drugs, rescuing mitochondrial dysfunction, and epigenetic and dietary intervention. This review discusses the underlying mechanisms of alterations in energy metabolism in AD and provides potential therapeutic strategies in the treatment of AD.

Key words: Alzheimer's disease, energy metabolism, nerve cells, gut–brain axis

INTRODUCTION

The brain, accounting for approximately 2% of the adult body weight, consumes over 20% of energy under physiological conditions.[1] Brain energy metabolism mainly relies on adenosine triphosphate (ATP), which is used by Na^+/K^+-ATPase and Ca^{2+}-ATPase to maintain transmembrane ion gradients during neuronal signal transduction.[2, 3] Among the brain neurons, excitatory (glutamatergic) neurons utilize 80%–85% of the brain's total ATP, while the remaining neurons are inhibitory.[1, 4] ATP released from neurons, astrocytes, and microglia is also involved in a multitude of processes including immune response, axonal transport, microglial motility, DNA repair, and protein production.[5] Ninety-five percent or more of the ATP in the brain is produced by glucose metabolism, which is absorbed from the neurovascular unit, including brain capillary endothelial cells, pericytes, astrocytes, oligodendrocytes, microglia, and neurons.[6] In normal conditions, glucose uptake is driven by the energy requirements of the activated neurons in different regions of the brain. Glucose transport in the cortex, hippocampus, and cerebellum is associated with glucose transporters including glucose transporter 1 (GLUT1) (the capillary endothelium, membrane of astrocytes, and oligodendrocytes), GLUT2 (plasma membrane of astrocytes), GLUT3, and GLUT4 (neurons).[7-9] Glucose reaches the neurons

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Access this article online

Website: www.intern-med.com

DOI: 10.2478/jtim-2022-0024

either by diffusing directly or by being channeled by the end-feet of astrocytes surrounding the capillary walls. In astrocytes, glucose is metabolized to ATP or converted to lactate, an alternative energy source.[10] The ATP is predominantly generated by oxidative phosphorylation of glucose via the tricarboxylic acid cycle (TCA cycle) within the mitochondria.[11]

Research has shown that aberrant brain energy metabolism is involved in the progression of disorders of the central nervous system (CNS), such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and frontotemporal dementia (FTD).[12-14] AD is the most common neurodegenerative disease and is characterized by extracellular senile plaques composed of amyloid-β (Aβ) and intracellular neurofibrillary tangles (abnormal phosphorylated tau aggregates) within the neocortex.[15] Additional pathological changes, beyond Aβ and tau, are incompletely understood. Evidence has demonstrated that impaired brain energy metabolism is involved in the progression of AD, and may occur before clinical symptoms arise, driving, and being driven by cognitive dysfunction in a destructive cycle.[16, 17] For example, positron emission tomography (PET) studies showed that glucose uptake is 10%–12% lower in the entorhinal cortex and parietal lobes of patients with mild cognitive impairment (MCI), which becomes anatomically widespread in the progression of AD.[1] Lower glucose uptake, TCA activity, mitochondrial function, and energetic transport of astrocytes and oligodendrocytes are associated with AD; therefore, weight loss and type 2 diabetes mellitus (T2DM) are considered a particular type of AD.[18, 19] Neuroinflammation is one of the pathological features of AD, rapidly consuming glucose and depleting energy to the neurons.[20, 21] The regional brain metabolism impairment may distinguish AD from other pattern dementia, including FTD, PD, or Lewy body disease.[22]

