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Review Article

Glucose metabolism: A link between traumatic brain injury and Alzheimer's disease

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ABSTRACT

Traumatic brain injury (TBI), a growing public health problem, is a leading cause of death and disability worldwide, although its prevention measures and clinical cares are substantially improved. Increasing evidence shows that TBI may increase the risk of mood disorders and neurodegenerative diseases, including Alzheimer's disease (AD). However, the complex relationship between TBI and AD remains elusive. Metabolic dysfunction has been the common pathology in both TBI and AD. On the one hand, TBI perturbs the glucose metabolism of the brain, and causes energy crisis and subsequent hyperglycolysis. On the other hand, glucose deprivation promotes amyloidogenesis via β-site APP cleaving enzyme-1 dependent mechanism, and triggers tau pathology and synaptic function. Recent findings suggest that TBI might facilitate Alzheimer's pathogenesis by altering metabolism, which provides clues to metabolic link between TBI and AD. In this review, we will explore how TBI-induced metabolic changes contribute to the development of AD.

Introduction

Traumatic brain injury (TBI) is a devastating public health problem, with 50 million new cases each year worldwide. TBI has a high mortality rate, representing 30%–40% of all injury-related deaths across all ages.[1] The majority of survivors suffer from chronic neurobehavioral sequelae, including psychiatric and cognitive deficits, emotional and personality changes, etc., which pose a huge burden on patients, their families and the society.[2] TBI pathogenesis is a complex process that results from primary and secondary insults.[3] Primary injury is caused by mechanical force and occurs at the moment of injury, followed by delayed and protracted secondary injury.[4] Secondary injuries occur as a consequence of diverse pathological mechanisms, such as excitotoxicity,[5,6] oxidative stress,[7–9] cerebral metabolic dysfunction,[10,11] cerebrovascular pathology,[12,13] chronic inflammatory events,[14–16] and mitochondrial dysfunction.[17,18]

Alzheimer's disease (AD) is the most common form of dementia, characterized by progressive memory loss, cognitive impairment and personality changes. However, currently, no effective treatments are available to prevent, halt or reverse AD.[19] The two prominent neuropathological hallmarks of AD include extracellular deposits of amyloid-β (Aβ) in the form of senile plaques and intracellular accumulation of neurofibrillary tangles composed of hyperphosphorylated tau, both of which comprise highly insoluble, densely packed filaments.[20] The Aβ peptide, consisting of about 40 amino acids, is derived from the sequential enzymatic cleavages of the amyloid precursor protein (APP) by β- and γ-secretase.[21] β-secretase (β-site APP cleaving enzyme, BACE), the rate-limiting enzyme for Aβ production, was identified as the transmembrane aspartic protease responsible for initial cleavage of APP to form a membrane bound C-terminal fragment, which is in turn rapidly cleaved by γ-secretase to generate Aβ.[22,23] γ-secretase is a promiscuous protease, resulting in the heterogeneity of Aβ peptide.[24] Among all kinds of Aβ isoforms, Aβ40 and more hydrophobic

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Aβ42 are major components of accumulated Aβ in senile plaques.[25,26] On the other hand, the phosphoprotein tau is a principal neuronal microtubule-associated protein with a preferential axonal localization.[27,28] Tau promotes assembly and stabilizes microtubules, thereby contributing to the regulation of intracellular trafficking. The microtubule assembly activity of tau is tightly regulated by its degree of phosphorylation.[29] Hyperphosphorylated tau undergoes conformational changes and is polymerized into paired helical filaments and straight filaments, leading to the formation of intracellular neurofibrillary tangles in the brain.[30–32]

TBI and AD are debilitating neurological diseases,[33] and share common pathophysiology, including neuronal loss,[34–37] cytoskeletal disruption,[38–40] metabolic perturbation[41–44] and neuroinflammation.[45–48] And, a growing body of epidemiological and molecular evidence suggests TBI as a principle epigenetic risk factor for AD,[49–53] especially the identification of AD-like pathologies in the brains of both TBI patients and animal models.[33,54–56] However, despite the well-established clinical association between TBI and the development and progression of AD, the precise mechanisms linking TBI to AD have not yet been completely elucidated. On the one hand, the brain is an energy metabolism sensitive organ,[57] On the other hand, compelling data from neurological studies demonstrate that metabolism perturbation is closely involved in the pathology of TBI and AD, implying that metabolic dysfunction may be the missing link between TBI and AD. Here, the review intends to explore the metabolic link between TBI and AD, focusing on metabolism of glucose, which could lead to a better understanding of correlations between TBI and AD.

Glucose metabolism in brain

Glucose is the obligatory fuel source of the adult brain.[58] To maintain and restore ion gradients used for synaptic transmission, action potential and the recycling of neurotransmitters, the brain, 2% of the total body mass, utilizes approximately 20% the oxygen and 25% of the glucose consumed by the resting body.[57] Glucose is transported across the cell membranes by specific sodium-independent facilitated glucose transporters (GLUTs), which contains 14 members and comprises 12 membrane-spanning regions with intracellularly located animo- and carboxyl-ternini.[59,60] Among them, GLUT1 and GLUT3 are the major brain glucose transporters. GLUT1 is predominantly located both in the luminal and the abluminal membranes of the endothelial cells of blood-brain barrier, and in astrocytes, whereas GLUT3 is highly expressed in neurons.[61–63]

Upon entry into the cell, glucose is phosphorylated by hexokinase, a key enzyme for glucose utilization, to produce glucose-6-phosphate.[64] Glucose-6-phosphate constitutes the metabolic crossroad of different pathways (Fig. 1),[57] including (1) glycolysis with pyruvate or lactate as the end product; (2) the tricarboxylic acid (TCA) cycle and oxidative phosphorylation in mitochondria for energy production in the form of ATP; (3) the pentose phosphate pathway (PPP) which generates reducing equivalents in the form of NADPH, used for reductive biosynthesis such as fatty acid synthesis and against oxidative stress, and provides ribose-5-phosphate for nucleotide biosynthesis; (4) glycogenesis exclusively in astrocytes. Highly coordinated interactions among these processes guarantee cerebral glucose utilization and energy requirement, and either abnormality of glucose transportation or intracellular catabolism perturbation would influence cerebral glucose metabolism, which possibly results in metabolic disorders of the brain, such as AD.

Glucose metabolism in TBI

Metabolic perturbation of glucose is the predominant cellular process accompanying TBI, which mainly results from imbalance of demand and supply of cerebral energy requirements induced by primary and secondary insults. Initially, the primary mechanical damage occurring at the moment of impact causes cell membrane disruption, which leads to significant excitatory neurotransmitter dependent efflux of K^+ and alters the membrane potential.[65,66] To restore ionic equilibrium and maintain normal synaptic transmission, cerebral neurons and glias uptake more glucose to obtain cellular energy in the form of ATP.[67] Besides, TBI triggers DNA damage by both oxidative and nitrosative stresses, which in turn activates poly (ADP-ribose) polymerase-1 (PARP-1).[68] PARP-1, a nuclear NAD^+-consuming enzyme responsible for post-translational modification of proteins by poly ADP-ribosylation, is involved in DNA repair and genomic stability.[69,70] However, excessive PARP-1 activation leads to energetic depletion due to consumption of ATP for NAD^+ synthesis.[71] Taken together, increased ATP demand for maintenance of ionic equilibrium and DNA repair partly contributes to the post-TBI energy crisis.

The facilitative hexose GLUTs mediate glucose transport from the circulation across the endothelial cells of the BBB into neurons and glia.[72] Abnormality of the expression and activity of GLUT1 and GLUT3 could affect glucose uptake. Cornford and colleagues showed that GLUT1 was complete loss in areas of microvessel endothelial cells adjacent to small vessel injury in the resected tissues of two patients 7–8 h after acute TBI.[73] Accordingly, in the rat model of moderate closed head injury,[74] the expression of GLUT1 was significantly decreased in both impacted brain sections and isolated microvessels, and the changes were sustained until 24 h post-injury. Altered expression of GLUT1 could result in impairment of cerebral glucose utilization and metabolism. In contrast, Hamlin et al.[75] demonstrated that severe diffuse traumatic brain in rats induced rapid upregulation of neuronal specific GLUT3 in cortex and cerebellum, while glial specific GLUT1 underwent no significant change. Increased expression of GLUT3 were likely the consequence of excessive energy demands for neuronal repair after TBI, whereas paradoxical change of GLUT1 in endothelial cell and GLUT3 in neuron possibly pointed to imbalance of demand and supply of glucose in injured brain.

Pyruvate generated by glycolysis can subsequently be oxidized to CO_2 and water in mitochondria for energy production, or converted to lactate by lactate dehydrogenase.[76] Following TBI, it is well-known that the extracellular lactate concentration is dramatically elevated.[77] Hyperglycolysis-derived lactate could result from compromised cerebral blood flow, disruption of TCA cycle, and the activity of glycolytic enzyme such as glyceraldehyde-3-phosphate dehydrogenase (GAPDH).[67] GAPDH, a key enzyme in glycolysis, catalyzes the conversion of glyceraldehyde-3-phosphate to 1,3-bisphosphoglycerate, which takes NAD^+ as cofactor.[78] As already mentioned, NAD^+ could be massively consumed by PARP-1, which limits the activity of GAPDH. However, the conversion of pyruvate to lactate regenerates the NAD^+, thereby maintaining the high glycolytic cascades for ATP production. Besides, increasing evidence demonstrates that glutamatergic transmission induced activation of astrocytes can convert glucose to lactate for neurons to generate ATP, which is the central point of the astrocyte-neuron lactate shuttle.[57,79] Therefore, glutamate release after TBI, on the one hand, causes neuronal excitotoxicity in brain[80]; on the other hand, possibly stimulates lactate production from glucose in astrocytes and leads to cerebral extracellular lactate accumulation.

Decreased ATP production, even significantly increased cerebral glucose uptake during the acute period, together with injury induced self-protection and repair biological processes, suggest that glucose could be directed to different metabolic pathway in TBI. Accumulating evidence demonstrates that PPP is crucial for prevention of secondary injury or recovery, including defense against oxidative stress and repair and synthesis of

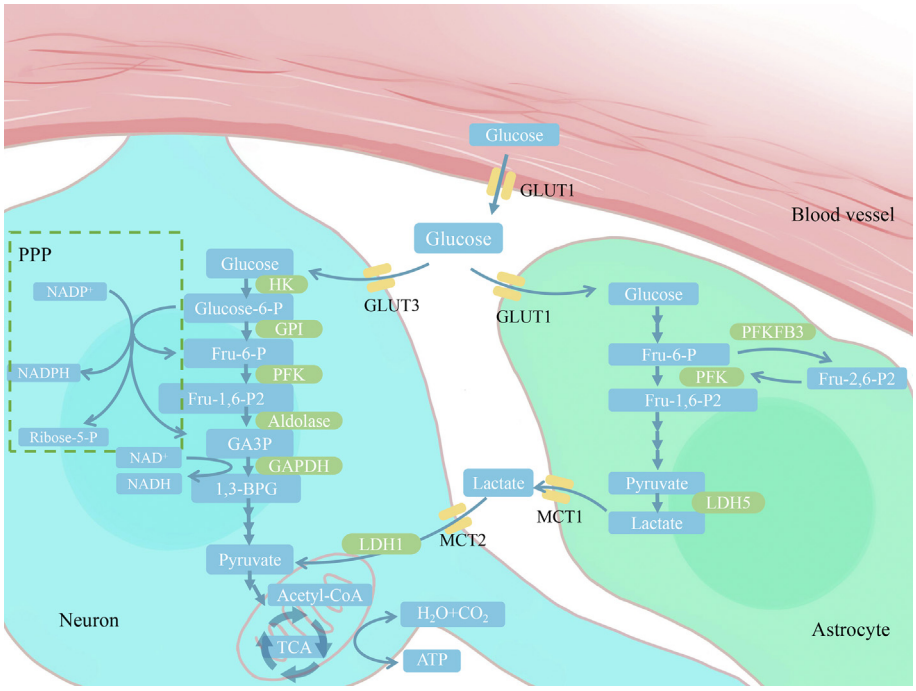

Fig. 1. Schematic diagram of glucose metabolism in the brain. Glucose is transported via glucose transporter 1 (GLUT1) across the endothelial cells of the blood-brain barrier, and then enters neurons and astrocytes through GLUT3 and GLUT1. In neurons, HK catalyzes the conversion of glucose to glucose-6-P, which is the irreversible process and ATP-driven phosphorylation. Glucose-6-P, the crossroad-metabolite, connects different pathways of intracellular glucose metabolism. It can be catabolized by glycolysis in cytoplasm to produce pyruvate. Pyruvate can then enter mitochondria and be subsequently utilized to generate ATP via TCA cycle and oxidative phosphorylation. Additionally, glucose-6-P can also enter the pentose phosphate pathway (PPP), which is the main source of reducing equivalents (NADPH) and provides the precursors for biomacromolecules synthesis such as ribose-5-P. In astrocytes, glutamatergic neurotransmission can induce the astrocyte-neuron lactate shuttle (ANLS). Increased lactate in astrocytes is shuttled to neurons by monocarboxylate transporters, which can be used by neurons to generate ATP.
HK: hexokinase; GPI: glucose-6-phosphate isomerase; Fru-6-P: fructose-6-phosphate; PFK: phosphofructokinase-1; GAPDH: glyceraldehydes-3-phophate dehydrogenase; GA3P: glyceraldehydes-3-phosphate; 1,3-BPG: 1,3-bisphosphoglycerate; TCA: tricarboxylic acid cycle; Fru-1,6-P2: fructose-1,6-bisphosphate; Fru-2,6-P2: fructose-2,6-bisphosph ate; PFKFB3: 6-phosphofructose-2-Kinase/fructose-2,6-bisphophatase-3; LDH: lactate dehydrogenase.

biomacromolecules, through providing reducing equivalents NADPH and precursor of biomacromolecules such as ribose-5-phosphate.[81] Using *ex vivo* ^{13}C NMR spectroscopy to determine the metabolic fate of [1,2−$^{13}C_2$] glucose, Bartnik et al.[82] showed that PPP activity was significantly enhanced in the cortex of controlled cortical impact injured rats at 3.5 h and 24 h after impact, which was further corroborated by data from patients with severe TBI. Based on intravenous infusion of [1,2−$^{13}C_2$] glucose, Dusick et al.[81] found that PPP flux was significantly higher in six severe TBI patients than in six healthy controls, on average 19.6% versus 6.9% within 7 days of injury. Consistently, Jalloh et al.[83] demonstrated that several TBI patients exhibited elevated PPP activity by adopting microdialysis catheter mediated infusion of [1,2 $^{13}C_2$] glucose.

Glucose metabolism in AD

Disturbance of cerebral glucose metabolism is a prominent pathological feature of AD, and precedes the manifestation of clinical symptoms even decades.[43,84,85] Impaired cerebral glucose metabolism in AD could result from several ways. Among them, the earliest change in glucose metabolism is the decreased glucose transport.[86,87] And the marked reduction in expression of cerebral glucose transporters has been established in the brains of AD patients and rodent AD models.[86,88] Two major brain glucose transporters GLUT1 and GLUT3 were remarkably decreased in AD patients, which correlated with O-GlcNAcylation reduction, thereby contributing to abnormal hyperphophorylation of tau and neurofibrillary degeneration.[89] Moreover, GLUT1 deficiency in endothelium of mice overexpressing Aβ could lead to BBB breakdown and related cerebrovascular degenerative changes, and induce Aβ pathology and progressive neuronal neurodegeneration.[87] Besides, genetic overexpression of GLUT1 in an adult-onset *Drosophila* model of AD attenuated neuronal degeneration and prolonged lifespan, which was associated with down-regulation of the unfolded protein response (UPR) negative master regulator Grp78 and enhanced UPR.[90,91] Overall, these findings present an intimate relationship between glucose transporters and AD pathology, and causative role of glucose transporters in AD.

The mitochondrial pyruvate dehydrogenase complex (PDC) catalyzes the oxidative decarboxylation of pyruvate and controls the irreversible conversion of pyruvate into acetyl-CoA. PDC plays a vital role in the metabolism of pyruvate to maintain glucose homeostasis.[92,93] The protein level and activity of PDC were significantly decreased in AD, which had the highest correlation with clinical state.[94,95] Furthermore, the activity of cytochrome c oxidase, the major regulation site for oxidative phosphorylation,[96] was significantly diminished in both platelets and temporal cortex and hippocampus of AD patients,[97,98] which was also confirmed by AD animal model.[95] The decreased activity of cytochrome c oxidase contributed to impaired glucose metabolism and energy generation. Altogether, these data indicate that mitochondrial dysfunction induced abnormality of glucose metabolism likely evokes neuronal perturbation in AD.

Possible cascades linking TBI and AD

TBI evokes the prolonged glucose metabolic depression and consequent energy crisis, which reflects that glucose uptake into brain could not meet the demand of neuronal function.[67] Impaired cerebral glucose metabolism could induce diverse biological cascades, leading to AD-like pathology. Energy deprivation *in vitro* or *in vivo* could trigger phosphorylation of the translation initiation factor eIF2α, which directly enhances the translation of BACE1, thereby promoting amyloidogenesis.[99,100] Furthermore, through activating the p38 mitogen-activated protein kinase (MAPK) cascade, impaired glucose metabolism and utilization could induce tau phosphorylation and neuronal apoptosis, which would, in turn, cause the defect of memory and synaptic function (Fig. 2).[101] Taken together, impaired glucose may build a bridge between TBI and AD.

Besides, TBI could directly regulate p38 MAPK and eIF2α through post-translational modifications.[102,103] MAPK pathway was dramatically activated post-TBI. And the phosphorylation of p38 MAPK was significantly elevated, thereby exacerbating the secondary injury after TBI. p38 MAPK signaling could elicit the chronic microglia activation after diffuse and focal TBI injury and cause motor deficits and synaptic protein loss, whereas knockout of p38α attenuated multiple pro-inflammatory responses and improved outcome.[104,105] Additionally, TBI mediated p38 activation evoked mitochondrial damage and mitochondrial apoptosis as well as astrocyte activation while overexpression of SIRT1, the NAD^+-dependent protein deacetylases, mitigated the activity of p38 MAPK and improved the neurobehavioral function, which implied that TBI might influence the activity of p38 MAPK through phosphorylation and acetylation.[106,107]

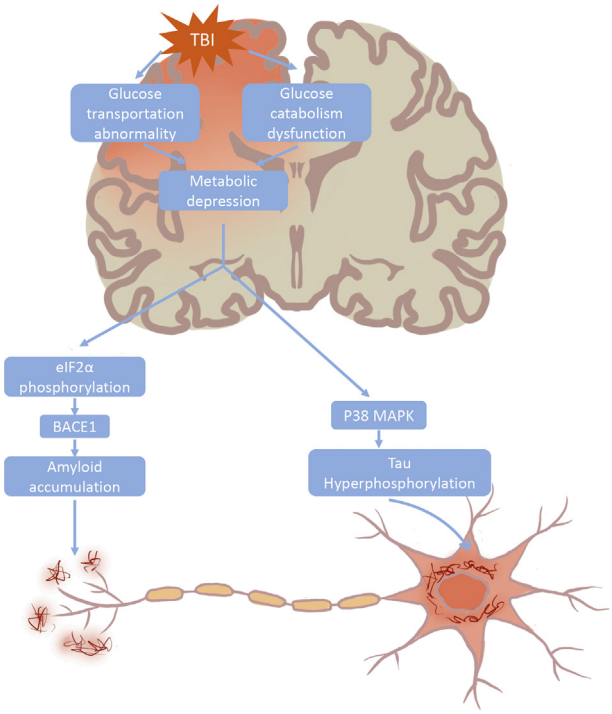

Fig. 2. Hypothetical pathogenic cascades linking TBI and Alzheimer's disease. TBI perturbs cerebral glucose metabolism by affecting glucose transportation and intracellular glucose catabolism, thereby resulting in metabolic depression. Reduced energy availability triggers eIF2α phosphorylation and in turn enhances the translation of BACE1, which ultimately leads to amyloidogenesis. On other hand, energy deprivation could induce activation of p38 MAPK cascade and consequent hyperphosphorylated tau protein, which eventually no longer binds microtubules and aggregates into intracellular neurofibrillary tangles.
TBI: traumatic brain injury; BACE: β-site APP cleaving enzyme; MAPK: mitogen-activated protein kinase.

Phosphorylation of eIF2α compromises general translation, and concurrently selectively triggers the translation of a subset of mRNAs.[108] Emerging evidence shows that increased phosphorylation of eIF2α impairs long-term memory formation.[108–111] TBI could induce integrated stress response mediated eIF2α phosphorylation and result in cognitive dysfunction, whereas integrated stress response inhibition attenuated TBI associated memory deficits.[111] Furthermore, TBI triggered endoplasmic reticulum stress and subsequent phosphorylation of eIF2α, which consequently led to increased expression of APP and phosphorylated tau in the frontal cortex.[112] The data summarized above imply that TBI may contribute to the development of AD through regulation of p38 MAPK and eIF2α by glucose metabolism and post-translational modification.

Conclusion

The correlation between TBI and AD is enormously complex, especially metabolic connection. The direct metabolic link between them is unavailable, although they share common impaired energy metabolism. However, the existing data imply that glucose perturbation may be the point that TBI aggravates the risk of developing AD, particularly in severe TBI patients. So, clarifying the metabolic link with TBI and AD would assist with drug development and therapies for neurodegenerative disease.

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Ethical statement

This is a review and ethical requirement was inapplicable.

Declaration of competing interest

All authors declared no conflicts of interest.

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