Deregulation of brain insulin signaling in Alzheimer's disease

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Contrary to the previous belief that insulin does not act in the brain, studies in the last three decades have demonstrated important roles of insulin and insulin signal transduction in various functions of the central nervous system. Deregulated brain insulin signaling and its role in molecular pathogenesis have recently been reported in Alzheimer's disease (AD). In this article, we review the roles of brain insulin signaling in memory and cognition, the metabolism of amyloid β precursor protein, and tau phosphorylation. We further discuss deficiencies of brain insulin signaling and glucose metabolism, their roles in the development of AD, and recent studies that target the brain insulin signaling pathway for the treatment of AD. It is clear now that deregulation of brain insulin signaling plays an important role in the development of sporadic AD. The brain insulin signaling pathway also offers a promising therapeutic target for treating AD and probably other neurodegenerative disorders.

Keywords: Alzheimer's disease; APP metabolism; brain insulin signaling; glucose metabolism; memory and cognition; tau

Introduction

Alzheimer's disease (AD) is the most common form of dementia, accounting for an estimated 60% to 80% of all cases^[1]. It is characterized by progressive loss of memory and other cognitive functions. It is genetically classified into late-onset sporadic AD (SAD) and early-onset familial AD. Familial AD constitutes <5% of all AD cases and is caused by mutations in genes for amyloid- β precursor protein (APP), presenilin-1, or presenilin-2^[2]. The majority of AD cases are sporadic. Despite extensive efforts toward understanding the pathogenesis of AD, the etiology of SAD is still not well understood. The key brain histopathological hallmarks of AD are extracellular senile plaques, composed predominantly of amyloid- β (A β) peptides, and intraneuronal neurofibrillary tangles (NTFs) formed by abnormally hyperphosphorylated tau. Instead of focusing directly on these hallmarks, recent studies have

suggested that SAD might be a metabolic disorder.

Accumulating evidence supports the hypothesis that AD is a degenerative metabolic disease, in which glucose uptake and utilization are impaired. Decreased cerebral glucose metabolism and energy deficiency occur at the early stage of the disease and deteriorate further with its progression^[3–7]. The impairment in cerebral glucose metabolism is associated with brain insulin deficiency and dysregulated signal transduction that have been identified in the AD brain. A common molecular feature of type 2 diabetes and obesity is insulin resistance. Epidemiological studies have demonstrated that insulin resistance increases the risk for developing dementia^[8–13], suggesting that it may play a role in AD. It is now proposed that defective insulin signaling in the AD brain contributes to the aggregation and deposition of A β , hyperphosphorylation of tau, promotion of neuroinflammation, disruption of synaptic plasticity, and

subsequently the impairment of memory and cognition^[14]. Therapeutics targeting the brain insulin signaling pathway, such as intranasal administration of insulin and insulin sensitizing agents, have been reported to be promising in treating AD.

The Insulin Signaling Pathway

Insulin, a small protein of ~6 kDa, is mainly produced by pancreatic β -cells. Its principal functions in the periphery are regulating glucose utilization and storage as well as the metabolism of fat and protein. The actions of insulin are mediated *via* the insulin receptor (IR), which belongs to the family of tyrosine kinase receptors. Insulin binds to the IR, promotes the activation of its intrinsic tyrosine kinase activity, and leads to its autophosphorylation. The phosphorylated/activated IR then recruits insulin receptor substrate (IRS) protein to the plasma membrane^[15] and phosphorylates it^[16], which in turn promotes the recruitment and activation of phosphatidylinositol-3 kinase (PI3K) and growth factor receptor-bound protein 2. The two main downstream pathways, mediated by serine/threonine protein kinase AKT and mitogen-activated protein kinase (MAPK), are then activated (Fig. 1).

Activation of the PI3K/AKT pathway regulates a wide variety of proteins/enzymes involved in metabolism, and is considered the major pathway in the control of the metabolic actions of insulin^[17, 18]. MAPK has multiple cellular substrates, most of which are related to cell and synapse growth as well as cell repair and maintenance. Hence, this pathway is generally considered to be important in the insulin regulation of cell growth^[19].

Roles of Insulin Signaling in the Brain

Brain Insulin Signaling

The brain was considered to be insulin-independent until the discovery of the widespread distribution of IRs in the brain^[20-23]. IRs are located on both astrocytes and neurons, and have the highest density in the olfactory bulb, cerebral cortex, hippocampus, hypothalamus, cerebellum, and choroid plexus^[20, 24-27].

Most of the insulin in the brain may come from the periphery. Insulin can cross the blood-brain barrier by a saturable, receptor-mediated transport mechanism^[28].

The specific receptor/transporter has not been identified, but the transport appears to saturate at euglycemic concentrations of insulin^[28]. Many factors, such as fasting, obesity, aging, and dexamethasone treatment, can lead to a decreased transport of insulin into the central nervous system (CNS)^[29, 30]. Whether insulin can also be produced in the mammalian brain is still under debate. Direct evidence of a central source of insulin in the brain is still lacking. Havrankova *et al.*^[21] identified insulin in whole-brain extracts, and its concentration differed in extracts from various regions of the brain. Thereafter, more efforts have been made to confirm the local synthesis of insulin. A series of studies have found preproinsulin mRNA in animal brain^[31, 32]. The release of insulin^[33], and the presence of insulin mRNA^[34] and insulin-like immunoreactivity^[35], have also been detected in cultured neurons, suggesting the neuronal synthesis of insulin. Moreover, insulin is proposed to be only produced by a subset of neurons like pyramidal neurons in the hippocampus, prefrontal cortex, entorhinal cortex, and olfactory bulb, but not by glial cells^[33, 36, 37].

