Understanding Tau phosphorylation in Alzheimer’s disease

Mohammed Razeeth Shait

Department of Biochemistry, Bharathidasan University, Tiruchirappalli-620024, Tamil Nadu, India.
* For correspondence email: razeeth.new@gmail.com

Article Info: Received 05 Jan 2014; Revised: 17 Apr 2014; Accepted 24 June 2014

ABSTRACT

Alzheimer’s disease (AD) is a fatal developing neurodegenerative disorder, associated with amyloid protein β-amyloid (Aβ) and tau-protein. Insoluble β-amyloid (Aβ) deposits are found in extracellular matrix in the form of plaques of AD brain and hyper phosphorylated tau-proteins inside the cells constructs neurofibrillary tangles which leads to synaptic alterations. The cognitive defects are the major clinical manifestations in AD. Dysfunctional synaptic activity leads to ultimately nerve cell loss. Understanding the formation of tauopathies and abnormal hyperphosphorylation of tau is still milestone in AD research. The present review focuses on exploration in tau pathology, tau hyperphosphorylation, role of O-GlcNAcylation, kinase and phosphatase in tau phosphorylation.

Keywords: Alzheimer’s disease, tau phosphorylation, O-GlcNAcylation, Neurofibrillary tangle, β-amyloid.

1. INTRODUCTION

Alzheimer’s disease (AD) is the most universal form of age related dementia with leads to severe consequences of neurodegeneration to the central nervous system. This facilitates ultimately slow down of cognitive function and dementia. The principal neuropathological features of AD are neurofibrillary tangles and β-amyloid (Aβ). Formation of neurofibrillary tangles (NFTs) in the brain is a characteristic lesion of AD. NFTs are composed of paired helical filaments (PHFs) and straight filaments (SFs). The major protein component of PHFs is the microtubule associated protein tau [1].

The tau protein is normally cytosolic protein, stimulate and stabilize microtubule assembly from tubulin subunits. However, tau protein in PHFs are diverse from than the normal tau. Hyperphosphorylation and accumulation of tau protein in neurons and glial cells is one the main pathological characteristic in AD [2]. The tau protein is aggregated in the brain of AD and all other tauopathies is always abnormally hyperphosphorylated. Numerous studies have been focused on the roles of abnormal hyperphosphorylation and the mechanism leading to tau hyperphosphorylation. The tau molecular mechanisms leading to abnormal tau hyperphosphorylation in AD and other neurodegenerative diseases are not yet fully understood [3].

Although in AD, hyperphosphorylated tau protein accumulates in the somatodendritic compartment of neurons. In AD, tau protein gets hyperphosphorylated due to mutation, activities of kinase, regulation of protein phosphatase and quinolinic acid. However there are several protein kinases that may catalyze tau phosphorylation in the brain. Several recent reviews have covered the post-translational modifications of tau, which mainly focused on abnormal
hyperphosphorylation [4]. The tau protein in PHFs is abnormal hyperphosphorylation and other post-translational modifications, includes glycosylation, ubiquitination, glycation, polyamination, nitration and proteolysis. β-amyloid (Aβ) formation due to A peptide derived from the amyloid protein precursor (APP) through beta and gamma secretase activity [2, 3]. Presenilin-1 (PS-1) and presenilin-2 (PS-2) are crucial components of the secretase machinery. Early onset familial AD is caused by mutations in APP, PS-1 and PS-2.

2. The tau Protein

The tau is known as axonal protein that regulates microtubule-associated (MT) stability and MT-dependent processes. The tau protein is a low molecular weight microtubule associated protein (MAP). The human tau gene is located on the long arm of chromosome 17 (position 17q21) and contains 16 exons. In human tau protein are found in neurons of both the peripheral and central nervous system. They are very low levels of tau protein expression have also been reported in glial cells [1-6] reveals tau protein is best characterized for its ability to bind to stabilize and promote the polymerization of microtubules. In human tau encode single gene located on chromosome 17q21-22 that consists of 16 exons. Isoforms generated by alternative mRNA splicing. Alternative splicing of exons (E) 2 (E2), 3(E3) and 10 (E10). It produce 6 isoforms, it ranging in length from 352 to 441 amino acids. It has 3R and 4R carboxy-terminal repeats. Along with specifically identified adjacent sequences are responsible for the binding of tau to MT. The tau is a phosphoprotein with 79 potential serine or threonine. It has (Ser/Thr) phosphorylation acceptor sites.

The tau phosphorylation is a typical physiological process which decreases tau’s binding affinity for MT [3]. Though the role of tau protein in regulating microtubule dynamics is well established, much less is known regarding the role of tau protein in other cellular functions. Given the ability of tau to interact with the plasma membrane and to bind a variety of proteins, tau is proposed to participate in cell signaling. Potential signaling proteins that bind tau include PP1, PP2A, the scaffolding protein 14-3-3 and phospholipase Cγ (PLCγ1) Additionally, tyrosine kinases (Fyn, cSrc, Lck and Fgr), the p85 are regulatory subunit of phosphatidylinositol 3-kinase and PLCγ1 have been shown to bind tau protein through their SH3 domains. SH3 domains recognize the PxxP motif in proteins, seven of which are present in tau close to known tau phosphorylation sites. The binding of tau to signaling molecules implies that tau is either a substrate to the binding enzyme or that tau regulates the activity of the protein to which it is bound.