ENERGY BALANCE OF NERVE CELL MICROENVIRONMENT IN AD

Neuron

The brain, one of the most energy-dependent organs in the body, relies primarily on glucose for its energy requirements under physiological conditions. Dysfunction of energy supply has been demonstrated in CNS disorders, including AD. Cerebral glucose metabolism in patients with AD is significantly diminished compared to that in controls. However, cognitive dysfunction is correlated with a reduced glucose metabolism in the regions dependent on glucose metabolism such as the posterior cingulate and parietal, temporal, and prefrontal cortices.[18, 23] In AD, energy-related metabolisms, such as TCA cycle, oxidative phosphorylation, ATPase, glycolysis, ketone body, and creatine metabolisms, are significantly dysregulated.[18, 24] Increasing evidence has shown that syndrome components including T2DM display increasing risk of MCI and AD.[25, 26] Insulin resistance plays an important role in the progression of T2DM, which is observed in approximately 80% of the patients with AD.[27] Insulin signaling pathways, including altered levels of insulin and insulin-like growth factor (IGF), are impaired in the brains of AD patients.[28, 29] Insulin-related signaling pathways play a key role in energy homeostasis, neuronal survival, and memory processes, all of which are critical for learning and cognitive functions in the cortical and hippocampal areas.[30] Thus, insulin may directly modulate cognitive ability. Insulin signaling dysfunction impairs Aβ degradation or *vice versa* and contributes to neurotransmitter release, neuronal survival, and cognitive damage, thereby leading to AD.[31] Soluble Aβ oligomers bind to membrane insulin receptors in the neurons, leading to cytotoxicity.[32] The insulin-degrading enzyme (IDE) degrades both insulin and Aβ and has a higher affinity to bind to insulin. In mice lacking IDE, Aβ degradation was reduced, leading to Aβ deposits in the brain.[33] In addition to Aβ metabolism, insulin and IGF1 regulate the expression and phosphorylation of tau by activation of related kinases,[34, 35] including the tau kinases (glycogen synthase kinase[GSK]-3β, c-Jun N-terminal kinase [JNK], and adenosine 5'-monophosphate-activated protein kinase [AMPK]) and the tau phosphatases (PP2A and PP1), which play an important role in tau pathology.[36] In insulin receptor substrate 2 (IRS-2)-deficient mice, tau phosphorylation is increased by disrupting the tau kinases.[37] Altered insulin signaling in the brain promotes tau cleavage and restricts alternative splicing of tau.[38-40]

A number of energy-related enzymes, which play an important role in the function of the TCA cycle, are dysregulated in AD. The dysfunction of the AMPK signaling pathway may be involved in AD as AMPK is a key sensor and regulator of energy metabolism. Increased AMPK phosphorylation has been observed in the brains of patients with AD and mice models.[41, 42] Neurofibrillary tangles, aggregates of hyperphosphorylated tau protein, are the main pathological markers of AD and are regulated at numerous sites by AMPK.[43, 44] In contrast, activation of AMPK decreases the accumulation of Aβ both *in vitro* and *in vivo*.[45] Thus, AMPK modulates energy metabolism, affecting both tauopathy and amyloidogenesis in AD. The mammalian target of rapamycin (mTOR) signaling pathway also regulates protein synthesis, mitochondrial function, and energy homeostasis, which affect aging and neurodegeneration. Several studies have shown that the mTOR signaling pathway is aberrantly upregulated in the brains of patients with AD and mouse models during

neurodegeneration, resulting in association with Braak stages and/or cognitive decline in patients with AD.[46-48] The upstream signaling pathway of mTOR, PI3K/Akt axis, was also impaired in AD.[49, 50] Reports have shown that continuous activation of PI3K/Akt/mTOR signaling in neurons inhibits the insulin receptor substrate 1 (IRS1) in the brains of MCI, patients with AD, and AD models, demonstrating energy metabolism dysfunction in AD pathology.[51, 52] Poly(ADP-ribose) polymerase-1 (PARP-1) plays an important role in maintaining genome stability, transcriptional regulation, and long-term potentiation.[53] Under pathological conditions, excessive activation of PARP-1 results in nicotinamide adenine dinucleotide (NAD^+) depletion, inducing abnormal energy metabolism in the mitochondria by regulating the expression of mitochondrial proteins.[54] PARP-1 activity and PAR accumulation are enhanced in AD, particularly in the neurons of the frontal and temporal lobes.[55] In the mitochondria, Aβ contributes to PARP-1 over-activation, inducing energy metabolism dysfunction and alterations in mitochondrial membrane potential by superoxide radical production.[56, 57] Also, TCA substrates prevent PARP-1-mediated neuronal damage by inhibiting the oxidative stress induced by Aβ.[58, 59]

