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Tau as a Potential Novel Therapeutic Target in Ischemic Stroke

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ABSTRACT

Stroke is associated with high mortality and major disability burdens worldwide, but there are few effective and widely available therapies. Tau plays an important role in promoting microtubule assembly and stabilizing microtubule networks with phosphorylation regulating these functions. Based on the "ischemia-reperfusion theory" of Alzheimer's disease, some previous studies have focused on the relationship of tau and Alzheimer lesions in experimental brain ischemia. Thus, we hypothesize that the alterations in phosphorylation of tau are critical to microtubule dynamics and metabolism, and contribute to the pathophysiologic mechanisms during brain ischemia and/or reperfusion processes. We infer that regulation of phosphorylation of tau may be considered as a potential new therapeutic target in ischemic stroke. J. Cell. Biochem. 109: 26–29, 2010.

KEY WORDS: TAU PROTEINS; ISCHEMIC STROKE; THERAPEUTIC TARGET

Stroke is the second most common cause of death after heart attacks and the major cause of disability, which may soon become the leading cause of death worldwide [Feigin, 2005; Donnan et al., 2008]. Ischemic stroke refers to focal brain infarction that produces sudden neurologic deficits persisting for longer than 1 h and accounts for 80–85% of all strokes. Effective therapy in modern medicine is the application of thrombolysis, but thrombolysis has a limited therapeutic time window within 3 h and the potential side effect of intracranial hemorrhage. Over 6 h, the optimization of clinical treatment with acute stroke was only an integrative and aggressive supportive care as well as secondary prevention [Feigin, 2005; Panagos, 2008]. Thus, understanding the cellular mechanisms associated with ischemic brain injury and identifying potential novel therapeutic target in ischemic stroke are critical for stroke therapy.

STRUCTURE AND FUNCTION OF TAU

Tau proteins are microtubule-associated proteins that are abundant in neurons and at lower levels in astrocytes and oligodendrocytes [Tashiro et al., 1997]. Tau is coded by a single gene on chromosome 17 and consists of 16 exons [Andreadis et al., 1992], but is expressed in six important isoforms that are generated by alternative splicing of its mRNA [Himmler et al., 1989]. These six tau isoforms differ in containing three (3R taus) or four (4R taus) microtubule binding repeats (R) of 31–32 amino acids in the carboxy terminal half and one (1N), two (2N), or zero (0N) amino terminal inserts of 29 amino acids each; the extra repeat in 4R tau is the second repeat (R2) of 4R taus [Iqbal et al., 2009]. Tau promotes microtubules assembly and helps stabilize their structure by binding to them via an interaction with the 3R or 4R at the C terminus of the protein. Microtubules are involved in the maintenance of neuronal morphology, formation of axonal and dendritic processes, and play a vital role in vesicular transport, axonal polarity, and signal transduction [Gendron and Petrucelli, 2009]. Tau contains a particularly high content of (>80) serine and threonine residues, which are potential phosphorylation sites. And the state of phosphorylation, which is controlled by a balance of kinase and phosphatase activity, affects the microtubule-binding affinity [Mazanetz and Fischer, 2007]. Under pathological conditions, tau becomes hyperphosphorylated. The equilibrium of tau binding to the microtubules is perturbed, resulting in reduced affinity for microtubules [Bramblett et al., 1993]. Therefore, the normal function of tau seem to promote microtubule assembly and to stabilize microtubule networks with phosphorylation regulating these functions.

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TABLE I. The State of Tau Phosphorylation Following Ischemic Stroke

References	Animal	Model	Time	State of tau phosphorylation
Geddes et al. [1994]	Rat	Four-vessel occlusion model	20 min ischemia/30 min to 2 h reperfusion	Dephosphorylation
Dewar and Dawson [1995]	Rat	Focal cerebral ischaemia, MCA occlusion	2 h or 6 h ischemia	Dephosphorylation
Mailliot et al. [2000]	Canine	Cardiac arrest -induced cerebral ischemia	10 min global cerebral ischemia and 2 h, 24 h reperfusion	Dephosphorylation and differential rephosphorylation
Shackelford and Yeh [1998]	Rat	Four-vessel occlusion model	5 min, 15 min ischemia	Dephosphorylation
Burkhart et al. [1998]	Rat and human	Neocortical brain slices	30 min and 60 min oxygen and glucose of deprivation and reestablishing 15–60 min	Dephosphorylation and an apparent recovery in phosphorylated tau
Wen et al. [2004]	Rat	Transient cerebral ischemia, an intraluminal filament model	1 h ischemia/24 h reperfusion	Site-specific hyperphosphorylation
Uchihara et al. [2004]	Human	Patients with cerebral infarction	8 days to 11 months	Microglial tau undergoes phosphorylation-independent modification
Morioka et al. [2006]	Mongolian Gerbils	Transient forebrain ischemia, occluded the bilateral common carotid arteries	5 min ischemia/0, 6 h, 12 h, 1 day, 2 days reperfusion	Hyperphosphorylation at serine 199/202 of tau factor
Gordon-Krajcer et al. [2007]	Mongolian gerbils	Occluded the bilateral common carotid arteries	5 min ischemia/20 min to 2 h, 3–7 days reperfusion	Dephosphorylation of the PHF-1 epitope, quickly rephosphorylation and hyperphosphorylation
Liao et al. [2009]	JNPL-3^{tau} transgenic mice and C57BL/6, B6D2F1 mice	The right common carotid artery was permanently occluded. Hypoxia was maintained for 40 min through a gas mask	24 h after hypoxia/ischemia	Hypoxia/ischemia insults led to a marked decrease in tau phosphorylation at residue T231 in wild-type but not transgenic mice

MCA, middle cerebral artery.

PATHOPHYSIOLOGY OF TAU IN ISCHEMIC STROKE

Alzheimer's disease (AD) is one of major tauopathy. In AD, tau no longer binds to the microtubules, but becomes sequestered into neurofibrillary tangles in neurons, and into glial tangles in astrocytes or oligodendroglia. However, in recent years a few researchers have recognized that brain ischemia as a prominent feature in AD plays a crucial role in neuronal damage and clinical pathophysiology of disease [Pluta, 2004]. The ''ischemia-reperfusion theory'' stimulated and redirected the focus of investigations towards ischemic cellular mechanisms of AD. Therefore, some previous studies specially focused on Alzheimer lesions in experimental brain ischemia. The preliminary studies showed that neuronal and glial tau immunoreactivity were seen in the thalamus, hippocampus and cortex, etc. both in stroke of human [Uchihara et al., 1995, 2000; Irving et al., 1996] and in experimental rodents [Geddes et al., 1994; Irving et al., 1997; Dewar and Dawson, 1995]. The preliminary studies also reported that patterns of tau phosphorylation changed in different time following ischemia and/or reperfusion both in vivo and in vitro (Table I). Tau was rapidly dephosphorylated during early brain ischemia and/or immediately upon reperfusion in several stroke models of different animals [Geddes et al., 1994; Dewar and Dawson, 1995; Shackelford and Yeh, 1998; Mailliot et al., 2000], potentially due to the activation of phosphatases. In both human and rat neocortical brain slices, tau undergoes a rapid, but reversible dephosphorylation following brief periods of in vitro hypoxia/hypoglycemia [Burkhart et al., 1998]. During prolonged ischemia or continued reperfusion, tau proteins are slowly rephosphorylated and accumulated, which may reflect the dynamic regulation of phosphatases and/or the corresponding tau kinases in response to brain ischemia/reperfusion process. Transient cerebral ischemia 24 h after blood occlusion induces site-specific hyperphosphorylation of tau protein [Wen et al., 2004]. In hippocampal delayed neuronal death after transient forebrain ischemia, hyperphosphorylation at serine 199/202 of tau factor is induced by MAP kinase, CDK5, and GSK3, and contributes to ischemic neuronal injury [Morioka et al., 2006]. Gordon-Krajcer et al. [2007] revealed that PHF-1 immunoreactivity declined to 6% after 5 min ischemia, then recovered near to control levels after 20 min to 2 h of blood recirculation and subsequently increased above control values 3 and 7 days later, suggesting a strong hyperphosphorylation effect. Liao et al. [2009] recently found that hypoxia/ischemia insults led to a marked decrease in tau phosphorylation at residue T231 in cortex of wild-type but not young adult P301L tau transgenic mice. Potently, Liao et al. [2009] also demonstrated that brain infarct volume in young adult P301L tau transgenic mice was significantly smaller than those in wild-type mice 24 h after hypoxia/ischemia induction. Furthermore, Uchihara et al. [2004] founded that microglial tau undergoes phosphorylation-independent modification after ischemia.

Tau is a phosphoprotein and its biological activity is regulated by the degree of its phosphorylation. As tau proteins are phosphorylated by kinases involved in different transduction signal pathways, their phosphorylation state is proposed to regulate their binding to microtubules, influencing the dynamics of microtubule assembly necessary for axonal growth and neurite plasticity [Shackelford and Yeh, 1998]. Tau hyperphosphorylation does not bind nor stabilize microtubules, while fully dephosphoryated tau binds to microtubules with high affinity [Burkhart et al., 1998]. Ischemia destroys the neuronal cytoskeleton both by promoting proteolysis of its components and by affecting kinase and phosphatase activities that

alter its assembly [Shackelford and Nelson, 1996]. The state of tau phosphorylation changed in different time following ischemia and/or reperfusion. The change of tau phosphorylation may alter its distribution between axon and cell body, and affect its susceptibility to proteolysis, influence microtubule stability, possibly contribute to disruption of axonal transport, but also facilitate neurite plasticity in a regenerative response [Shackelford and Yeh, 1998]. Tau hyperphosphorylation may contribute to the brain damage induced by transient cerebral ischemia, and may be involved in the pathogenesis of neurodegenerative disorders after stroke [Wen et al., 2004].

Therefore, alterations in tau phosphorylation may play an important role during the process of ischemic brain damage.

TAU AS A THERAPEUTIC TARGET FOR ISCHEMIC STROKE

Ischemic stroke is a high cause of death and long-term disability worldwide, but there is no effective therapeutic intervention other than the use of thrombolytics. Tau is critical to microtubule dynamics and metabolism, and contribute to neuron cell death during brain ischemia and/or reperfusion processes. Therefore, regulation of tau phosphorylation should be considered as a potential new therapeutic target in ischemic stroke. First, while formulating strategies targeting tau in stroke therapy, the state of tau phosphorylation at different phase during the ischemia and/or reperfusion processes has to be carefully considered in the development of any targeted intervention. Second, in tau protein, the phosphorylation sites cluster in the flanking region of the tubulin-binding domain and negatively regulate tau's binding affinity to microtubules [Kanemaru et al., 1992]. The mechanisms responsible for changes in tau phosphorylation and differential rephosphorylation during cerebral ischemia and reperfusion likely involve changes in the activities of specific phosphatases and kinases [Mailliot et al., 2000]. Therefore, specific tau-directed phosphatase regulators may promote recovery from ischemic insults. Third, immunoreactivity of tau in neuron and glia is a differential response to focal cerebral ischemia [Dewar and Dawson, 1995]. And neurons and glia react differently to an ischemic insult by exhibiting different tau epitopes [Uchihara et al., 2000]. Therefore, both the neurons and the glial cells should be considered as new therapeutic targets.

CONCLUDING REMARKS

Tau plays a crucial role in neuronal damage and clinical pathophysiology of ischemic stroke. Although the role of alterations in tau phosphorylation during and after ischemia/reperfusion process is generally complex and need further clarify and tau represents a relatively under-explored therapeutic target in ischemic stroke, we have reasons to believe that to unravel the role of tau in ischemic stroke may contribute to the understanding of intervention and offer an opportunity to develop a potent novel target for stroke therapy.

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