IRs have been shown to be highly enriched in postsynaptic densities in rat cerebral cortex, hippocampus, and cerebellum, where IRS is also highly enriched^[38]. In addition, IRs co-localize with IRS in cerebellar and hippocampal neurons. Another study also showed that IRS-1 mRNA is co-localized with IR mRNA in neuronal cell bodies of the hippocampus and olfactory bulb^[39]. The expression of other downstream effectors such as PI3K, AKT, and glycogen synthase kinase-3 (GSK-3) also reveals a pattern somewhat overlapping that of IRs in the brain^[40-42]. All this evidence suggests the presence of active insulin signal transduction in brain regions closely associated with cognition and the importance of insulin signaling for synaptic function.

Recent Recognition of the Functions of Insulin Signaling in the Brain

One of the first recognized functions of insulin in the brain was its effect on food intake and weight control *via* regulating neuronal activity in the hypothalamus^[43-46]. Infusion of insulin into the CNS suppresses peripheral glucose production^[47] and decreases food intake and body weight^[43-46]. Brain insulin signaling is also involved in the central regulation of reproductive function. Studies have shown that insulin stimulates the release of luteinizing

Fig. 1. Possible mechanisms by which deficient brain insulin signaling contributes to AD. Brain insulin signaling cross-talks with many other signaling pathways and regulates brain metabolism, neuroplasticity, and cognition. The exact molecular mechanisms/pathways by which brain insulin signaling regulates multiple brain functions remain largely elusive. This diagram outlines only the major brain insulin signaling pathway and the possible known consequences (indicated by the red arrows) of deficient brain insulin signaling with respect to the pathogenesis of AD. In the AD brain, deficient insulin signaling leads to decreased PI3K-AKT signaling activity *via* decreased IR activation, resulting in over-activation of GSK-3. Over-activation of GSK-3 β not only leads directly to hyperphosphorylation of tau, but also causes cognitive impairments *via* other pathways. Insulin deficiency also leads to decreased GLUT expression/function and thus decreased glucose uptake/metabolism in the brain. Decreased intraneuronal glucose metabolism results in a reduction of intraneuronal generation of ATP through the TCA cycle and thus impaired synaptic activity and cognitive function. It also leads to decreased levels of UDP-GlcNAc *via* the hexosamine biosynthetic pathway (HBP) and, consequently, decreased tau O-GlcNAcylation. Because the latter inversely regulates tau phosphorylation, decreased O-GlcNAcylation facilitates the hyperphosphorylation of tau, which, in turn, forms toxic tau oligomers and eventually leads to neurofibrillary degeneration. On the other hand, activation of GSK-3 α and reduction of O-GlcNAcylation of amyloid precursor protein lead to over-production of A β that is neurotoxic and facilitates amyloid plaque formation. In this figure, G on tau protein represents the O-GlcNAc group, and P represents the phosphate group. Abbreviations used in this figure: A β , amyloid β peptide; ADP, adenosine diphosphate; AKT, protein kinase B; ATP, adenosine triphosphate; F-6-P, fructose-6-phosphate; Glc, glucose; GlcNAc, β -N-acetylglucosamine; Gln, glutamine; Glu, glutamate; GLUT, glucose transporter; Grb2, growth factor receptor-bound protein 2; GSK-3, glycogen synthase kinase-3; IR, insulin receptor; IRS, insulin receptor substrate; MAPK, mitogen-activated protein kinases; mTOR, mammalian target of rapamycin; NFTs, neurofibrillary tangles; OGA, O-GlcNAcase; OGT, O-GlcNAc transferase; PDK1, phosphoinositide-dependent kinase 1; PI3K, phosphoinositide 3-kinase; PIP2, phosphatidylinositol (3,4)-bisphosphate; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PP2A, protein phosphatase 2A; PTEN, phosphatase and tensin homolog; TCA, tricarboxylic acid cycle; UDP, uridine diphosphate.

hormone releasing hormone^[48, 49] and gonadotropin-releasing hormone^[43]. Moreover, insulin has been shown to regulate neuronal proliferation and differentiation^[50, 51], promote neurite outgrowth^[52, 53], prevent neuron apoptosis^[54, 55], and protect neurons against oxidative stress^[56, 57]. Besides,

insulin signaling is associated with the regulation of memory and cognition, modulation of tau phosphorylation, APP expression and A β clearance, and cerebral glucose metabolism^[58-67].

Consistently, deficits in brain insulin signaling occur

in AD; they are characterized by reduced amounts of insulin in the brain^[68], reduced levels of IR-binding^[69-71], and decreased responsiveness of downstream effectors to the activation of IRs^[72, 73]. Brain regions with the most abundant expression of IRs such as the hippocampus, the temporal lobe, and the cerebral cortex, are the most vulnerable targets of AD^[38]. The reduced insulin mRNA levels and insulin-binding in the frontal cortex and hippocampus are associated with the Braak stage of AD pathology^[69, 70]. However, Frolich *et al.* reported increased IR-binding in the occipital cortex that is not associated with cognition^[74]. Insulin signaling defects may account for many of the clinical manifestations of AD, and they actually begin early and progress with the development of the disease. Experimental animals, in which the brain insulin signaling pathway is impaired, exhibit cognitive impairment and neurodegeneration with features in common with AD^[64, 75]. It is now proposed that brain insulin signaling defects can lead to the overexpression of APP, accumulation of A β , hyperphosphorylation of tau, reduction in glucose metabolism and energy utilization, promotion of oxidative stress and neuroinflammation, synaptic failure, and as a result, a decline in cognition and the development of AD^[14]. Small clinical trials have shown potential beneficial effects of therapeutics targeting the insulin signaling pathway in treating AD^[76-79], though more larger-scale clinical trials with longer durations are still needed to confirm the effectiveness and safety of these drugs.