Recent studies have shown that vascular mechanisms also play an important role in the metabolic alterations in AD. [60-62] In aged individuals, cerebral amyloid angiopathy occurs in the brain vasculature and is more severe in AD.[63] The neurovascular unit consists of neurons, astrocytes, and vasculature. It is required to maintain basic energy metabolism and brain function. In AD, Aβ, which is involved in vascular pathology, induces progressive neurovascular unit dysfunction, characterized by vascular reactivity failure, smooth muscle cell loss, and vessel integrity breakdown.[64] Functional hyperemia, which disturbs neurodegeneration, is also perturbed in AD.[65, 66]

In the adult brains of animals and humans, neurogenesis is mainly located in the subventricular zone (SVZ) of the lateral ventricle and the subgranular zone (SGZ) of the dentate gyrus (DG) in the hippocampus.[67-69] Hippocampal neurogenesis contributes to the progression of learning and memory and inhibition of neurogenesis hampers trace-related memory formation.[70, 71] Energy metabolism affects the proliferation of neural stem cells and the differentiation of newborn cells, modulating neurogenesis in the AD brain.[72, 73] In neurogenesis, the expression of energy metabolism-related proteins, including insulin-like growth factor binding protein 3, cytochrome c oxidase, and acetyl-coenzyme A synthetase 1, is dysregulated in AD.[74-76] These data indicate that abnormal metabolism in neurons, related to energy-related enzymes, may facilitate the process of AD.

Vascular endothelial cells

To sustain tissue homeostasis, blood vessels formed by endothelial cells (ECs) contribute to the delivery of oxygen and nutrients and the removal of metabolites.[77] To meet the energy requirements of tissue cells, ECs migrate from existing vessels forming new blood vessels in a process called angiogenesis.[78] In nutrient exchange, various organotypic metabolism mechanisms occur, for example, the brain and skeletal muscles rely on glucose as the main energy substrate, whereas the heart and brown adipose tissue favor fatty acids.[79] In the brain vasculature, nutrients are transported in the form of a continuous, nonfenestrated, tightly sealed endothelium.[80]

The main components of the neurovascular system, the ECs, play an important role in maintaining the integrity of the blood–brain barrier (BBB). In AD, neurovascular system impairment leads to reduced brain perfusion and disruption to the BBB leading to the entry of neurotoxic metabolites, resulting in synapse loss.[81, 82] It is also associated with the upregulation of angiogenic factors and receptors, including ETS-related gene (ERG), FMS-related tyrosine kinase 1 (FLT1), and von Willebrand factor (VWF).[83] The ECs fuel their own energy from glycolytic breakdown of glucose or lactate, even under quiescent conditions.[84] The GLUT1 in ECs facilitates glucose diffusion, which is regulated by vascular endothelial growth factor(VEGF).[85] Levels of GLUT1 in the BBB are higher than those in other organs, and reduced GLUT1 levels lead to decreased glucose delivery and lower cerebrospinal fluid (CSF) glucose levels.[86, 87] Reduced GLUT1 levels may be characterized by seizures, movement disorders, and neurodevelopmental delays.[87, 88] The downregulation of GLUT1 is related to microvascular impairment and BBB dysfunction, exacerbating AD.[89, 90] Growing evidence suggests that mitochondrial dysfunction precedes the onset of AD,[91] by causing vascular degeneration and hypoperfusion, and cognitive dysfunction.[92] Mitochondrial dysfunction produces reactive oxygen species (ROS), which contributes to ECs apoptosis, BBB damage, and degeneration.[93] The activation of NADPH oxidase(NOX) may also contribute to EC dysfunction.[93, 94] For example, NOX2 knockout in ECs abrogates ROS production and vascular dysfunction in AD.[95, 96] In conclusion, vascular endothelial cells transport energy elements and metabolic waste bidirectionally between the blood and the brain in a receptor-dependent manner, modulating the development of AD.

Astrocyte

Astrocytes, structure support cells, play critical roles in contacting neurons and maintaining a milieu for proper neuronal function, such as regulating ion channels, providing metabolites for neurons, and sustaining the

integrity of the BBB.[97] Communication between astrocytes and neurons contributes to the regulation of brain signaling and synaptic functions. Astrocytes also release nutrients, such as the bioenergetic substrate lactate, glycogen-derived lactate, and pyruvate, which protect neurons from nutritional damage and maintain homeostatic synaptic plasticity.[4, 98, 99] Aging results in a shift of brain energy metabolism into an age-dependent astrocytic metabolic form.[100] Lactate released from anaerobic glycolysis in astrocytes becomes the main energy source for neurons.[2, 101] However, the age-dependent astrocytic metabolic shift exacerbates the brain hypometabolic state, which is caused by mitochondrial oxidative metabolism in astrocytes.[102] In the hippocampus and cerebellum, the transport and metabolism of glucose are faster in astrocytes than those in neurons. Therefore, astrocytes may have a greater impact on glucose metabolism in the brain than neurons.[103] Glucose metabolism is the main energy source for brain function. However, glucose transport and utilization dysfunction are found in cognitively normal individuals with AD risk genes and in patients diagnosed with early AD.[104, 105] Although the precise mechanisms contributing to the disorder of glucose metabolism in AD is still unclear, the GLUT1 in astrocytes may play an important role in glucose transport. The GLUT1 is reduced in the brain of patients with AD [106] exacerbating the pathophysiological progression of AD.[89] However, increasing the expression of GLUT1 in AD mice decreased the Aβ content.[89]

The change in the morphology and function of astrocytes in the brains of AD mice and humans is known as astrogliosis. The Aβ may be responsible for the activation of glial cells.[107, 108] Studies showed that a reduction in glucose metabolism contributes to plaque formation. In astrocytes, glycolysis plays an important role in amyloid accumulation and cytotoxicity, and the inhibition of glycolysis leads to the accumulation of Aβ and Aβ-induced cytotoxicity.[109] In postmortems of the brain tissue of patients with AD, astrocytes were surrounded by plaques,[110] which may reduce amyloid plaque deposits.[111] Bioenergetic dysfunction in astrocytes may contribute to amyloid accumulation and cytotoxicity via glycolysis, and inhibition of astrocytic 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) may lead to Aβ accumulation and cytotoxicity.[109] Astrocytes can internalize different forms of Aβ into lysosome-like granules, as shown in the brain tissue of patients with AD.[112, 113]

Cholesterol synthesis in astrocytes is maintained at a low rate due to the BBB. Astrocytes have higher cholesterol levels in their membranes, crucial for cholesterol metabolism, than neurons.[114] The higher cholesterol content in the astrocyte membrane is susceptible to an Aβ-induced Ca^{2+}-dependent influx.[115] Consequently, the increased production of nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase and free radicals activates PARP, thereby impairing the NAD^+ cycle.[116, 117] Apolipoprotein E (ApoE) is secreted mainly from astrocytes and plays an important role in both cholesterol metabolism and the degradation and clearance of Aβ. The uptake of Aβ may be associated with surface ApoE receptors, including low-density lipoprotein receptors (LDLR) and low-density lipoprotein receptor-related protein 1 (LRP-1),[107] ultimately leading to oxidative stress and neuronal degeneration. Thus, metabolic dysfunction in astrocytes leads to Aβ accumulation, oxidative stress, and damage to cholesterol metabolism, contributing to AD.

Microglia

As the resident macrophages, microglia prevents damage to the neurons by clearing toxic proteins, such as toxins, infectious agents, and pathogens. The hyperactivation of microglia plays a key role in neuroinflammation, neurodegenerative diseases, and neuronal energy dysfunction.[118, 119] Energy from microglia is rooted in oxidative phosphorylation; however, a shift to an aerobic glycolysis-predominant phenotype occurs in neurodegenerative diseases via the upregulation of GLUT1 and GLUT4 expression.[120, 121] When neuroinflammation is sustainably induced, activated microglia require more energy, thereby reducing the available energy to the neurons.[122] Recent studies showed that microglia dysfunction is correlated with an increased risk of AD, whereas microglia recovery may slow disease progression.[123, 124] Unlike astrocytes, microglia do not directly provide energy to neurons. However, during inflammation, local neurons retrieve lactate from the activated microglia.[125]

Increasing evidence indicates that neuroinflammation and oxidative stress as a consequence of microglial activation are associated with AD pathophysiology.[123] In AD, the role of microglia is dynamically regulated depending on the stage of the disease.[126] However, the relationship between microglial bioenergetics, neuroinflammation, and brain energy in AD is poorly understood. Studies using multiple-tracer PET showed that glucose hypermetabolism of inflammatory cells was observed in the brains of patients with AD and not in healthy individuals.[127] Microglial energy metabolism contributed to neuroinflammation by regulating glycolytic flux and enzyme expression in mitochondria.[64] Furthermore, the triggering receptor expressed on myeloid cells 2 (TREM2) was identified as a risk factor for AD in coding variants.[128] Microglia TREM2 mice exhibited dysfunctional ATP levels and biosynthetic pathways, altering the cellular energetic and biosynthetic metabolism processes in AD.[129] These results demonstrated that microglia energy metabolism dysfunction limits the energy available to

neurons and activates neuroinflammation, accelerating the pathology of AD.

GUT–BRAIN AXIS DYSFUNCTION IN ENERGY METABOLISM OF AD

The gut microbiota modulates the overall energy homeostasis, inhibits intestinal surface pathogen adhesion, synthesizes vitamin K, salvages energy from short-chain fatty acid production, regulates the immune system, and maintains the integrity of the intestinal barrier.[130, 131] Recent studies demonstrated that gut microbiota plays pivotal roles in adjusting bidirectional communication between the gastrointestinal tract and the brain.[132, 133] Studies showed that exogenous butyrate generated by the gut microbiota facilitated the confirmation of dendritic spines, long-term potentiation, and cognitive formation.[134] Gut microbiota also synthesizes neurotransmitters essential for brain activity, including gamma-aminobutyric acid, butyrate, 5-hydroxytryptamine, dopamine, serotonin, and histamine, which can be released into the bloodstream and can cross the BBB.[135-138] Disruptions and changes in the gut microbiota (dysbiosis) are involved in the pathogenesis of many CNS diseases, including autism, PD, schizophrenia, multiple sclerosis, and AD.[139-141] In individuals with AD, reduced microbiota levels can decrease the level of the by-product, butyrate, in the brain, aggravating cognitive dysfunction.[142] In AD mouse models, the *Firmicutes* numbers were reduced and the *Bacteroides* numbers increased in the intestine, leading to amyloid deposition.[143] Correspondingly, Aβ pathology was alleviated in the cerebrum in germ-free AD mice.[143] Several species of gram-negative bacteria produce lipopolysaccharide (LPS), contributing to the prolonged elevation of Aβ in the hippocampus of AD patients, resulting in cognitive dysfunction.[144] Recently, studies showed that treatment with a probiotic mixture containing *Bifidobacterium longum* and different *Lactobacillus* strains positively influenced the cognitive function and metabolic status of patients with AD.[145] In addition, *Helicobacter pylori (H. pylori)* induced high levels of amino acids, activating the mammalian target of rapamycin complex 1 (mTORC1), modulating AD.[146] Furthermore, *H. pylori* modulates the hyperphosphorylation of tau proteins in AD.[147] Thus, the gut–brain axis provides another potential explanation for energy metabolism dysfunction in AD.

POTENTIAL THERAPIES FOR AD BASED ON BRAIN ENERGY METABOLISM

At present, there are many different metabolic pathways and processes that reduce brain energy metabolism dysfunction in AD, including supporting mitochondrial function, maintaining the stability of the TCA cycle, increasing insulin sensitivity, and restoring downstream signaling.[1] A proprietary tricyclic pyrone, CP2, enhanced mitochondrial biogenesis by binding to and inhibiting complex I, thereby improving cognitive function in transgenic AD mice.[148] In AD, mitochondrial division decoupled from the normal fission–fusion cycle is increased, and inhibiting mitochondrial fission improves mitochondrial biogenesis thereby improving functioning of complex I.[149] The ratio of NAD^+/NADH is also a marker of brain energy status, reflecting the redox state of cells. Furthermore, a higher ratio of NAD^+/NADH or NAD^+ precursor nicotinamide riboside mitigates cognitive impairment in AD by improving the energetic status of the brain.[17, 150] Clinical trials demonstrated that patients with AD following ketogenic diets containing medium-chain triglycerides and very low carbohydrate ketogenic diets showed increased cognitive ability in most adherent patients, in contrast to the control group.[151, 152] The mechanisms might be associated with the retrieval of TCA cycle activity, which increases the levels of acetyl-CoA, thereby fueling aerobic glycolysis in the AD brain.[153-155] Peripheral insulin sensitivity, which depends on energy intake or use, is correlated with energy metabolism in the brain. Liraglutide is a GLP1 receptor agonist approved for the treatment of insulin resistance, obesity, and T2DM.[156] Liraglutide enhances glucose uptake in the brain; however, it has no effect on cognitive outcomes.[157] Dipeptidyl peptidase 4 (DPP4) inhibitors, other T2DM medications, prolong the activation of GLP1, and sitagliptin improves cognitive damage in older individuals suffering from diabetes with or without AD.[158, 159]

CONCLUSION

Here, we demonstrated that brain energy metabolism dysfunction, including reduced glucose uptake, insulin resistance, impaired TCA cycle, and glycolysis, is involved in the pathology of AD, which impairs axonal transport, mitochondrial function, and ATP production. In addition, brain energy metabolism may serve as a potential biomarker for AD treatment. Based on the multiple brain energetic pathways, many pharmacological agents targeting metabolic enzymes, receptors, or proteins are used to ameliorate cognitive function by enhancing the energy metabolism level in AD. This simultaneously clears aggregated Aβ/tau and/or suppresses the reactive oxygen response and neuroinflammation.[160, 161] Metformin and ketone-based interventions restored brain energy metabolism and delayed the onset and progression of AD by improving neuronal integrity, synaptic remodeling, and neuronal–glial interactions.[162-164] Hormone-based interventions delayed the onset of neuropathology and cognitive decline by

modulating appetite and energy expenditure, and epigenetic modification strategies have shown promising effects in improving brain energetics.[19, 165] Further investigations using imaging, metabolite, and hormone approaches will provide a precise understanding of the AD pathology.[166, 167]

In conclusion, aberrant energy metabolism in the brain plays a critical role in cognitive dysfunction in patients with AD, while maintaining energy homeostasis might be a promising treatment to delay the onset and progression of AD.

Source of Funding

This work was supported by the grants from the National Key Research and Development Program of China (2018YFC1704400), the National Nature Science Foundation of China (82001122, 81630028, and 81920108017), the Natural Science Foundation of Jiangsu Province (BK20200129 and BK20211005), and the Fundamental Research Funds for the Central Universities (021414380519).

Conflict of Interest

The authors declare that there are no conflicts of interest.

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How to cite this article: Yu L, Jin J, Xu Y, Zhu X. Aberrant energy metabolism in Alzheimer's disease. J Transl Intern Med 2022; 10: 197-206.