REVIEW

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Tau pathology in diabetes mellitus

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Neurodegenerative tauopathy characterized by hyperphosphorylation tau has been implicated in the pathophysiology of diabetic central nervous system (CNS) complication. Emerging evidence has suggested that hyperphosphorylation tau is caused by an imbalance of protein kinase and phosphatase activity. This review focuses on the contributions of impaired insulin signaling to diabetes-related tauopathy through disrupting the balance of tau-related protein kinases and phosphatases. In addition, we describe tau pathology as a potential target for central neuronal degeneration in diabetes mellitus.

1. Introduction

Impaired central insulin signaling observed in both type 1 and type 2 diabetes has been implicated in the pathophysiology of diabetic central nervous system (CNS) complication (Li et al. 2005; Liu et al. 2011; Sima et al. 2009). Brain tissue of diabetes shows marked neuronal loss and degeneration that ultimately results in deficits in cognitive performance (Sima 2010; Umegaki 2012). However, little is known about the mechanism of diabetic central neuropathy. Epidemiological studies have demonstrated that type 2 diabetes is a risk factor for developing Alzheimer's disease (AD) (Kopf and Frolich 2009; Sims-Robinson et al. 2010). There is strong evidence to support a link between central insulin dysfunction and AD (de la Monte 2012; Liu et al. 2011). Neurodegenerative tauopathy characterized by hyperphosphorylation tau is thought to be a critical event in the pathogenesis of AD (Trojanowski and Lee 1994). Interestingly, AD-like hyperphosphorylated tau was also observed in both type 1 and type 2 diabetes brain (Kim et al. 2012; Planel et al. 2007), suggesting tau pathology caused by insulin dysfunction may be the common mechanism of diabetes and AD. That is why antidiabetic drugs could work against AD.

2. Tau pathology in diabetes

Tau protein is a member of a large family of microtubule-associated proteins (MAPs) whose function is to bind to and stabilize microtubles (MTs) in neurons (Weingarten et al. 1975). Through stabilizing MTs, tau protein plays a major role in the maintaining appropriate neuron morphology and intercellular transport. Tau binding to MTs is regulated by different post-translational modification, including phosphorylation (Weingarten et al. 1975), ubiquitination (Mori et al. 1987) and acetylation (Min et al. 2010). Of these, phosphorylation has been most extensively studied. Hyperphosphorylated tau looses its binding ability to MTs and sequesters normal tau and prevents them binding to MTs, resulting in the disruption of the MTs (Alonso et al. 2001; Zhou et al. 2006). Tau pathology begins intracellularly with tau hyperphosphorylation and sequestration of normal tau and other microtubule-associated proteins, causing microtubule disassembly, and ultimately leads to neuronal degeneration (Iqbal et al. 2005).

In different diabetic models different phosphorylation sites of tau were detected. The levels of Ser199/202- and Ser396-phosphorylated tau were increased in diabetic Otsuka Long Evans Tokushima Fatty (OLETF) rats compared to control Long Evans Tokushima Otsuka (LETO) rats (Kim et al. 2012). Increased phosphorylated tau at Ser396 was detected in the type 2 BBZDR/Wor rats, but not type 1 BB/Wor rats (Li et al. 2007). Buffie et al. found that rapid and massive increases in the phosphorylation of brain tau at multiple residues, including Thr181, Ser199, Ser202, Thr211, Thr231, Ser262, and Ser396/404 in STZ-induced diabetic mice (Clodfelder-Miller et al. 2006). In another study, the tau phosphorylations at AT8 (pS202 and pT205) and PHF-1 (pS396 and Ps404) epitopes in response to STZ treatment were found to be biphasic (Planel et al. 2007). A mild hyperphosphorylation of tau could be observed 10, 20, and 30 days after STZ injection, and a massive hyperphosphorylation of tau was detected after 40 days, which impaired tau binding to MTs (Planel et al. 2007). Interestingly, tau aggregation was not observed in STZ-induced mice brain (Planel et al. 2007). And, intracytoplasmic phosphorylated tau-positive tangle-like inclusions were not detected in both type 1 and type 2 diabetes brain (Li et al. 2007).

In normal adult brain, tau mainly locates in neuronal axons. Abnormally hyperphosphorylated tau in DM bain is localized in the neuropil and the axonal tracks of the fimbria (Singh et al. 2007), which is similar to the earliest tau pathology in AD brain (Bancher et al. 1989; Trojanowski and Lee 1994).

In the central nervous system, six isoforms of tau exist. The imbalance of tau isoforms is thought to lead to neuronal instability and degeneration. Among these tau isoforms, three-repeat (3R) tau: four-repeat (4R) tau ratio is maintained at 1:1. Recently, Jung et al. (2011) found that increased 3R tau aggregates in

neurons and contributes to tau pathology in a chronic type 2 diabetes mellitus model using aged Otsuka Long-Evans Tokushima Fatty(OLETF) rats with obesity.
It has been reported that hyperphosphorylated tau was detected in Langerhans islets in type 2 diabetic patients, suggesting that tauopathy may also occur in other organs than the brain (Maj et al. 2010; Miklossy et al. 2010).

3. Tau pathology and an imbalance of protein kinase and phosphatase activity

An imbalance of protein kinase and phosphatase activity is believed to be the main mechanism behind the formation of hyperphosphorylation of tau (Grundke-Iqbal et al. 1986). Several protein kinases, such as glycogen synthase kinase 3(GSK-3), cyclin-dependent protein kinase 5 (cdk5), cell-division cycle kinase (cdc2), protein kinase (PK)A, PKB/AKT and mitogen-activated protein kinase (MAPK), including extracellular signal-regulated kinase 1/2 (ERK1/2), c-Jun N-terminal kinase (JNK) and p38 are considered to be tau kinases (Grimes and Jope 2001; Hamdane et al. 2003; Illenberger et al. 1998; Ksiezak-Reding et al. 2003; Pei et al. 1999, 2002, 1998, 1997; Reynolds et al. 2000; Shahani and Brandt 2002). Among these tau kinases, AKT and GSK-3β lie with the PI3K pathway, and ERK1/2, JNK and p38 in the MAPK pathway. GSK-3β is one of the most favourable tau candidate kinases. It regulates microtubule stability through tau phosphorylation (Wang et al. 2007). For example, phosphorylation of Thr231 in tau by GSK-3β regulates tau' ability to bind microtubules (Cho and Johnson 2004). The hyperphosphorylation of tau in diabetic brain is partly due to the over-activation of GSK-3β (Yang et al. 2013). Ser9 phosphorylation inhibits GSK-3β activity, whereas Tyr216 phosphorylation stimulates its activity (Grimes and Jope 2001). Both Ser9 and Tyr216 phosphorylation of GSK-3β can be mediated by PI3K/AKT and MAPK pathways (An et al. 2005; Cole et al. 2004).
Most recently, Pei et al. found that the mammalian target of rapamycin (mTOR) /70-kDa ribosomal protein S6 kinase (p70S6K) pathway was involved in regulation of phosphorylation of GSK-3β and followed by phosphorylation of tau (An et al. 2005). Importantly, p70S6K can directly phosphorylate tau at S262, S214, and T212 sites and up-regulate the synthesis of tau through phosphorylating S6 at S235 and S236 sites *in vitro* (Pei et al. 2006). The phosphorylation and activation of p70S6K are regulated by PI3K and MAPK pathways (An et al. 2005). Therefore, these PI3K and MAPK pathway-related tau kinases such as AKT, ERK1/2, JNK and p38 may not only directly phosphorylate tau but also regulate tau mRNA translation via p70S6K. In addition, over-activation of JNK and p38 was detected in diabetic brain, which may contribute to the diabetes-related tau pathology (Li et al. 2012; Sharma et al. 2010).
Several protein phosphatases (PP) such as PP1, PP2A, PP2B and PP5 have been shown to dephosphorylate tau. Among these phosphatases, PP2A is believed to be the major tau phosphatase that dephosphorylates tau on Thr205, Thr212, Ser262 and Ser409 (Liu et al. 2005). It is well documented that inhibition of PP2A activity leads to tau hyperphosphorylation at several sites, such as the PHF-1 and Ser262 sites seen in the diabetic brain (Clodfelder-Miller et al. 2006; Qu et al. 2011). The activity of PP2A is inhibited during STZ-induced diabetes, which leads to the DM-related tau pathology (Planel et al. 2007). Besides directly dephosphorylating tau, PP2A indirectly regulates phosphorylation of tau by dephosphorylate other kinases, such as p70S6K and GSK-3β (Meske et al. 2008; Peterson et al. 1999). For example, PP2A dephosphorylates GSK-3βat Ser9, resulting in the up-regulation of GSK-3β (Meske et al. 2008). The activity of PP2A is post-translational modified. For example, PP2A phosphorylation at the Y307 site and demethylation at the L309 site down-regulate PP2A activity (Tolstykh et al. 2000). Several studies have shown that mTOR restrains the activity of PP2A and rapamycin activates the PP2A (Bishop et al. 2006; Hartley and Cooper 2002; Meske et al. 2008; Peterson et al. 1999). The mechanism may involve the direct phosphorylate/inactivate PP2A by mTOR (Meske et al. 2008; Peterson et al. 1999).