2.1. Tau Phosphorylation and its site

Tau phosphorylation capacity has a developmental role in early ontogenesis and hyperphosphorylation of tau is highly pathogenic mechanism in AD. All six isoforms of tau are aggregated into PHFs in abnormally hyperphosphorylated forms in AD brain. The tau protein phosphorylated in early postnatal period much more than adulthood. Phosphorylation tau isoform in embryonic development it start disappear after postnatal period. It was believed that tau was phosphorylated only at serine and threonine residues. However, recent evidence suggests that tau protein is also phosphorylated on tyrosine residues. The longest form of adult human brain tau has 80 Ser or Thr residues and 5 Tyr residues; therefore, almost 20% of the molecule has the potential to be phosphorylated [7].

To date, at least 37 serine and threonine residues have been found to be phosphorylated in PHF-tau. These residues include Thr39, Ser46, Thr69, Thr123, Ser137, Thr153, Thr175, Thr181, Ser198, Ser199, Ser202, Thr205, Ser208, Ser210, Thr212, Ser214, Thr217, Thr231, Ser235, Ser237, Ser238, Ser241, Ser262, Ser285, Ser305, Ser324, Ser352, Ser356, Ser396, Ser400, Thr403, Ser404, Ser409, Ser412, Ser413, Ser416, and Ser422 [3] and also to date Casein kinase 1 and glycogen synthase kinase-3 were each found to phosphorylate numerous sites, and each kinase phosphorylated at least 15 sites that are also phosphorylated in PHF-tau from Alzheimer brain. A combination of casein kinase 1 and glycogen synthase kinase-3 activities could account for over three-quarters of the serine/threonine phosphorylation sites identified in PHF-tau, indicating that casein kinase 1 may have a role, together with glycogen synthase kinase-3, in the pathogenesis of Alzheimer disease [8]. Several proline-directed and non-proline-directed protein kinases have been suggested to have a role in the generation of PHF-tau in Alzheimer brain, including casein kinase 1 (CK1), but this enzyme has been relatively little studied as a tau kinase.

2.2. Role of O-GlcNAcylation in tau Phosphorylation

Glycosidic bonds are classified as either N-linked or O-linked. In N-linked glycosylation, the sugar is linked to the amide group of asparagine residues of proteins, while in O-linked glycosylation, sugars are
attached to a hydroxyl group of serine or threonine residues. Hyperphosphorylated tau and PHF-tau purified from AD brains are glycosylated, mainly through N-linkage. O-GlcNAc glycosylation occurs on numerous cytoplasmic and nuclear proteins, such as cytoskeletal proteins, transcription factors and viral proteins. It has been suggested that this type of glycosylation shares certain features with protein phosphorylation mainly by occupying the same or neighboring sites on the peptide backbone. N-linked glycosylation, human brain tau can be modified by O-linked monosaccharide β-N-acetylglucosamine (O-GlcNAc).

O-GlcNAcylation regulates tau phosphorylation in a site-specific manner in both cultured cells over expressing tau protein and in rodent brains at most of the phosphorylation sites examined that O-GlcNAcylation reduces tau phosphorylation. Consistent with this finding, in neuroblastoma cells transfected with tau and O-GlcNAc mainly modifies the less phosphorylated tau species, while highly phosphorylated tau is devoid of O-GlcNAc residues. In starved mice, a model used to mimic the fall in glucose uptake and metabolism experiential in the AD brain, O-GlcNAcylation is decreased and tau hyperphosphorylation is increased in the brains of the mice. In the AD brain, the level of O-GlcNAcylation is lower than that in control brains, indicating that O-GlcNAcylation is compromised.

Based on these findings, it was proposed that impaired glucose metabolism in AD may contribute to disease pathogenesis by reducing tau O-GlcNAcylation and consequently increasing tau phosphorylation. Scott [2008] reported that Theme-G an inhibitor of O-GlcNAcase that enhances O-GlcNAcylation, markedly reduces tau phosphorylation in PC12 cells at pathologically relevant sites, like Thr231 and Ser396. Moreover, Thiamet-G also efficiently reduces phosphorylation of tau at Thr231, Ser396 and Ser422 in both the rat cortex and hippocampus. Collectively, these findings emphasize the active relationship between the O-GlcNAcylation and phosphorylation of tau.

2.3. Role of kinase in tau phosphorylation

There are several kinases which involve in cause of tau protein hyperphosphorylation and formation of PHFs. That are observed during in vitro glyogen synthase kinase-3 (GSK-3), cyclin dependent kinase-5, mitogen activated protein kinase, extracellular signal-regulated kinases (MAPK/ERK1 and MAPK/ERK2, p44 and p42), stress activated protein kinases c-Jun N-terminal kinase (SAPK/JNK) and p-38 kinase (p38). GSK-3, MAPK/ERK, SAPK/JNK and p38 can phosphorylate tau at multiple sites phosphorylation of tau at Thr181 can be conveyed by MAPK/ERK, SAPK/JNK, p38 and GSK-3b, phosphorylation at Ser202 by MAPK/ERK, SAPK/JNK, p38 and GSK-3a, phosphorylation at Ser214 by cAMP dependent protein kinase (PKA) and GSK-3b. Ser396 is phosphorylated by MAPK/ERK, SAPK/JNK, p38 and GSK-3b, whereas Ser422 is mainly phosphorylated by members of the MAPK family, including MAPK/ERK, SAPK/JNK, and p38. Ser262 is phosphorylated by microtubule-affinity regulating kinase (MARK), PKA and GSK-3b. Phosphorylation of tau by a given kinase depends on the cell type on which the experiment is conducted; many in vitro experiments have been carried in various cell types other than neurons. The mechanisms of action of certain kinases such as GSK-3 are extremely complex and not completely understood. The function of GSK-3b depends on its specific state of phosphorylation; GSK-3b is inactivated by phosphorylation at Ser9 and GSK-3 catalyzed phosphorylation of tau is regulated by other kinases.

Modifications in tau phosphorylation do not essentially similar total levels of the kinases, and rather depend on the relative abundance of their active and inactive forms, for example whereas the levels of phosphorylated (active) MAPK/ERK1 and MAPK/ERK2 (MAPK/ERK-P Tyr204) are markedly increased in AD brain homogenates, and phospho-ERK is exclusively expressed in a percentage of neurons with phospho-tau deposits in AD but not in control cases. The reason for MAPK/ERK activation in AD is not known, but MAPK kinase 1 (MEK1). Moreover, Ras, an upstream activator of the MEK-1, is activated in AD. The role of GSK in the pathogenesis of AD is enormously complex. On one hand, GSK-3a regulates the production of amyloid peptides. On the other, GSK-3b phosphorylated at Tyr216 (active form) has been reported in association with NFTs in one study.

In contrast, GSK-3b phosphorylated at Ser9 (inactive form) has been shown to be present in neurons with neurofibrillary tangles and in dystrophic neurites surrounding b-amyloid plaques. Increased expression of active SAPK/JNK and p38 has been observed in association with abnormal tau deposits in AD, including NFTs and dystrophic neurites of senile plaques. SAPK/JNK phosphorylate at site of Tyr183/185, P-38 phosphorylate at site of Thr180/Tyr182. Furthermore, JNK kinase 1 (JNK1), an upstream activator of JNK/SAPK, is activated in AD.
2.4. Role of phosphatase PP2A in tau Phosphorylation

Phosphatases that regulate tau phosphorylation level among protein phosphatases, PP2A has been shown to be the major tau phosphatase in the brain. The comparison of the catalytic kinetics of tau dephosphorylation by various major brain protein phosphatases and determined the relative contributions of these phosphatases to the regulation of tau phosphorylation quantitatively. It show that PP2A accounts for 70% of the total tau phosphatase activity but PP1, PP2B, and PP5 each accounts for only 10% of the total tau phosphatase activity. Because PP2B activity is up regulated rather than down regulated in AD brain [11]. On the other hand, both the activity and the expression of PP2A as well as the activities of PP1 and PP5 are decreased in the selected areas of AD brain [12]. Down regulation of the phosphatases, especially of PP2A, might underlie the abnormal hyperphosphorylation of tau and other proteins in AD brain. Studies of metabolically active rat brain slices and transgenic mice suggest that the downregulation of PP2A may produce hyperphosphorylation of tau, not only by the deficient dephosphorylation of tau, but also through the activation of several PP2A-regulated protein kinases, including PKA, CaMK-II, MAP kinases, and stress-activated protein kinases [13]. Nevertheless inhibition of PP2A activity in animal brain could only induce hyperphosphorylation of tau at some of the hyperphosphorylation sites seen in PHF tau. Downregulation of PP2A expression and upregulation of PP2A endogenous inhibitor proteins IPP2A1 and IPP2A2 in AD brain may both put in to the downregulation of PP2A activity [14]. Because the activities of PP1 and PP5, which contribute to regulation of tau phosphorylation to a much smaller extent than PP2A [15], are also decreased in AD brain, there might be a common factor that down regulates the activities of the major brain protein phosphatases in AD brain.

3. CONCLUSION

The tau phosphorylation is regulated by multiple kinase and phosphates activity. Expression of kinase play a predominate role in regulating tau phosphorylation. Kinase and phosphatase hold the key role in regulating major cellular mechanism. Glycosylation is interlinked various signaling pattern and phosphorylation. Exploring pathway facilitates indirect relationship for kinase up regulation and down regulation of phosphates will facilitate in understanding the formation of NFTs.

Conflict of Interest

The authors declare that they have no conflicts of interest

Acknowledgement

The valuable support of Department of Biochemistry, Bharathidasan University, Tiruchirappalli is greatly acknowledged.

References