Brain Insulin Signaling and Cognition

The hippocampus and cortex, structures responsible for memory and other cognitive functions, display highly enriched distributions of IRs, IRS, and other downstream effectors^[38-42], suggesting that brain insulin signaling might be involved in memory and cognition. Intracerebroventricular or intrahippocampal administration of insulin improves spatial memory consolidation and retrieval in the Morris water maze test^[80, 81], and enhances performance in the passive-avoidance task in rats^[82, 83]. Selective blockade of endogenous intrahippocampal insulin signaling impairs memory performance^[84]. Besides, chronic intranasal insulin treatment enhances short-term and long-term object-recognition memory in mice^[85] and slows down the impairment of object recognition memory in diabetic mice^[86]. On the other hand, short- and long-term memory formation induce significant up-regulation of IR expression

in the hippocampus^[87, 88]. Changes in downstream molecules, such as upregulation of IRS-1 and Akt in synaptic membrane, translocation of Shc protein to synaptic membrane, and activation of MAPK, also occur after long-term memory formation^[88], suggesting the involvement of insulin signaling in spatial memory processing. This is also supported by clinical trials: intravenous insulin infusion using the hyperinsulinemic-euglycemic clamp method improves memory performance and attention in humans^[89, 90]; intranasal insulin treatment improves cognition and memory in healthy people and in people with mild cognitive impairment (MCI) or AD^[76, 91, 92].

Inhibition of brain insulin signaling, on the other hand, results in the impairment of memory and cognition. We have found that intracerebroventricular administration of streptozotocin in mice impairs brain insulin signaling, leading to reduced long-term spatial memory and short-term object-recognition memory^[63], and further exacerbates the memory impairment in 3 $\times$ Tg-AD mice^[93]. However, mice with brain/neuron-specific IR knockout display normal spatial learning in the Morris water maze task^[94]. This might be because an early lack of IRs can be compensated over time by other pathways.

The mechanisms underlying the effects of insulin on cognition are still not clear. One possible mechanism is its regulatory effect on glucose metabolism and energy utilization, which will be discussed in detail later in this review. The brain insulin signaling pathway has also been implicated in cortical and hippocampal synaptic plasticity, thus affecting memory and learning. Studies have shown that insulin is able to induce both long-term potentiation and long-term depression (LTD) in a PI3K-dependent manner in the CA1 region of rat hippocampal slices^[95, 96], through the modulation of α -amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA), N-methyl-D-aspartic acid (NMDA), and γ -aminobutyric acid (GABA) receptors^[97-99]. Insulin accelerates the endocytosis of AMPA receptors containing the glutamate GluR2 subunit, thus decreasing its numbers in the plasma membrane, and resulting in LTD of AMPA receptor-mediated synaptic transmission in hippocampal CA1 neurons^[97]. Insulin is also reported to promote the rapid delivery of NMDA receptors to the cell surface by exocytosis^[100], and influence their activity. It is reported that insulin can cause transient phosphorylation of NR2A and NR2B subunits of NMDA

receptors at tyrosine residues in hippocampal slices, and this is responsible for insulin-induced potentiation^[98]. All this evidence suggests that the beneficial effects of insulin on memory result, at least partially, from the modulation of glutaminergic neurotransmission. In addition, GABAergic neurotransmission plays a role, as insulin increases the expression of GABA receptors on the postsynaptic and dendritic membranes of neurons and the number of functional postsynaptic GABA receptors, thereby increasing the amplitude of miniature inhibitory postsynaptic currents mediated by GABA receptors^[99]. Furthermore, the production of acetylcholine^[101] and uptake of norepinephrine^[102] that influence cognitive function are also regulated by insulin.

Brain Insulin Signaling and APP Metabolism

A β peptides generated by the proteolytic processing of APP are neurotoxic. Their accumulation results in oligomeric A β , amyloid fibril formation, and finally deposits of senile plaques in the brain, one of the hallmarks of AD. Insulin signaling affects A β accumulation and aggregation through influencing the secretion and translocation of APP and A β degradation.

Insulin promotes APP metabolism and increases the rate of secretion of APP in a PI3K-dependent manner^[60]. It has been shown that insulin stimulation accelerates APP/A β trafficking from the trans-Golgi network, a major cellular site for A β generation, to the plasma membrane, and reduces the intracellular accumulation of A β ^[61, 62]. This molecular mechanism is further supported by clinical trials showing that insulin infusion increases the A β ₄₂ level in the cerebrospinal fluid (CSF) of non-demented humans^[103, 104].

Insulin may also modulate the extracellular degradation of A β via insulin degrading enzyme (IDE), a metalloproteinase that catabolizes insulin. IDE is highly expressed in the brain as well as in liver, kidney and muscle tissue, and plays a crucial role in A β clearance by both degradation and oligomerization^[105–107]. When the IDE gene is knocked out in the mouse brain, the A β level is elevated^[108]. In addition to A β , IDE also degrades a variety of peptides including insulin itself. Therefore, by competing with A β for binding, insulin inhibits A β degradation and increases its extracellular concentration. On the other hand, the expression of IDE in the brain can be affected by insulin. Studies have shown that insulin increases the

IDE protein levels via activation of PI3K^[109]. This is also supported by the finding that deficient insulin signaling is correlated with reduced IDE in the AD brain^[109]. The A β -degrading activity of IDE, as well as its mRNA and protein levels, are decreased in the AD brain, and these decreases correlate negatively with the A β level^[110–112]. Induction of insulin resistance in Tg2576 mice reduces the amount and activity of IDE and, as a result, increases A β levels in the hippocampus and cerebral cortex^[109].