4. Tau pathology and impaired insulin signaling in diabetic brain

In the CNS, insulin plays critical roles in regulating and maintaining cognitive function. It has been document that peripheral insulin deficiency impaired central insulin pathway activity, which contributes to tau pathology in the DM brain (Jolivalt et al. 2008). In insulin-deficient mice, reduced insulin signaling was associated with a concomitant increase in tau phosphorylation (Jolivalt et al. 2008). Furthermore, a rapid and large increase in tau phosophorylation in the brain was observed in STZ-induced diabetic mice (Clodfelder-Miller et al. 2006). Compared with spontaneous onset of type 1 diabetes, tau hyperphosphorylation was more severe in the type 2 diabetic model and appeared to be associated with insulin resistance (Li et al. 2007). Because of reduced insulin transport via the blood brain barrier, hyperinsulinemia induced by insulin resistance may be accompanied by central insulin deficiency (Umegaki 2012), which is another main reason behind tauopathy of type 2 diabetes. In a peripheral hyperinsulinemia model without impaired central insulin receptor signaling, no tau hyperphosphorylation was detected (Becker et al. 2012), suggesting that only central insulin dysfunction contributes to the brain tau pathology. Besides abnormally phosphorylated tau, cleaved tau also contributes to the tau pathology. Increased cleaved tau was found in a type 2 mouse model, but not in a type 1 mouse model, suggesting that hyperglycemia-mediated tau cleavage may be the key feature in type 2 diabetes (Kim et al. 2009).
By the binding of insulin to its receptor, insulin signaling is activated. Activation of PI3K, the major insulin downstream signaling, leads to activation of AKT. A major target of AKT is GSK-3β, which is the major tau kinase. It was examined that insulin modulated tau phosphorylation *in vivo* and *in vitro* (Freude et al. 2005; Hong and Lee 1997; Lesort et al. 1999). Decreases in the levels and activities of insulin-PI3K-AKT signaling components were found in human brain of type 2 DM (Liu et al. 2011). Impaired insulin-PI3K-AKT signaling might contribute to abnormal tau pathology through over-activation GSK-3β (Liu et al. 2011). Insulin treatment prevents tau hyperphosphorylation through rescuing the disorder of AKT/GSK-3β (Qu et al. 2011). In addition, insulin deficiency within the brain induces JNK and p38 hyperphosphorylation resulting in hyperphosphorylation of tau (Schechter et al. 2005; Sharma et al. 2010).
Multiple sites of tau, including Ser199, Ser202, Thr205, Ser396 and Ser404, phosphorylated by GSK-3β can be antagonized by PP2A (Meske et al. 2008). Insulin dysfunction induces a deregulation of PP2A activity, resulting in abnormal tau hyperphosphorylation (Papon et al. 2013; Planel et al. 2007; Qu et al. 2011). At 10 d after STZ injection, a ∼15% decrease in brain PP2A activity was detected, leading to the reduction in tau dephosphorylation (Planel et al. 2007). Both decreased PP2A activity and increased phosphorylated tau were reversed by insulin treatment (Planel et al. 2007).
It is established that reduced insulin signaling mediated the impaired tau gene expression (de la Monte et al. 2003). In type 2 diabetes, the expression of total tau was markedly increased

(Jung et al. 2011), suggesting that the abnormal synthesis of tau was also involved in DM-related tau pathology.

5. Therapeutic targeting of tau pathology in diabetes

Hyperphosphorylation of tau leads to disruption of MTs and neurodegeneration and is involved in the pathophysiology of diabetic CNS complication. Inhibition of tau hyperphosphorylation is the therapeutic target of diabetic CNS complication. Tau hyperphosphorylation is mediated by inappropriate activation of tau kinase, including GSK3β, p38 MAPK, and JNK, and inhibition of phosphatases that dephosphorylate tau, for example PP2A (Wang et al. 2007). Therefore, treatment with tau kinase inhibitors or phosphatase activators may rescue the tau pathology in diabetes. Lithium, a specific GSK3β inhibitor, reversed phosphorylation of tau at Ser396/404 in STZ-induced diabetic rats (Qu et al. 2010). In db/db mice, the increased phosphorylated tau at Ser396 was attenuated by metformin through inhibiting JNK activation (Li et al. 2012). Based on the fact that insulin dysfunction contributes to the hyperphosphorylation of tau, insulin and many insulin sensitizers are benefit for diabetes-related tau pathology. In type 1 and type 2 diabetic model, insulin administration ameliorated tau hyperphosphorylation through normalizing AKT and GSK-3β activation (Qu et al. 2011; Yang et al. 2013). The thiazolidinediones (TZDs), peroxisome proliferator-activated receptor gamma agonists, including rosiglitazone and troglitazone are insulin sensitisers used to treat type 2 diabetes. Rosiglitazone treatment reduced tau phosphorylation only in the hippocampus of type 2 diabetes, but not in type 1 diabetes (Yoon et al. 2010). The reduction of tau phosphorylation caused by rosiglitazone was assoiated with reduction of JNK activity, not of GSK3β activity (Yoon et al. 2010). d'Abramo et al. found that another TZD, troglitazone, decreased tau phosphorylation through regulating PDK1/p70S6K/mTOR signaling (d'Abramo et al. 2006). Glucagon-like peptide-1 (GLP-1), a novel anti-diabetes agent prevented impairment of spatial learning and ultra-structural cellular damage induced by STZ intracerebroventricular injection (Li et al. 2012). The neuroprotective effects of GLP-1 have a possible link to GSK3 modification (Gao et al. 2011).

6. Conclusions

In summary, tauopathy characterized by hyperphosphorylation tau is a critical event in diabetic CNS complication. Hyperphosphorylation of tau is caused by an imbalance of protein kinase and phosphatase activity, which is due to impaired central insulin signaling in type 1 and type 2 diabetes. Treatment of targeting tauopathy with tau kinases inhibitiors, phosphatase activators, and anti-diabetes drugs which rescue insulin dysfunction may be of benefit for the diabetic patients with CNS complications.

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