Mutual Relationship between Tau and Central Insulin Signalling: Consequences for AD and Tauopathies?

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Keywords

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Abstract

Alzheimer disease (AD) is a progressive neurodegenerative disorder mainly characterized by cognitive deficits and neuropathological changes such as Tau lesions and amyloid plaques, but also associated with non-cognitive symptomatology. Metabolic and neuroendocrine abnormalities, such as alterations in body weight, brain insulin impairments, and lower brain glucose metabolism, which often precede clinical diagnosis, have been extensively reported in AD patients. However, the origin of these symptoms and their relation to pathology and cognitive impairments remain misunderstood. Insulin is a hormone involved in the control of energy homeostasis both peripherally and centrally, and insulin-resistant state has been linked to increased risk of dementia. It is now well established that insulin resistance can exacerbate Tau lesions, mainly by disrupting the balance between Tau kinases and phosphatases. On the other hand, the emerging literature indicates that Tau protein can also mod-

ulate insulin signalling in the brain, thus creating a detrimental vicious circle. The following review will highlight our current understanding of the role of insulin in the brain and its relation to Tau protein in the context of AD and tauopathies. Considering that insulin signalling is prone to be pharmacologically targeted at multiple levels, it constitutes an appealing approach to improve both insulin brain sensitivity and mitigate brain pathology with expected positive outcome in terms of cognition.

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Central Insulin Signalling: Impact on Cognition and Metabolism

Brain Insulin and Receptor

Insulin is a peptidic hormone containing two chains, discovered in 1921 by Banting and Best [1]. In peripheral tissues, insulin facilitates glucose utilization and suppresses hepatic glucose production. Interestingly, insulin

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was first detected in the rat brain through immunostaining in 1978 [2] in much higher concentration than in the plasma and seemed to be independent of the peripheral concentration [3]. Few years later, insulin mRNA was detected by in situ hybridization in various brain areas including hypothalamus, hippocampus, and olfactory bulb in rodents [4, 5], suggesting that the central nervous system might be able to produce the hormone. While central insulin production is still controversial, insulin transport from the periphery to the brain is well documented. Physiological transport of insulin through the blood brain barrier (BBB) was first reported in rabbits using radiolabeled insulin [6]. Immunoreactive insulin was also found in dog's brain and seemed to be correlated with basal plasma levels [7] and dependent on feeding state, being lower during fasting [8]. Insulin transport requires binding to the insulin receptor (IR) and transcytosis of the IR insulin complex through brain endothelial cells. Interestingly, this transport can be modulated, for instance by high-fat diet, astrocyte stimulation, or nitric oxide inhibition [9].

IR is a heterotetrameric membrane glycoprotein belonging to the tyrosine kinase receptor family which is composed of two α - and two β -subunits. IR is widely expressed in peripheral tissues, and radiolabeled ^{125}I -insulin allowed the detection of the receptor in the brain of monkeys, pigeons, humans and rats [10–12]. IRs found in the brain and liver showed different patterns of migration during electrophoresis, suggesting 2 different isoforms [13]. In addition, in contrast to peripheral IRs, brain receptors are not downregulated by insulin excess [14]. Brain IR is present at all stages of development, although its distribution and concentration vary between embryonic and adult brain, consistent with the role of insulin in neurogenesis [12]. In situ hybridization of IR mRNA in the adult rat brain revealed high gene expression in the hypothalamus, more particularly in the anterior nuclei, in the hippocampus, olfactory bulbs, and the choroid plexus [15], regions concerned with olfaction, appetite, cognition, and autonomic functions [16].

As it does in the periphery, brain insulin signalling through its receptor involves the tyrosine phosphorylation of cellular substrates, including several IR substrates (IRSs) [17] as well as other scaffold proteins such as Src-homology collagen (Shc) [18, 19] and Grb2-associated docking protein (Grb2-SOS) [20]. The IRSs ensure metabolic effects of insulin through the activation of phosphatidylinositol 3-kinase (PI3K) which recruits both the Ser/Thr 3-phosphatidylinositol-dependent protein kinase (PDK) and protein kinase B (PKB or Akt) to the plasma membrane, where Akt is activated by PDK1- and PDK2

[21] (Fig. 1). At the end of this pathway, mTOR links insulin signalling to nutrient sensing [22]. Mitogenic effects of insulin involve the recruitment of mitogen-activated protein kinases through small G-protein Ras leading to the translocation of ERK to the nucleus, where it controls gene expression [23].

Role of Central Activation of IR on Metabolism

The role of central IR activation in the regulation of glucose metabolism and feeding behavior is well described. For instance, study of the neuron-specific knockout mouse model of the IR (NIRKO mice) showed that neuronal inactivation of the IR in the central nervous system led to increased food intake and obesity, together with insulin resistance, hyperinsulinaemia, and hypertriglyceridaemia [24]. More particularly, the arcuate nucleus (ARC) of the hypothalamus plays a pivotal role in the metabolic action of insulin in the brain. In the ARC, two neuronal populations are antagonist in the regulation of food intake and energy expenditure: neurons producing pro-opiomelanocortin (POMC neurons) and neurons producing agouti-related protein (AgRP) and neuropeptide Y (NPY) (AgRP-neurons) which project to each other and to second-order neurons, in different hypothalamic areas (paraventricular nucleus, ventromedial hypothalamus...). POMC neurons decrease food intake and increase energy expenditure via the release of α -melanocyte-stimulating hormone (α -MSH) and through activation of melanocortin receptors (MCRs) [25, 26]. AgRP-neurons increase feeding by opposing the anorexigenic actions of the neighboring POMC neurons [27–29] through the release of AgRP, a competitive inhibitor of MCRs [26, 30]. Acute depletion of AgRP neurons leads to life-threatening anorexia [31–34]. IRs are highly expressed on the surface of both POMC and AgRP neurons [35, 36]. Selective inactivation of IR in these neurons showed that AgRP neurons, rather than POMC neurons are required for central insulin control of hepatic glucose production [18]. In the same manner, inactivation of IRs in NPY-expressing neurons induced an obese phenotype, leading to the conclusion that insulin signalling in NPY neurons controls food intake and energy expenditure [37]. Furthermore, insulin decreases expression of the orexigenic peptides AgRP and NPY, leading to decreased food intake and increased expression of POMC [38], resulting in increased levels of α -MSH, which promotes anorexia and increases energy expenditure [39]. In addition to the hypothalamus, insulin signalling was also shown to play a role in reward dopaminergic circuitry, since inactivation of IR in tyrosine hydroxylase-expressing cells re-

Fig. 1. Intracellular mechanisms linking insulin signalling, Tau, and A β pathology. Under physiological conditions (blue arrows), insulin binds to its receptor and induces phosphorylation and activation of the PDK1 and Akt pathway through PI3K, leading to increased cognition and metabolism regulation. Insulin beneficial effects on Tau protein involve inhibition of Tau kinases such as GSK3 β and p38 by Akt, thus limiting Tau hyperphosphorylation. Monomers of Tau protein also contribute to normal insulin signalling by inhibiting the conversion of PIP3 back to PIP2 through PTEN. In Alzheimer's pathology (red arrows), a vicious circle between insulin resistance, Tau pathology and A β pathology takes place. Insulin resistance leads to a decrease in Akt stimulation thus diminishing insulin action on cognition and metabolism. Reduction of Tau kinase inhibition leads to Tau hyperphosphorylation, aggregation in Tau oligomers and NFTs. Insulin resistance can be promoted by A β oligomers and ApoE4. A β oligomers can contribute to insulin resistance by competitively binding and internalizing

IRs and by increasing the phosphorylation of IRS-1 and JNK. ApoE4 reduces insulin-IR interaction and impairs IR trafficking. Inflammation triggered by Tau and A β oligomers induces release of cytokines such as IL1 β and TNF α by activated microglia which stimulate Tau kinases (JNK, p38), thus precipitating Tau pathology. Resulting NFTs then lead to cognitive impairments and metabolism dysregulation, which contribute to the propagation of AD pathogenesis. IR, insulin receptor; IRS-1/2, insulin receptor substrate 1/2; PI3K, phosphatidylinositol-3-kinases; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PTEN, phosphatase and tensin homolog; PDK1, 3-phosphoinositide-dependent protein kinase-1; Akt, protein kinase B; GSK3 β , glycogen synthase kinase 3 beta; JNK, c-Jun N-terminal kinases; P38, p38 mitogen-activated protein kinases; PP2A, protein phosphatase 2; IL1 β , interleukin 1 beta; TNF α , tumor necrosis factor alpha; TNFR, tumor necrosis factor receptor; NFTs, neurofibrillary tangles.

sulted in increased body weight, increased fat mass, and hyperphagia, and seemed to be dependent on dopaminergic neurons in the ventral tegmental area and substantia nigra [40].

Experiments using intranasal insulin, which allow the uptake of insulin from olfactory nerves [41], bypassing the BBB, were of significant importance to isolate insulin effects on the brain from the periphery. In humans, intranasal insulin has been shown to regulate response to food cues and smelling capacity [42], to increase satiety [43], and to decrease food intake [44]. In animal models, brain insulin has been reported to be involved in satiety [45], reduction of lipolysis in adipose tissue [46], and regulation of insulin sensitivity in skeletal muscles and liver, where brain insulin is notably required for glucose production [47]. In the rat brain, insulin regulates enzymes of cerebral glucose metabolism such as hexokinase and phosphofructokinase [48]. Like at the periphery, insulin is involved in glucose uptake in the brain, although to a lesser extent since the most abundant glucose transporters in the brain, Glut-1 (entire brain, astrocytes, and endothelial cells), Glut-2 (hypothalamus), and Glut-3, (the major glucose transporter in the neurons of the cerebellum, striatum, cortex, and hippocampus and some glial and endothelial cells) are not insulin-dependent (reviewed in [49]). Indeed, insulin-dependent Glut-4 is found at much lower levels in selective areas of the brain, including the olfactory bulb, dentate gyrus of the hippocampus, hypothalamus, and cortex [50]. The neuron-specific glucose transporter Glut-8 (also known as Glutx1), also insulin-dependent, is expressed in several areas of the brain, in particular in the hippocampus where it is thought to contribute to glucose homeostasis in neurons [51, 52].

Role of Central Activation of IR on Cognition

The location of IR in regions involved with cognition such as the cortex and hippocampus suggests a role of the hormone beyond metabolism. Insulin, through Glut-4 and Glut-8, supports cognition by ensuring cognitive areas receive the necessary amount of fuel to function. Several studies in mice indicate that insulin contributes to changes in hippocampal synaptic plasticity by favouring long-term potentiation (LTP) [53] and long-term depression [54], two molecular mechanisms involved in hippocampal-dependent learning and memory. In accordance, impaired LTP and spatial learning deficits have been reported in mice with a downregulation of IRs in the hippocampus [55]. One of the underlying mechanisms is based on the regulation of N-methyl-D-aspartate receptor membrane expression by insulin [56]. These changes are

thought to involve insulin activation of ERK1/2 [57] or PI3K signalling [58]. Insulin signalling has also been shown to contribute to synaptogenesis and synaptic remodeling in the rat brain and cultured hippocampal neurons [59], two mechanisms essential for neuronal plasticity. Recently, an interesting study has shown that brain insulin-resistance induced by high-fat diet impairs memory and underlying synaptic plasticity through hyperphosphorylation of AMPA glutamate receptor subunit GluA1 [60], indicating that intact insulin signalling is required for memory formation. Besides experimental models, in humans, intranasal insulin has been shown to improve memory functions in healthy subjects [61, 62], with no effect on word recall and non-declarative memory but rather on declarative, hippocampus-dependent memory contents [62, 63]. Conversely, both type 1 and type 2 diabetic patients have been shown to exhibit cognitive impairments and an increased risk of Alzheimer disease (AD) [64] consistent with the above-mentioned idea that unfavourable metabolic conditions reduce insulin transport into the brain [9]. Considering the presumable role of insulin regarding brain glucose uptake, this also fits with the reduced brain glucose uptake associated with dementia [65].

Overview on Tau and Tauopathies

Since its discovery in 1975 [66], Tau protein became of great interest when it was identified as the main component of neurofibrillary tangles (NFTs) in the brains of patients with AD [67–69]. Tau protein is expressed mainly in the human brain as 6 isoforms, generated by alternative splicing [70, 71]. Tau belongs to the microtubule-associated proteins (MAPs) family which includes MAP2 and MAP4 [72] and is well known for its role in microtubule assembly and stability, playing a role in diverse cellular processes such as cell morphogenesis, cell division, and intracellular trafficking. It is however now considered that, beyond microtubules, Tau exerts much larger neuronal functions, notably at the level of synapses and nuclei [73–75]. Tau is also physiologically released by neurons [76] even if the natural function of extracellular Tau remains to be uncovered [77].

Tau protein sequence contains more than 85 phosphorylated or phosphorylable sites [78]. Hyperphosphorylation of Tau leads to conformational changes that notably impair its ability to bind to microtubules. Free monomers of misfolded Tau then start to accumulate, oligomerize and aggregate. During the aggregation pro-

cess, repeated domains of Tau adopt a beta sheet conformation [79] and form filaments [80]. Tau aggregates can deposit in NFTs that are the hallmark of a group of diseases called tauopathies [81, 82], divided into primary tauopathies (Pick disease, progressive supranuclear palsy, frontotemporal dementia...) and secondary or mixed tauopathies (AD...) characterized by different clinical features and pathological hallmarks, reviewed elsewhere [83]. Tauopathies particularly differ from the cell types exhibiting NFTs and Tau isoform aggregation [78]. Notably, in AD, NFTs are observed early in life and increase during aging [84]. The spatiotemporal progression of NFTs from the entorhinal cortex and the hippocampus to the isocortical areas has been shown to be correlated with cognitive deficits [85], supporting a pivotal role for Tau pathology and spreading in AD-related memory impairments [86]. Interestingly, hypothalamus that plays a key role in the central control of energy metabolism has been also shown to display alterations in AD [87, 88]. In a study investigating 28 patients with AD, 22 patients showed plaques and NFTs in the hypothalamus [87]. In the AD stages described by Braak, plaques and tangles are found in the hypothalamus at stages III and IV [84]. Interestingly, these stages correspond to early-moderate AD, whereas disturbances in metabolism, such as weight loss, which is regulated by hypothalamus, are often described to appear prior to cognitive impairments. This could suggest that factors other than Tau and A β accumulation in the hypothalamus could contribute to metabolic deregulation. Indeed, studies of early cases of AD show neuronal loss in several nuclei of the hypothalamus in the supraoptic nucleus, and the paraventricular nucleus and even more in the suprachiasmatic nucleus (SCN), with minimal deposits of Tau or A β [89, 90]. Atrophy of the hypothalamus was also evidenced in other tauopathies such as behavioral variant frontotemporal dementia (bvFTD) [91]. SCN degeneration in AD and FTD was correlated with circadian rhythm deregulation of body temperature [92]. Notably, deregulation of body temperature is well characterized to promote Tau pathology in vivo [93–96]. Hyperphosphorylated Tau as well as NFTs [97] and atrophy [98] in the hypothalamus have also been reported in mouse models of tauopathies.

Tau hyperphosphorylation is the result of deregulation in a balance between kinases and phosphatases. More than 30 kinases have been described as regulating Tau phosphorylation in vitro, while only a few have been confirmed in vivo. Among them, GSK3- β is an important kinase which phosphorylates Tau on more than 30 sites and seems to play a pivotal role in AD and NFT develop-

ment [99]. All serine/threonine phosphatases in the brain are prone to dephosphorylate Tau in vitro except PP2C [100–104], with PP2A contributing to 71% of the phosphatase activity on Tau [105]. Notably, several kinases and phosphatases of the Tau protein are involved in the regulation of insulin signalling such as GSK3- β , AMPK, ERK, JNK, PP1, and PP2A (Fig. 1).

Brain Insulin Resistance in AD and Tauopathies: Cause or Consequence?

The Brain of AD Patients Is Insulin Resistant

Insulin resistance is defined as the inability of insulin to optimally stimulate the transport of glucose into the cell (hyperinsulinaemia or impaired glucose tolerance) as a result of altered insulin signalling [106]. In the brain, more particularly, insulin-resistance leads to reduced cerebral glucose metabolism that eventually causes neuronal loss or dysfunction [107]. Considering the prominent role exerted by insulin towards plasticity and cognition, it is not surprising that the AD brain has been described to exhibit an insulin-resistance state, the so-called “type 3 diabetes” [108, 109]. Indeed, CSF insulin levels have been described to be lower in AD patients than in healthy subjects [110, 111], although these data have not always been confirmed by others [112, 113]. Some explained reduced CSF insulin levels by a decreased transport of insulin across the BBB as suggested by Banks et al. [118, 119] who reported that chronic plasma hyperinsulinaemia, often reported in AD patients [110, 114–117], impairs the transport of insulin into the brain. However, whether all AD patients with reduced CSF insulin exhibit hyperinsulinaemia remains to be established, and other mechanisms could be instrumental. The IR signalling pathway and ability to respond to insulin have been described to be strongly impaired in the brains of AD patients [120, 121]. A notable increase in inhibitory IRS-1 phosphorylation at serine 616 and 636/639 has been particularly observed [121]. Tau pathology would likely contribute to the establishment of such brain insulin resistance. Indeed, a study by Yarchoan et al. [122] found increased phosphorylation of serine IRS-1 in primary tauopathies, including Pick disease, corticobasal degeneration and progressive supranuclear palsy, even to a lesser degree than in AD.

Consequences of Brain Insulin Resistance for Cognition, Longevity, and Metabolism

Considering the above-mentioned role of insulin in the regulation of synaptic plasticity and memory, a cor-

relation between increased serine phosphorylation of IRS-1 and cognitive scores in AD patients (episodic and working memory) sounds logical [121]. Moreover, changes in insulin signalling in different models of rodents led to memory impairments [55, 123] and other age-related cognitive alterations [124]. Noteworthy, paradoxically, deletion of IRS-2 in AD mouse model has previously been shown to reduce amyloid deposition and to rescue behavioral deficits [54]. These protective effects could relate to the IGF-1 pathway rather than the insulin pathway since similar results have been reported in AD mouse models with altered IGF-1 signalling [125, 126], suggesting a paradoxical action of IGF-1 and insulin in the brain [127].

The signalling pathway related to insulin may also relate to change in longevity. Studies on genetic polymorphisms in humans showed enrichment of a haplotype in the IR gene in Japanese semisupercentenarians [128], and Akt variants were found associated with longevity in three Caucasian cohorts [129]. Similarly, polymorphisms of several genes related to insulin signalling were associated with reduced mortality and improved cognitive function in elderly women in the Leiden 85-plus study [130]. Interestingly, mice with a genetic alteration of insulin signalling display increased longevity. For instance, deletion of IRS-2 in the mouse brain increases the life span of mice maintained on a high-energy diet [131]. Similar observations have been reported in mice deleted for the IRS-1 gene [132]. IRS-1 and IRS-2 mediate actions of both insulin and IGF-1. The latter being strongly linked to longevity [133], these effects could likely reflect an IGF-1-dependent effect. The controversial effect of brain insulin signalling alterations on longevity and AD led Lovestone and Killick to make an interesting hypothesis. They suggested that relatively defective insulin signalling is an evolutionary acquisition of humans that allows us to live longer [134]. However, the molecular mechanisms that have evolved to increase longevity specifically induce AD, suggesting that AD is in fact not a disorder of ageing but of longevity itself.

While brain insulin signalling finely tunes energy homeostasis and peripheral glucose homeostasis, much less is known about the potential impact of brain insulin resistance towards metabolic disturbances in AD. Metabolic alterations have been reported in AD patients, regardless of whether patients are diabetic or not. Weight loss was already described by Alois Alzheimer [135, 136] and it is now recognized as a clinical feature of AD [137], affecting 20–45% of patients [138–142]. Weight loss in patients with dementia is associated with accelerated pro-

gression of AD, higher rate of institutionalization [143] and increased mortality [144–146]. Although dementia-associated weight loss often begins before the onset of the clinical syndrome and accelerates by the time of diagnosis, it is unclear if it is a cause or a consequence of AD pathology [147]. Metabolic deregulations in animal models of tauopathies resemble those found in patients with Tau-related dementia. Indeed, decreased body weight has been described in a mouse model of Tau deposition such as THY-22 [148] or Tg4510 [149, 150], sometimes despite increased feeding behavior [151]. Additionally, genetic deletion of Tau resulted in increased body weight [152]. Impaired satiation and increased feeding behavior [153], as well as changes in body temperature [154] were also observed in a mouse model combining amyloid plaques and Tau pathology (3xTgAD). In Tg4510 mice, weight loss was specific to fat mass and co-occurred with deregulation of metabolic rate [151] as well as disturbances in circadian rhythm [98]. In both cases, Tau pathology was found in the hypothalamus.

One could wonder if these metabolic alterations, appearing for most before the detection of pathological deposits in the brain, could really be the result of early deregulation of central insulin signalling. However, only rare observations support that brain insulin resistance may play a role in the metabolism of AD patients. First, paradoxical overeating concomitant with weight loss has been observed in patients with AD [155] as well as in FTD [156–158]. Second, an increased risk to develop type 2 diabetes has been reported in AD patients (35% diabetics + 46% with glucose intolerance) [159]. Furthermore, some sparse studies report that AD patients can exhibit hyperinsulinaemia or alterations in glucose metabolism [110, 114–117, 160].

What Is the Trigger for Brain Insulin Resistance in AD?

AD brain insulin resistance has been originally ascribed to the detrimental impact of A β oligomers. A β peptide in the oligomeric form can promote insulin resistance by competitively binding and internalizing IRs [161] and by increasing the phosphorylation of IRS-1 and JNK [162] in vitro. In vivo, these results were confirmed in crabgrass macaques and APP/PS1 transgenic mice, which received intracerebroventricular (ICV) injections of A β oligomers [162]. Consistently, several rodent models of amyloid pathology develop metabolic alterations such as glucose intolerance [163–166]. Particularly interesting is the observation of impaired glucose homeostasis following ICV injections of A β oligomers [162]. Recent data also pointed out that ApoE4 could be strongly re-

lated to the development of brain insulin resistance (Fig. 1) [167], ApoE4 significantly impairing insulin-IR interaction and IR trafficking [167].

While the impact of A β oligomers on insulin resistance has been well established, the role of Tau has been poorly evaluated so far. Our recent study [168] demonstrated that Tau deletion induces a disruption of hippocampal response to insulin and impairs the hypothalamic anorexigenic effect of insulin associated with energy metabolism alterations (enhanced food intake and body weight, increased adipose tissue mass, hyperinsulinaemia and glucose intolerance). These findings strongly supported a function of Tau protein as a regulator of brain insulin signalling. The potential mechanism by which Tau regulates hippocampal response to insulin seems ascribed to the regulation of both IRS-1 and PTEN. Indeed, we reported decreased activation of IRS-1 and Akt after insulin exposure in Tau KO mice, suggesting brain insulin resistance. This is consistent with altered IRS-1 activity in AD brains that correlates with NFTs deposition [121, 169, 170], whereas a direct interaction between Tau and IRS-1 has never been reported. On the other hand, we found that Tau interacts with PTEN, known to inhibit insulin signalling, reducing its lipid phosphatase activity (Fig. 1) [168]. Our study thus identified a novel function of Tau protein as a modulator of brain insulin signalling and highlighted a potential mechanistic explanation whereby alteration of insulin signalling would occur in AD via pathological Tau loss-of-function. Importantly, a recent study confirmed that Tau deletion promoted alteration of glucose homeostasis [171]. Interestingly, this work suggested that peripheral metabolic impairment of Tau knockout mice could also be related to the ability of pancreatic Tau to regulate insulin synthesis and secretion [171]. Tau would therefore be prone to control peripheral metabolism through both central and pancreatic regulations. In line with such a role in metabolism, we have reported, using GWAS cohorts [172, 173], an association between Tau H1 haplotype, known to impact the risk of tauopathies [174], and glucose homeostasis in a glucose tolerance test. While the number of studies remained limited regarding the regulatory role of Tau towards brain insulin signalling and peripheral metabolism, other studies support this view. Indeed, previous works have reported colocalization and correlation between the decrease in total IRS-1 and IRS-2 along with increased phosphorylated IRS-1 on Ser^{636/639} and Ser⁶¹⁶ in the brains of AD patients together with NFT deposition [121, 122, 169, 170]. Further, increased serine phosphorylation of IRS-1 has been clearly associated with primary tauopathies

[122]. Moreover, a recent study by Rodriguez-Rodriguez et al. [175] reported accumulated insulin as oligomers in hyperphosphorylated Tau-bearing neurons in AD and other tauopathies. They notably demonstrated that insulin oligomer accumulation in neurons is dependent on Tau hyperphosphorylation and results in a decrease in IRs and alteration of Akt phosphorylation [175]. If one considers Tau hyperphosphorylation/pathology as leading, at least partially, to a Tau loss-of-function, this would suggest that impaired Tau function would lead to a defect of insulin signalling but also a defect of the hormone itself. Although this hypothesis warrants future evaluations, our current knowledge supports that Tau pathology is instrumental for brain insulin resistance in AD and pure tauopathies.

Overall, these data open the possibility that cognitive and metabolic deficits seen in AD patients are the consequence of a Tau loss-of-function. For a long time, Tau aggregation into NFTs was thought to be the only culprit of neurodegeneration and cognitive deficits. But obviously, previous observations supported that this is not the case [176, 177]. More recent data ascribed Tau oligomers as detrimental species towards plasticity. Interestingly, as Tau oligomers [178], Tau deletion also impairs hippocampal plasticity and spatial behavior [179–182]. This raises the possibility that both “toxic gain of Tau function” and “loss of normal Tau function” play a role in the development of cognitive deficits in tauopathies. Respective contribution of both phenomena will need to be further elucidated in the future.

Consequences of Insulin Resistance State on Tau Lesions

Although the interest in the impact of Tau protein on insulin signalling in the brain is very recent, it has for many years been known that, conversely, insulin is capable of modulating Tau protein, mainly its phosphorylation state [183]. There are increasing data showing that insulin regulates Tau phosphorylation and could exacerbate NFT development in AD [184–189] (Fig. 1). In vivo, mice deficient in IRs in neurons show inhibition of the PI3K/Akt signalling pathway and exhibit Tau hyperphosphorylation [190]. Similarly, the deletion of IRS-2 causes inhibition of the PI3K/Akt pathway and therefore induces Tau hyperphosphorylation [188]. Overall, the pathological effect of brain insulin resistance on Tau has mostly been attributable to the modulation of several downstream pathways [183], involving some Tau kinases (GSK-3 β , JNK, ERK, and AMPK) and Tau phosphatases (PP2A and PP1), known to play a pivotal role in the de-

Fig. 2. Impaired homeostasis between brain insulin signalling and Tau: mutual relationship and consequences on cognition.

velopment of Tau pathology [99, 191–203]. Therefore, the chronic insulin signalling impairment seen in the brains of patients with AD and tauopathies is prone to favour the development of Tau pathology through the disruption of the balance between Tau kinases and phosphatases. Moreover, brain insulin signalling would also promote Tau pathology by favouring Tau cleavage [204, 205] and deregulating Tau alternative splicing [206].

Inflammation: The Trigger of Both Tau Pathology and Brain Insulin Resistance?

Neuroinflammation is an early and chronic event in AD. Glial activation resulting in the release of proinflammatory cytokines such as TNF- α and IL-1 β seems to play a major role in the initiation and propagation of AD pathogenesis [207–209]. Besides A β , Tau pathology is itself prone to promote the development of innate and adaptive immune reaction in the brain [210, 211]. Increased IL-1 β has also been reported in the brains of progressive supranuclear palsy patients [212]. Moreover, neuroinflammation induced by lipopolysaccharide injection or traumatic brain injury exacerbated Tau pathology in transgenic mouse models of tauopathies [213–215]. Interestingly, numerous Tau kinases can be activated through inflammatory pathways such as JNK, ERK, Akt, or p38 [216]. These data suggest that neuroinflammation could contribute to, and maybe initiate, Tau pathology [217, 218]. On the other hand, inflammatory processes are also well known to affect insulin signalling. Indeed, in periphery, inflammation linked to obesity induced insulin resistance in visceral adipose tissue through TNF- α [219]. Similar involvement of the TNF- α /JNK pathway

has been suggested in AD brains to explain insulin resistance (Fig. 1). A study has particularly demonstrated that IRS-1 inhibition caused by A β oligomers could be abolished with a TNF- α -neutralizing antibody [220]. Interestingly, Ma et al. [169] have demonstrated that A β oligomers can induce both Tau hyperphosphorylation and insulin signalling alteration through the TNF- α /JNK pathway. Taken together, these data suggest that neuroinflammation seen in AD and other tauopathies could be the trigger of the vicious circle between Tau pathology and insulin resistance by promoting both.

Conclusion

Seminal works postulate that AD can be seen as “type 3 diabetes.” The mechanisms underlying brain insulin resistance in AD, formerly ascribed to amyloid pathology, appear however far more complex and involve Tau. A virtuous physiological homeostasis would exist in the brain between Tau and insulin-dependent pathways: Tau favouring insulin signalling and insulin signalling reducing Tau hyperphosphorylation/aggregation. A disruption of this homeostasis regulation induced by a Tau loss-of-function, promoted by hyperphosphorylation/conformational changes, promoted by peripheral impairments (changes in the metabolic environment, stress...), neuroinflammation, or A β , would then lead to insulin resistance and Tau hyperphosphorylation (Fig. 2). While it remains hard to define whether brain insulin resistance or Tau pathology is the primary event of this vicious circle, it is nevertheless well established that both are able to

favour memory deficits, plasticity impairments, and peripheral metabolic alterations through different pathways. Any means to reinstate the homeostatic regulation between Tau and insulin signalling can then be considered of therapeutic interest. This could be directly achieved by activating IRs or targeting downstream pathways using PTP1B inhibitors [221], GLP-1 receptor agonists [162, 222, 223], or intranasal insulin administration [224, 225]. Alternatively, one could imagine that strategies aimed at clearing pathological forms of Tau (such as Tau immunotherapy) [226, 227] could allow reestablishment of proper brain insulin signalling. Combined strategies aimed at reducing insulin resistance will thus be of high interest in the future.

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