On the other hand, A β is intimately associated with defective insulin signaling. Treatment of cultured hippocampal neurons with A β oligomers and intracerebroventricular injection of A β oligomers in monkeys both increase IRS1 phosphorylation at multiple serine residues in cells and monkey brains^[113]. A β oligomers can also bind to hippocampal neurons and trigger the removal of IRs from the plasma membrane, resulting in reduction of the number of surface IRs and the responsiveness to insulin^[114]. This has also been verified in the AD brain, where IRs are concentrated inside the intracellular compartment, unlike its distribution throughout the neuronal soma and dendrites in control brains^[68]. This A β oligomer-induced loss of surface IRs and the subsequent loss of synaptic spines can be completely prevented by insulin treatment^[114, 115].

Brain Insulin Signaling and Tau Phosphorylation

Abnormally-hyperphosphorylated tau is the principal component of paired helical filaments in the neurofibrillary lesions associated with AD^[116]. Abnormal hyperphosphorylation reduces the affinity of tau to microtubules and is crucial for neurodegeneration in AD and other tauopathies^[117, 118]. Negative regulation of tau phosphorylation by insulin has been reported. Treatment of cultured human neuronal NT2N cells with insulin results in decreased tau phosphorylation^[119]. In contrast, depletion of IRs in the brain, as seen in brain/neuron-specific IR-knockout mice, results in increased tau phosphorylation^[120]. In IRS2-knockout mice, a type 2 diabetes model, accumulation of hyperphosphorylated tau is detectable in the hippocampus^[94]. Inhibition of brain insulin signaling by intracerebroventricular administration of streptozotocin also induces hyperphosphorylation of tau at multiple sites and reduces its ability to bind to microtubules in rodents^[63, 64]. This treatment also exacerbates tau pathology in 3 $\times$ Tg-AD mice^[93]. These findings are consistent with the negative

regulation of GSK-3 β activity by insulin signaling, because GSK-3 β is the major kinase for tau phosphorylation in the brain^[121]. However, a transient increase in tau phosphorylation also occurs in SH-SY5Y cells and in primary cortical neurons after insulin treatment^[122, 123]. Therefore, the regulation of tau phosphorylation by insulin signaling may be dynamic and time-dependent.

We previously showed that altered tau O-GlcNAcylation, an O-linked post-translational modification of nucleocytoplasmic proteins by the monosaccharide β -N-acetylglucosamine (GlcNAc), links the impairment of brain glucose metabolism to tau hyperphosphorylation^[124-126]. In the AD brain, impaired glucose metabolism may lead to the down-regulation of O-GlcNAcylation that, in turn, facilitates abnormal hyperphosphorylation of tau and neurodegeneration^[127, 128] (Fig. 1). Decreased glucose uptake/metabolism in the brain partially results from impaired brain insulin signaling, leading to decreased tau O-GlcNAcylation and increased tau phosphorylation, which is also evidenced by animal studies^[64]. On the other hand, insulin might increase tau expression *via* accelerating protein synthesis through the PI3K-mTOR pathway^[129].

Deficiency of Brain Insulin Signaling and Glucose Metabolism in AD

Accumulating evidence supports the hypothesis that AD is a metabolic disease with impaired brain insulin signaling, leading to neurodegeneration. Deficient insulin signaling begins early and progresses with the development of the disease^[69, 70]. The level of insulin in the CSF and/or the CSF/plasma insulin ratio is decreased in the AD brain^[68]. Increasing Braak stages of AD neuropathology are associated with progressively reduced mRNA levels of insulin/IGF and their receptors^[69, 70]. We and others have demonstrated reduced protein levels and activity of downstream effectors of insulin signaling in the AD brain, including IRs, IRS, PI3K, and AKT^[68, 71, 73], as well as reduced responsiveness of the insulin signaling pathway to insulin/IGF stimulation^[72]. All this evidence indicates that insulin signaling is impaired in the AD brain and may play a critical role in the pathogenesis and progression of the disease.

Impairment of cerebral glucose metabolism occurs at the early stage of AD and deteriorates further with

progression of the disease^[3-7]. However, the underlying mechanism is still unclear. Neurons are unable to synthesize or store glucose, and thus they are fully dependent on glucose transport across the blood-brain barrier, which is facilitated by glucose transporters (GLUTs). In mammalian brain, GLUT1 and GLUT3 are predominant in glucose transport into the neuron^[130]. GLUT1 is highly expressed in endothelial cells of the blood-brain barrier and is responsible for transporting glucose from blood into the extracellular space of the brain^[131]. GLUT3 is the major neuronal GLUT and helps transport glucose from the extracellular space into neurons^[132]. Decreased GLUT1 and GLUT3 have been reported in the AD brain^[65-67]. We further demonstrated that the decreases in GLUT1 and GLUT3 levels correlate with the decrease in O-GlcNAcylation and hyperphosphorylation of tau in the AD brain^[66, 67].

Because GLUT1 and GLUT3 are insulin-insensitive, brain glucose metabolism was previously viewed as being independent of insulin. However, these glucose transporters do appear to be regulated by insulin^[133, 134]. Furthermore, the existence of GLUT4, an insulin-sensitive GLUT, in brain regions involved in memory and cognition such as the hippocampus and temporal cortex^[135] adds the possibility that insulin might also influence memory in part through GLUT4-mediated glucose uptake. A fludeoxyglucose F18-positron emission tomography study revealed a regional association between a lower cerebral glucose metabolic rate and greater insulin resistance^[136]. When insulin signaling is inhibited in the human brain, hippocampal energy metabolism is significantly reduced during cognitive activity^[137]. Intracerebroventricular injection of insulin stimulates the translocation of GLUT4 to the plasma membrane in rat hippocampus in a time- and PI3K-dependent manner, providing a mechanism through which neurons rapidly increase glucose utilization during increases in hippocampus-associated activities such as learning and memory^[138]. Collectively, brain glucose metabolism is impaired in the AD brain; this is associated with reduced GLUT1 and GLUT3 levels and impaired brain insulin signaling (Fig. 1).

Brain Insulin Signaling as a Therapeutic Target for AD

As reviewed above, defective insulin signaling is closely

associated with AD pathology and memory impairment. Therapeutics aimed at enhancing insulin signaling in the brain are expected to be promising in treating AD. Approaches using insulin, glucagon-like peptide-1 (GLP-1) agonists, metformin, and peroxisome proliferator-activated receptor gamma (PPAR- γ) agonists, have been investigated.

Systemic administration of insulin is certainly not a viable treatment for AD because of the risk for developing hypoglycemia and its effects on other hormones like cortisol. One way to avoid systemic exposure while targeting the brain is intranasal administration, initially developed by Frey at the University of Minnesota. This mode of delivery bypasses the blood-brain barrier and transports drugs directly to the CNS, mainly *via* extracellular pathways^[139]. Several studies have shown that both acute and chronic intranasal insulin treatment (160 IU/day) enhance memory and mood in healthy adults^[58, 59, 140, 141]. Acute intranasal administration of insulin at various doses (10, 20, and 40 IU) also improves declarative memory in adults with MCI and AD. In contrast, 60 IU of insulin does not facilitate memory^[78]. Interestingly, the beneficial effects of insulin differ according to the apolipoprotein E (APOE) genotype, a genetic risk factor for sporadic AD. Only APOE- ϵ 4-negative MCI or AD patients show improved declarative memory^[79]. In addition, chronic intranasal insulin (40 IU/day) of participants with early AD improves declarative memory and attention and induces an increased plasma A β ₄₀/A β ₄₂ ratio following 21 days of treatment^[77]. A follow-up study of 4 months of intranasal insulin treatment also showed improved delayed memory in MCI and AD patients, and the changes in CSF A β ₄₂ and tau/A β ₄₂ ratios are associated with cognitive and functional changes^[76]. All these studies have provided promising evidence that intranasal insulin may benefit MCI and AD patients. However, larger, longer, and multi-center clinical trials are still needed to further substantiate the beneficial effects of insulin on cognition and also evaluate the potential side-effects.

PPAR- γ agonists are also attractive candidates for treating defective insulin signaling. However, clinical trials using agonists such as rosiglitazone and pioglitazone fail to show consistent beneficial results in AD patients^[142–144]. In addition, safety concerns about the effects of PPAR- γ agonists on cardiovascular function and heart failure in diabetic patients have restricted its clinical use. It

will be worth performing clinical trials using intranasal administration of PPAR- γ agonists in the future.

Other drugs like GLP-1 agonists and metformin have been shown to ameliorate multiple pathological changes linked to AD in cell culture and animal models^[145, 146]. More studies and clinical trials are needed to determine the efficacy of these drugs in treating AD.

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REFERENCES

- [1] Thies W, Bleiler L. 2013 Alzheimer's disease facts and figures. *Alzheimers Dement* 2013, 9: 208–245.
- [2] Waring SC, Rosenberg RN. Genome-wide association studies in Alzheimer disease. *Arch Neurol* 2008, 65: 329–334.
- [3] Fukuyama H, Ogawa M, Yamauchi H, Yamaguchi S, Kimura J, Yonekura Y, *et al.* Altered cerebral energy metabolism in Alzheimer's disease: a PET study. *J Nucl Med* 1994, 35: 1–6.
- [4] Drzezga A, Lautenschlager N, Siebner H, Riemenschneider M, Willoch F, Minoshima S, *et al.* Cerebral metabolic changes accompanying conversion of mild cognitive impairment into Alzheimer's disease: a PET follow-up study. *Eur J Nucl Med Mol Imaging* 2003, 30: 1104–1113.
- [5] Hoyer S. Glucose metabolism and insulin receptor signal transduction in Alzheimer disease. *Eur J Pharmacol* 2004, 490: 115–125.
- [6] Protas HD, Chen K, Langbaum JB, Fleisher AS, Alexander GE, Lee W, *et al.* Posterior cingulate glucose metabolism, hippocampal glucose metabolism, and hippocampal volume in cognitively normal, late-middle-aged persons at 3 levels of genetic risk for Alzheimer disease. *JAMA Neurol* 2013, 70: 320–325.
- [7] Cai H, Cong WN, Ji S, Rothman S, Maudsley S, Martin B. Metabolic dysfunction in Alzheimer's disease and related neurodegenerative disorders. *Curr Alzheimer Res* 2012, 9: 5–17.
- [8] Yaffe K, Blackwell T, Kanaya AM, Davidowitz N, Barrett-Connor E, Krueger K. Diabetes, impaired fasting glucose, and development of cognitive impairment in older women. *Neurology* 2004, 63: 658–663.
- [9] Whitmer RA, Gustafson DR, Barrett-Connor E, Haan MN,

- Gunderson EP, Yaffe K. Central obesity and increased risk of dementia more than three decades later. *Neurology* 2008, 71: 1057–1064.
- [10] Raffaitin C, Feart C, Le Goff M, Amieva H, Helmer C, Akbaraly TN, *et al.* Metabolic syndrome and cognitive decline in French elders: the Three-City Study. *Neurology* 2011, 76: 518–525.
- [11] Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry CP Jr, Yaffe K. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. *BMJ* 2005, 330: 1360.
- [12] Gustafson D, Rothenberg E, Blennow K, Steen B, Skoog I. An 18-year follow-up of overweight and risk of Alzheimer disease. *Arch Intern Med* 2003, 163: 1524–1528.
- [13] Stewart R, Masaki K, Xue QL, Peila R, Petrovitch H, White LR, *et al.* A 32-year prospective study of change in body weight and incident dementia: the Honolulu-Asia Aging Study. *Arch Neurol* 2005, 62: 55–60.
- [14] Craft S, Cholerton B, Baker LD. Insulin and Alzheimer's disease: untangling the web. *J Alzheimers Dis* 2013, 33 Suppl 1: S263–275.
- [15] Withers DJ, White M. Perspective: The insulin signaling system--a common link in the pathogenesis of type 2 diabetes. *Endocrinology* 2000, 141: 1917–1921.
- [16] White MF. Insulin signaling in health and disease. *Science* 2003, 302: 1710–1711.
- [17] Lochhead PA, Coghlan M, Rice SQ, Sutherland C. Inhibition of GSK-3 selectively reduces glucose-6-phosphatase and phosphatase and phosphoenolpyruvate carboxykinase gene expression. *Diabetes* 2001, 50: 937–946.
- [18] Fisher TL, White MF. Signaling pathways: the benefits of good communication. *Curr Biol* 2004, 14: R1005–1007.
- [19] Lizcano JM, Alessi DR. The insulin signalling pathway. *Curr Biol* 2002, 12: R236–238.
- [20] Havrankova J, Roth J, Brownstein M. Insulin receptors are widely distributed in the central nervous system of the rat. *Nature* 1978, 272: 827–829.
- [21] Havrankova J, Schmechel D, Roth J, Brownstein M. Identification of insulin in rat brain. *Proc Natl Acad Sci U S A* 1978, 75: 5737–5741.
- [22] Sara VR, Hall K, Von Holtz H, Humbel R, Sjogren B, Wetterberg L. Evidence for the presence of specific receptors for insulin-like growth factors 1 (IGF-1) and 2 (IGF-2) and insulin throughout the adult human brain. *Neurosci Lett* 1982, 34: 39–44.
- [23] Potau N, Escofet MA, Martinez MC. Ontogenesis of insulin receptors in human cerebral cortex. *J Endocrinol Invest* 1991, 14: 53–58.
- [24] Unger JW, Livingston JN, Moss AM. Insulin receptors in the central nervous system: localization, signalling mechanisms and functional aspects. *Prog Neurobiol* 1991, 36: 343–362.
- [25] Hill JM, Lesniak MA, Pert CB, Roth J. Autoradiographic localization of insulin receptors in rat brain: prominence in olfactory and limbic areas. *Neuroscience* 1986, 17: 1127–1138.
- [26] Hopkins DF, Williams G. Insulin receptors are widely distributed in human brain and bind human and porcine insulin with equal affinity. *Diabet Med* 1997, 14: 1044–1050.
- [27] Marks JL, Porte D Jr, Stahl WL, Baskin DG. Localization of insulin receptor mRNA in rat brain by *in situ* hybridization. *Endocrinology* 1990, 127: 3234–3236.
- [28] Banks WA, Jaspan JB, Huang W, Kastin AJ. Transport of insulin across the blood-brain barrier: saturability at euglycemic doses of insulin. *Peptides* 1997, 18: 1423–1429.
- [29] Baskin DG, Woods SC, West DB, van Houten M, Posner BI, Dorsa DM, *et al.* Immunocytochemical detection of insulin in rat hypothalamus and its possible uptake from cerebrospinal fluid. *Endocrinology* 1983, 113: 1818–1825.
- [30] Banks WA, Jaspan JB, Kastin AJ. Effect of diabetes mellitus on the permeability of the blood-brain barrier to insulin. *Peptides* 1997, 18: 1577–1584.
- [31] Devaskar SU, Singh BS, Carnaghi LR, Rajakumar PA, Giddings SJ. Insulin II gene expression in rat central nervous system. *Regul Pept* 1993, 48: 55–63.
- [32] Schechter R, Beju D, Gaffney T, Schaefer F, Whetsell L. Preproinsulin I and II mRNAs and insulin electron microscopic immunoreaction are present within the rat fetal nervous system. *Brain Res* 1996, 736: 16–27.
- [33] Clarke DW, Mudd L, Boyd FT Jr, Fields M, Raizada MK. Insulin is released from rat brain neuronal cells in culture. *J Neurochem* 1986, 47: 831–836.
- [34] Singh BS, Rajakumar PA, Eves EM, Rosner MR, Wainer BH, Devaskar SU. Insulin gene expression in immortalized rat hippocampal and pheochromocytoma-12 cell lines. *Regul Pept* 1997, 69: 7–14.
- [35] Raizada MK. Localization of insulin-like immunoreactivity in the neurons from primary cultures of rat brain. *Exp Cell Res* 1983, 143: 351–357.
- [36] Hoyer S. The aging brain. Changes in the neuronal insulin/insulin receptor signal transduction cascade trigger late-onset sporadic Alzheimer disease (SAD). A mini-review. *J Neural Transm* 2002, 109: 991–1002.
- [37] Schechter R, Holtzclaw L, Sadiq F, Kahn A, Devaskar S. Insulin synthesis by isolated rabbit neurons. *Endocrinology* 1988, 123: 505–513.
- [38] Abbott MA, Wells DG, Fallon JR. The insulin receptor tyrosine kinase substrate p58/53 and the insulin receptor are components of CNS synapses. *J Neurosci* 1999, 19: 7300–7308.
- [39] Baskin DG, Schwartz MW, Sipols AJ, D'Alessio DA, Goldstein

- BJ, White MF. Insulin receptor substrate-1 (IRS-1) expression in rat brain. *Endocrinology* 1994, 134: 1952–1955.
- [40] Horsch D, Kahn CR. Region-specific mRNA expression of phosphatidylinositol 3-kinase regulatory isoforms in the central nervous system of C57BL/6J mice. *J Comp Neurol* 1999, 415: 105–120.
- [41] Moss AM, Unger JW, Moxley RT, Livingston JN. Location of phosphotyrosine-containing proteins by immunocytochemistry in the rat forebrain corresponds to the distribution of the insulin receptor. *Proc Natl Acad Sci U S A* 1990, 87: 4453–4457.
- [42] Leroy K, Brion JP. Developmental expression and localization of glycogen synthase kinase-3 β in rat brain. *J Chem Neuroanat* 1999, 16: 279–293.
- [43] Brown LM, Clegg DJ, Benoit SC, Woods SC. Intraventricular insulin and leptin reduce food intake and body weight in C57BL/6J mice. *Physiol Behav* 2006, 89: 687–691.
- [44] McGowan MK, Andrews KM, Grossman SP. Chronic intrahypothalamic infusions of insulin or insulin antibodies alter body weight and food intake in the rat. *Physiol Behav* 1992, 51: 753–766.
- [45] Morton GJ, Cummings DE, Baskin DG, Barsh GS, Schwartz MW. Central nervous system control of food intake and body weight. *Nature* 2006, 443: 289–295.
- [46] Woods SC, Lotter EC, McKay LD, Porte D, Jr. Chronic intracerebroventricular infusion of insulin reduces food intake and body weight of baboons. *Nature* 1979, 282: 503–505.
- [47] Obici S, Zhang BB, Karkanias G, Rossetti L. Hypothalamic insulin signaling is required for inhibition of glucose production. *Nat Med* 2002, 8: 1376–1382.
- [48] Arias P, Rodriguez M, Szwarcfarb B, Sinay IR, Moguilevsky JA. Effect of insulin on LHRH release by perfused hypothalamic fragments. *Neuroendocrinology* 1992, 56: 415–418.
- [49] Dong Q, Lazarus RM, Wong LS, Vellios M, Handelsman DJ. Pulsatile LH secretion in streptozotocin-induced diabetes in the rat. *J Endocrinol* 1991, 131: 49–55.
- [50] Farrar C, Houser CR, Clarke S. Activation of the PI3K/Akt signal transduction pathway and increased levels of insulin receptor in protein repair-deficient mice. *Aging Cell* 2005, 4: 1–12.
- [51] Wozniak M, Rydzewski B, Baker SP, Raizada MK. The cellular and physiological actions of insulin in the central nervous system. *Neurochem Int* 1993, 22: 1–10.
- [52] Heni M, Hennige AM, Peter A, Siegel-Axel D, Ordelheide AM, Krebs N, *et al.* Insulin promotes glycogen storage and cell proliferation in primary human astrocytes. *PLoS One* 2011, 6: e21594.
- [53] Mill JF, Chao MV, Ishii DN. Insulin, insulin-like growth factor II, and nerve growth factor effects on tubulin mRNA levels and neurite formation. *Proc Natl Acad Sci U S A* 1985, 82: 7126–7130.
- [54] Wu X, Reiter CE, Antonetti DA, Kimball SR, Jefferson LS, Gardner TW. Insulin promotes rat retinal neuronal cell survival in a p70S6K-dependent manner. *J Biol Chem* 2004, 279: 9167–9175.
- [55] Jafari Anarkooli I, Sankian M, Vahedi F, Bonakdaran S, Varasteh AR, Haghir H. Evaluation of insulin and ascorbic acid effects on expression of Bcl-2 family proteins and caspase-3 activity in hippocampus of STZ-induced diabetic rats. *Cell Mol Neurobiol* 2009, 29: 133–140.
- [56] Duarte AI, Santos P, Oliveira CR, Santos MS, Rego AC. Insulin neuroprotection against oxidative stress is mediated by Akt and GSK-3 β signaling pathways and changes in protein expression. *Biochim Biophys Acta* 2008, 1783: 994–1002.
- [57] Duarte AI, Proenca T, Oliveira CR, Santos MS, Rego AC. Insulin restores metabolic function in cultured cortical neurons subjected to oxidative stress. *Diabetes* 2006, 55: 2863–2870.
- [58] Krug R, Benedict C, Born J, Hallschmid M. Comparable sensitivity of postmenopausal and young women to the effects of intranasal insulin on food intake and working memory. *J Clin Endocrinol Metab* 2010, 95: E468–472.
- [59] Benedict C, Kern W, Schultes B, Born J, Hallschmid M. Differential sensitivity of men and women to anorexigenic and memory-improving effects of intranasal insulin. *J Clin Endocrinol Metab* 2008, 93: 1339–1344.
- [60] Solano DC, Sironi M, Bonfini C, Solerte SB, Govoni S, Racchi M. Insulin regulates soluble amyloid precursor protein release via phosphatidylinositol 3 kinase-dependent pathway. *FASEB J* 2000, 14: 1015–1022.
- [61] Gasparini L, Gouras GK, Wang R, Gross RS, Beal MF, Greengard P, *et al.* Stimulation of beta-amyloid precursor protein trafficking by insulin reduces intraneuronal beta-amyloid and requires mitogen-activated protein kinase signaling. *J Neurosci* 2001, 21: 2561–2570.
- [62] Gasparini L, Netzer WJ, Greengard P, Xu H. Does insulin dysfunction play a role in Alzheimer's disease? *Trends Pharmacol Sci* 2002, 23: 288–293.
- [63] Chen Y, Liang Z, Blanchard J, Dai CL, Sun S, Lee MH, *et al.* A non-transgenic mouse model (icv-STZ mouse) of Alzheimer's disease: similarities to and differences from the transgenic model (3xTg-AD mouse). *Mol Neurobiol* 2013, 47: 711–725.
- [64] Deng Y, Li B, Liu Y, Iqbal K, Grundke-Iqbal I, Gong CX. Dysregulation of insulin signaling, glucose transporters, O-GlcNAcylation, and phosphorylation of tau and neurofilaments in the brain: Implication for Alzheimer's disease. *Am J Pathol* 2009, 175: 2089–2098.
- [65] Simpson IA, Chundu KR, Davies-Hill T, Honer WG, Davies

- P. Decreased concentrations of GLUT1 and GLUT3 glucose transporters in the brains of patients with Alzheimer's disease. *Ann Neurol* 1994, 35: 546–551.
- [66] Liu Y, Liu F, Grundke-Iqbal I, Iqbal K, Gong CX. Brain glucose transporters, O-GlcNAcylation and phosphorylation of tau in diabetes and Alzheimer's disease. *J Neurochem* 2009, 111: 242–249.
- [67] Liu Y, Liu F, Iqbal K, Grundke-Iqbal I, Gong CX. Decreased glucose transporters correlate to abnormal hyperphosphorylation of tau in Alzheimer disease. *FEBS Lett* 2008, 582: 359–364.
- [68] Moloney AM, Griffin RJ, Timmons S, O'Connor R, Ravid R, O'Neill C. Defects in IGF-1 receptor, insulin receptor and IRS-1/2 in Alzheimer's disease indicate possible resistance to IGF-1 and insulin signalling. *Neurobiol Aging* 2010, 31: 224–243.
- [69] Rivera EJ, Goldin A, Fulmer N, Tavares R, Wands JR, de la Monte SM. Insulin and insulin-like growth factor expression and function deteriorate with progression of Alzheimer's disease: link to brain reductions in acetylcholine. *J Alzheimers Dis* 2005, 8: 247–268.
- [70] de la Monte SM, Wands JR. Alzheimer's disease is type 3 diabetes-evidence reviewed. *J Diabetes Sci Technol* 2008, 2: 1101–1113.
- [71] Steen E, Terry BM, Rivera EJ, Cannon JL, Neely TR, Tavares R, *et al.* Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease—is this type 3 diabetes? *J Alzheimers Dis* 2005, 7: 63–80.
- [72] Talbot K, Wang HY, Kazi H, Han LY, Bakshi KP, Stucky A, *et al.* Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. *J Clin Invest* 2012, 122: 1316–1338.
- [73] Liu Y, Liu F, Grundke-Iqbal I, Iqbal K, Gong CX. Deficient brain insulin signalling pathway in Alzheimer's disease and diabetes. *J Pathol* 2011, 225: 54–62.
- [74] Frolich L, Blum-Degen D, Riederer P, Hoyer S. A disturbance in the neuronal insulin receptor signal transduction in sporadic Alzheimer's disease. *Ann N Y Acad Sci* 1999, 893: 290–293.
- [75] Chen Y, Tian Z, Liang Z, Sun S, Dai CL, Lee MH, *et al.* Brain Gene Expression of a Sporadic (icv-STZ Mouse) and a Familial Mouse Model (3xTg-AD Mouse) of Alzheimer's Disease. *PLoS One* 2012, 7: e51432.
- [76] Craft S, Baker LD, Montine TJ, Minoshima S, Watson GS, Claxton A, *et al.* Intranasal insulin therapy for Alzheimer disease and amnesic mild cognitive impairment: a pilot clinical trial. *Arch Neurol* 2012, 69: 29–38.
- [77] Reger MA, Watson GS, Green PS, Wilkinson CW, Baker LD, Cholerton B, *et al.* Intranasal insulin improves cognition and modulates beta-amyloid in early AD. *Neurology* 2008, 70: 440–448.
- [78] Reger MA, Watson GS, Green PS, Baker LD, Cholerton B, Fishel MA, *et al.* Intranasal insulin administration dose-dependently modulates verbal memory and plasma amyloid-beta in memory-impaired older adults. *J Alzheimers Dis* 2008, 13: 323–331.
- [79] Reger MA, Watson GS, Frey WH, 2nd, Baker LD, Cholerton B, Keeling ML, *et al.* Effects of intranasal insulin on cognition in memory-impaired older adults: modulation by APOE genotype. *Neurobiol Aging* 2006, 27: 451–458.
- [80] Haj-ali V, Mohaddes G, Babri SH. Intracerebroventricular insulin improves spatial learning and memory in male Wistar rats. *Behav Neurosci* 2009, 123: 1309–1314.
- [81] Moosavi M, Naghdi N, Chooapani S. Intra CA1 insulin microinjection improves memory consolidation and retrieval. *Peptides* 2007, 28: 1029–1034.
- [82] Babri S, Badie HG, Khamenei S, Seyedlar MO. Intrahippocampal insulin improves memory in a passive-avoidance task in male wistar rats. *Brain Cogn* 2007, 64: 86–91.
- [83] Park CR, Seeley RJ, Craft S, Woods SC. Intracerebroventricular insulin enhances memory in a passive-avoidance task. *Physiol Behav* 2000, 68: 509–514.
- [84] McNay EC, Ong CT, McCrimmon RJ, Cresswell J, Bogan JS, Sherwin RS. Hippocampal memory processes are modulated by insulin and high-fat-induced insulin resistance. *Neurobiol Learn Mem* 2010, 93: 546–553.
- [85] Marks DR, Tucker K, Cavallin MA, Mast TG, Fadool DA. Awake intranasal insulin delivery modifies protein complexes and alters memory, anxiety, and olfactory behaviors. *J Neurosci* 2009, 29: 6734–6751.
- [86] Francis GJ, Martinez JA, Liu WQ, Xu K, Ayer A, Fine J, *et al.* Intranasal insulin prevents cognitive decline, cerebral atrophy and white matter changes in murine type I diabetic encephalopathy. *Brain* 2008, 131: 3311–3334.
- [87] