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

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Review Article

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Introduction

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. © 2020 Production and hosting by Elsevier B.V. on behalf of Chinese Medical Association. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Glucose metabolism in brain

Glucose metabolism is critical in maintaining the energy demand of the brain. Several pathways are involved in glucose metabolism, including glycolysis, the pentose phosphate pathway (PPP), and the tricarboxylic acid (TCA) cycle. These pathways are essential for the production of ATP, which is the main source of energy for neuronal and glial function. The brain uses approximately 20% of the oxygen and 25% of the glucose consumed by the resting body. Glucose is transported across the cell membranes by specific transporters, such as GLUT1 and GLUT3. GLUT1 is predominantly expressed in glias, whereas GLUT3 is highly expressed in neurons. The expression of these transporters can be altered in response to various conditions, such as traumatic brain injury (TBI) and Alzheimer's disease (AD).

In TBI, the disruption of blood-brain barrier (BBB) can lead to abnormal glucose transport and metabolism. Moreover, TBI induces inflammation and oxidative stress, which further disrupts glucose metabolism. In AD, the formation of amyloid plaques and neurofibrillary tangles disrupts glucose transport and metabolism, leading to the accumulation of hyperphosphorylated tau protein. This process, known as the excitotoxic cascade, contributes to neuronal damage and cell death.

Glucose metabolism in TBI

In TBI, the metabolic demand of the brain increases dramatically due to the energy demands for neuronal repair and inflammation. The brain's energy metabolism is highly sensitive, and any disruption in glucose transport can lead to metabolic disorders, such as AD. The disruption of metabolic pathways, such as the PPP and TCA cycle, can result in the accumulation of toxic metabolites, such as lactate and malate, which can further exacerbate neuronal damage.

Conclusion

In summary, understanding the metabolic link between TBI and AD is crucial for developing effective treatments. The metabolic alterations in TBI and AD are complex and involve multiple pathways. Further research is needed to elucidate the mechanisms underlying these metabolic changes and to develop targeted therapeutic strategies.
biomacromolecules, through providing reducing equivalents NADPH and precursor of biomacromolecules such as ribose-5-phosphate.\textsuperscript{81} Using \textit{ex vivo} \textsuperscript{13}C NMR spectroscopy to determine the metabolic fate of [1,2\textsuperscript{13}C\textsubscript{2}] glucose, Bartnik et al.\textsuperscript{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\textsuperscript{13}C\textsubscript{2}] glucose, Dusick et al.\textsuperscript{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.\textsuperscript{83} demonstrated that several TBI patients exhibited elevated PPP activity by adopting microdialysis catheter mediated infusion of [1,2\textsuperscript{13}C\textsubscript{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.\textsuperscript{83,84,85} Impaired cerebral glucose metabolism in AD could result from several ways. Among them, the earliest change in glucose metabolism is the decreased glucose transport.\textsuperscript{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.\textsuperscript{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 hyperphosphorylation of tau and neurofibrillary degeneration.\textsuperscript{89} Moreover, GLUT1 deficiency in endothelium of mice overexpressing A\textsubscript{\textbeta} could lead to BBB breakdown and related cerebrovascular degenerative changes, and induce A\textsubscript{\textbeta} pathology and progressive neuronal neurodegeneration.\textsuperscript{86} Besides, genetic overexpression of GLUT1 in an adult-onset \textit{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.\textsuperscript{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.\textsuperscript{92,93} The protein level and activity of PDC were significantly decreased in AD, which had the highest correlation with clinical state.\textsuperscript{94,95} Furthermore, the activity of cytochrome c oxidase, the major regulation site for oxidative phosphorylation,\textsuperscript{96} was significantly diminished in both platelets and temporal cortex and hippocampus of AD patients,\textsuperscript{97,98} which was also confirmed by AD animal model.\textsuperscript{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.\(^6\) 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 eIF2\(\alpha\), which directly enhances the translation of BACE1, thereby promoting amyloidogenesis.\(^9\)\(^,\)\(^10\) 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).\(^10\)\(^1\) Taken together, impaired glucose may build a bridge between TBI and AD.

Besides, TBI could directly regulate p38 MAPK and eIF2\(\alpha\) through post-translational modifications.\(^10\)\(^2\)\(^1\)\(^0\) 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 secondary injury after TBI.\(^1\)\(^0\)\(^4\)\(^,\)\(^5\) 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.\(^10\)\(^6\)\(^,\)\(^10\)\(^7\)

Phosphorylation of eIF2\(\alpha\) compromises general translation, and concurrently selectively triggers the translation of a subset of mRNAs.\(^10\)\(^8\) Emerging evidence shows that increased phosphorylation of eIF2\(\alpha\) impairs long-term memory formation.\(^10\)\(^8\)\(^–\)\(^11\) TBI could induce integrated stress response mediated eIF2\(\alpha\) phosphorylation and result in cognitive dysfunction, whereas integrated stress response inhibition attenuated TBI associated memory deficits.\(^11\) Furthermore, TBI triggered endoplasmic reticulum stress and subsequent phosphorylation of eIF2\(\alpha\), which consequently led to increased expression of APP and phosphorylated tau in the frontal cortex.\(^11\)\(^2\) The data summarized above imply that TBI may contribute to the development of AD through regulation of p38 MAPK and eIF2\(\alpha\) 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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