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Review

Tau Protein Dysfunction after Brain Ischemia

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Abstract. Brain ischemia comprises blood-brain barrier, glial, and neuronal cells. The blood–brain barrier controls permeability of different substances and the composition of the neuronal cells 'milieu', which is required for their physiological functioning. Recent evidence indicates that brain ischemia itself and ischemic blood-brain barrier dysfunction is associated with the accumulation of neurotoxic molecules within brain tissue, e.g., different parts of amyloid-β protein precursor and changed pathologically tau protein. All these changes due to ischemia can initiate and progress neurodegeneration of the Alzheimer's disease-type. This review presents brain ischemia and ischemic blood-brain barrier as a trigger for tau protein alterations. Thus, we hypothesize that the changes in pattern of phosphorylation of tau protein are critical to microtubule function especially in neurons, and contribute to the neurodegeneration following brain ischemia-reperfusion episodes with Alzheimer's disease phenotype.

Keywords: Blood-brain barrier, brain ischemia, dementia, experimental, gene expression, human, neurodegeneration, neuronal death, stroke, tau protein

INTRODUCTION

Ischemic stroke in humans is the second cause of death and the third cause of disability, and may soon become the leading cause of death worldwide [1, 2] and dementia of the Alzheimer's disease (AD) phenotype [3–11]. Acute brain ischemia in patients refers to focal brain infarction that causes sudden neurological deficits and accounts for approximately 87% of all strokes [2]. The latest epidemiological data indicate that about 17 million people suffer from ischemic stroke every year [1, 8]. The number of survivors of ischemic stroke has doubled in 1990-2010 and has now reached 33 million patients [1, 8]. According to epidemiological forecasts, this figure will increase to 77 million by 2030 [1]. Furthermore, stroke survivors are at an increased risk of developing cognitive impairment. Physical impairments following ischemic stroke tend to improve to a greater or lesser degree. However, for reasons unknown, the impairment of cognitive functions is gradually deteriorating. Every year, about 6 million stroke subjects die all over the world [1]. An effective treatment of ischemic stroke involves the use of thrombolysis, but thrombolysis has a limited window of therapeutic time and a potential

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risk of symptomatic hemorrhagic conversion [2]. Now ischemic stroke exerts a large burden on global public healthcare and clinical practice.

Brain ischemia reduces the supply of oxygen, energy substrates, and nutrients to the brain tissue. In addition, such defects impair the removal of neurotoxic substances, such as the amyloid-β (Aβ) peptide, which accumulates in non-neuronal brain cells, neurons, and extracellular space in animals and humans [12–19]. Recent evidence suggests that ischemia leads to acute and chronic neuronal dysfunction and death, and may contribute to the deposition of various types of neurotoxic proteins, such as various parts of the amyloid-β protein precursor (AβPP), the Aβ peptide, and dysfunctional tau protein, in brain neurons and cerebrovascular system [17, 20, 21]. Such changes include brain amyloidosis and cerebral amyloid angiopathy, which are caused by the progressive accumulation of the Aβ peptide in the brain tissue and vessel wall, respectively, and are recognized as features of AD [17, 22, 23]. It has been suggested that the history of ischemic stroke in humans and experimental brain ischemia are associated with the subsequent development of AD [4, 12, 17, 20, 21, 24–42]. An insidious consistency of post-ischemic brain changes is a slow and progressive development of post-ischemic dementia with AD phenotype [3, 5–11, 43–52]. Patients with AD, who had ischemic injuries, were found to have more intense dementia [53]. Pre-existing ischemic brain damage can further increase the likelihood of AD development by increasing the extent of injury by triggering the genomic and proteomic cascade of AD [20, 32–42]. Thus, the knowledge of the underlying progressive neuropathological mechanisms in the consequences of brain ischemia is urgently required. In this review, we discuss ischemic pathways to the neurodegeneration of the AD phenotype, focusing on the expression of the tau protein gene and its dysfunctional product. This is due to the fact that there is a lot of new information in the literature on genomic and proteomic changes in the tau protein after brain ischemia-reperfusion injury. Presentation of increased expression of the tau protein gene after brain ischemia sheds new light on a better understanding of dysfunctional tau protein as the cause of the effects of ischemic disease [42]. Although significant advances have recently been made in studies on the pathogenicity of tau protein following ischemia, the underlying mechanisms of tau protein-induced post-ischemic neurodegeneration are unclear. Below is an overview of the association of tau protein with post-ischemic neurodegenerative processes. The present review aims at updating knowledge about the connection between brain ischemia and development of AD neuropathology. Therefore, understanding the neuronal mechanisms associated with ischemic brain damage and identifying potential new pathological processes after ischemic stroke is critical to effective therapy for the consequences of stroke. Such studies can help determine the requirements for the implementation of new therapies for ischemic stroke and may be of importance in the conduct and assessment of future prevention priorities.

PROPERTIES OF TAU PROTEIN

Tau protein, a microtubule-associated protein, is present mainly in neurons and at lower levels in oligodendrocytes and astrocytes. Tau protein is coded by a gene on chromosome 17. There are six major isoforms of tau protein in the human brain. Tau protein combines microtubules together and helps stabilize their structure. Microtubules are involved in maintaining the morphology of neurons and creating axonal and dendritic processes, and play an important role in vesicular transport, polarity, and signal transduction. Tau protein may regulate axonal transport by binding to the microtubule surface. Recent reports have revealed several novel functions of tau protein, such as regulation of neuronal activity, maintenance of the integrity of genomic DNA, neurogenesis, iron export, and long-term depression [54, 55]. Understanding the additional functions of tau protein is not only essential to elucidate the tau protein pathogenesis, but it is also necessary to ascertain tau protein-based treatment strategy. Tau protein is natively unfolded with a low content of secondary structure and is divided into an N-terminal domain, a proline-rich region, a repeatable domain, and a C-terminal domain. Tau protein contains a large amount of serine and threonine residues (>80), which are potential phosphorylation sites, and the phosphorylation state, which is controlled by the balance of kinase and phosphatase activity, affects the affinity of microtubule binding. Therefore, the physiological action of tau protein seems to favor the formation of microtubules and stabilize microtubule networks with phosphorylation regulating these functions. In pathological conditions, the tau protein undergoes hyperphosphorylation, and the tau protein binding balance with the microtubule surface is disrupted, resulting in a decrease in affinity for the microtubules [54, 55].

CHANGES IN GENE EXPRESSION OF THE TAU PROTEIN AFTER BRAIN ISCHEMIA-REPERFUSION

Only one existing report in the literature indicates the relationship between the ischemic CA1 region of the hippocampus and the expression of the tau protein gene after transient 10-minute global brain ischemia in rats with a survival of 2, 7, and 30 days [42]. In the hippocampal region of CA1, the expression of the tau protein gene increased to a maximum of 3.3-fold change on the second day after brain ischemia [42]. After 7 days from ischemic episode, the expression was between 0.2 and -0.5-fold change [42]. On the 30th day of survival after ischemic damage to the brain, the expression of the tau protein gene decreased to -0.4-fold [42]. Statistical significance of changes in gene expression of the tau protein following global brain ischemia in rats was between 2 and 7, and between 2 and 30 days of survival [42].

TAU PROTEIN STAINING AFTER BRAIN ISCHEMIA-REPERFUSION

In recent years, several researchers have noted that brain ischemia is an important feature in the development of AD and plays a key role in genomic and proteomic (e.g., AβPP, amyloid processing secretases, autophagy, mitophagy, caspase 3, and tau protein) changes of the disease [20, 32–42, 56, 57]. Early studies revealed that the immunoreactivity of tau protein in neuronal and glial cells had been observed in the thalamus, hippocampus, and cortex in both experimental brain ischemia [58–63] and ischemic stroke in humans [64–66]. Modified tau protein was furthermore noted in microglial cells at the ischemic penumbra [65, 67, 68]. The above data indicate that some neuronal cells display alterations in tau protein following brain ischemia-reperfusion injury [60], which may show a prime neuropathological stage of the ischemic processes in these cells [62]. Another investigation showed that tau protein itself could inhibit transport of AβPP in the neuron body at axons and dendrites, leading to AβPP deposition in the neuronal cell body [69].

The level of tau protein was observed in blood samples after global brain ischemia with two peaks after days 2 and 4, probably indicating the progression of neuronal changes after recirculation [70]. Observed bimodal elevation kinetics of tau protein level in plasma is consistent with two types of neuronal loss: firstly, by necrosis and next via delayed neuronal death [71]. It seems likely that the profiles reflect a time course of primary and secondary ischemic neuronal injury [71]. The above studies suggest that tau protein level in plasma has the potential to be used as a predictor for the neurological outcome following ischemia-reperfusion brain injury [70, 71].

PATTERNS OF TAU PROTEIN PHOSPHORYLATION AFTER BRAIN ISCHEMIA-REPERFUSION

Studies have also shown that the phosphorylation patterns of tau protein differ in different models of brain ischemia (Table 1). Tau protein was dephosphorylated following brain ischemia in several experimental brain ischemia studies (Table 1) [60, 61, 72, 73]. After global brain ischemia and recirculation, tau protein was slowly re-phosphorylated and accumulated (Table 1) [73]. Transient focal brain ischemia with one-day reperfusion induces locally-specific hyperphosphorylation of rat tau protein [74]. In delayed neuronal death in the CA1 region of the hippocampus after transient forebrain ischemia, hyperphosphorylation at serine 199/202 of tau protein is regulated by MAP kinase, CDK5, and GSK3 activities [75]. Also, it was documented that microglia tau protein undergoes phosphorylation-independent modification after brain ischemia in humans (Table 1) [65]. The current investigations indicate that after ischemia, hyperphosphorylated tau protein dominates in cortical neuronal cells and accompanies apoptosis [67, 68, 74, 76–78]. The above-mentioned results indicate that following brain ischemia neuronal apoptosis is straightway associated with tau protein hyperphosphorylation. Wen et al. [74, 76, 77] provided evidence that reversible ischemic brain injury was engaged in neurofibrillary tangle-like development at the rat focal brain ischemia.

In addition, the combination of global brain ischemia with hyperhomocysteinemia in rats leads to massive neuronal pathology in the hippocampus and cortex [79]. In the above experimental conditions, 695-fold higher number of hyperphosphorylated tau protein-positive neurons in the cerebral cortex was found compared to the control conditions [79]. Finally, tau protein, a core hallmark of AD, exacerbates brain parenchyma injury in experimental brain ischemia models through tau protein-mediated iron export [80] and tau protein-dependent excitotoxicity [81, 82]. The above results provide a

Table 1
Various patterns of tau protein dysfunction after brain ischemia-reperfusion

Tau protein state	Ischemia	Animal/Human	References
Neurofibrillary tangle formation	Ischemic stroke	Human	[83]
Dephosphorylation	Complete brain ischemia	Rat	[61, 101]
Dephosphorylation	Focal brain ischemia	Rat	[60]
Rapid dephosphorylation, differential re-phosphorylation	Global brain ischemia	Dog	[73]
Microglia tau protein passes independent of phosphorylation modification	Ischemic stroke	Human	[65]
Four site-specific hyperphosphorylation at serine 202/214/422 and threonine 231	Focal brain ischemia	Rat	[74]
Hyperphosphorylation at serine 202 and threonine 205	Global brain ischemia	Rat	[79]
Hyperphosphorylation integrated with apoptosis	Focal brain ischemia	Rat	[76]
Hyperphosphorylation at serine 199/202	Forebrain ischemia	Gerbil	[75]
Dephosphorylation, rapid re-phosphorylation and hyperphosphorylation	Forebrain ischemia	Gerbil	[102]
Neurofibrillary tangle-like tauopathy involving Cdk5	Focal brain ischemia	Rat	[77]
Dephosphorylation associated with adenosine monophosphate kinase (AMPK) dephosphorylation	Global brain ischemia	Rat	[78]
Dephosphorylation and hyperphosphorylation at serine 396	Global brain ischemia	Rat	[67]
Hyperphosphorylation and cleavage isoforms of 4- and 3-repeat	Focal brain ischemia	Rat	[68]
Reduction tau protein-dependent excitotoxicity in tau–/– mice	Focal brain ischemia	Mouse	[82]
Functional damage of tau protein contributes to iron-mediated neurotoxicity	Focal brain ischemia	Mouse/Rat	[80]
Hyperphosphorylation involving asparagine endopeptidase	Focal brain ischemia	Mouse	[84]
Paired helical filament tau protein increase	Forebrain ischemia	Mouse	[85]

pathological basis for the progress of dementia after brain ischemia-reperfusion with AD phenotype [74, 76, 77].

DYSFUNCTION OF THE BLOOD-BRAIN BARRIER AND TAU PROTEIN AFTER BRAIN ISCHEMIA

Tau protein hyperphosphorylation following brain ischemia-reperfusion episode [67, 68, 74, 76–80, 82–85] induces neurofibrillary tangle-like tauopathy and neurofibrillary tangles [77, 83], which are known to occur in the brains of patients with AD. Brain ischemia causes blood-brain barrier (BBB) permeability [86–90], which may induce hyperphosphorylation of the tau protein [67, 68, 74, 76–80, 82–85, 91], and tau protein dysfunction may cause changes in the BBB, leading to detrimental feedback [92]. Amyloid pathology associated with ischemic BBB dysfunction [93, 94] may indirectly facilitate the onset of tau protein pathology, representing the automatic link between amyloid and tau protein accumulation during BBB failure [92]. Also, both neuroinflammation [95] and oxidative stress [96] induced by BBB insufficiency can trigger tau protein hyperphosphorylation and neurofibrillary tangles formation after brain ischemia [77, 83, 91, 97]. Additionally, blood-borne tau protein after ischemic brain episode [70, 71] can cross the ischemic BBB bidirectionally, and, derived from blood, tau protein may strengthen in brain tissue tau protein pathology [98]. In summary, the BBB insufficiency may potentiate the pathology of the brain tau protein in ischemic brain, and also suggest that brain ischemic neuropathology may contribute to blood tau protein level [70, 71, 98, 99].

DISCUSSION AND CONCLUSIONS

Brain ischemia and AD pathologies often coexist in brain [22, 23, 53, 100]. In recent years, epidemiological, clinical, and experimental studies

have revealed that cerebrovascular diseases including brain ischemia and their history can be proposed as one of the causal factor for AD development. How one condition predisposes to, interacts with, or perhaps causes the others remains unclear. The mechanism of how ischemic stroke could lead to the progression of AD remains obscure. Remarkably, similar etiopathological features can be found in brain ischemic diseases and AD like amyloid and tau protein changes (Table 1). Brain ischemia induces ischemic generation of amyloid plaques that can interact with vascular changes in the brain and progress to AD. Brain ischemia and post-ischemic amyloid accumulation may induce neurodegeneration of the AD phenotype. Generation and deposition of Aβ peptide and tau protein pathology are recognized in post-ischemic forms of neurodegeneration and are important key players in the etiology of the onset and progression of AD. To better understand the link between brain ischemia and AD, we focus in this review on tau protein gene expression and its product post-ischemia.

Tau protein is a phospho-protein and its biological activity is regulated by the degree of its phosphorylation. As tau protein is phosphorylated by kinases involved in different transduction signal pathways, its phosphorylation state is proposed to regulate its binding to microtubules, influencing the dynamics of microtubule assembly necessary for axonal growth and neurite plasticity [101]. Hyperphosphorylated tau protein does not bind or stabilize microtubules, whereas the fully dephosphorylated tau protein binds to microtubules with high affinity. Ischemic brain episode damages the neuronal cytoskeleton both by promoting the proteolysis of its components as well as by affecting the activity of kinases and phosphatases [72, 77]. The state of changes in the phosphorylation of tau protein in various models of brain ischemia and various periods after ischemia are presented in Table 1. Changes in phosphorylation of tau protein may alter its distribution between the axon and the cell body, and affect the susceptibility to proteolysis, affect the stability of microtubules, and may contribute to disruption of axonal transport, but also facilitate the plasticity of neurites in the regenerative response [101]. Hyperphosphorylation of tau protein may contribute to brain damage caused by transient ischemia and recirculation and may be involved in neurodegeneration after brain ischemia [67, 68, 74, 76–80, 82–85]. Thus, changes in phosphorylation of tau protein may play a key role in the process of post-ischemic brain damage.

The relationship between AD-associated tau protein and brain ischemia and ischemic stroke appears quite clear. The worldwide problem and enormous costs involved make it clear that there is an urgent need for advances in the prevention and/or treatment of brain ischemia-reperfusion injury and its irreversible consequences like post-ischemic dementia of AD phenotype. Tau protein plays a key role in neuronal damage and clinical pathophysiology of ischemic stroke. Although the role of ischemia in phosphorylation of tau protein is generally complex and requires further explanation, and the tau protein represents a relatively under-investigated factor in ischemic stroke, we have reason to believe that determining the role of tau protein in ischemic stroke may contribute to understanding the basis for developing a new target for the treatment of ischemic stroke. Finally, regulation of phosphorylation of tau protein can be considered as a potential new therapeutic target after ischemic stroke.

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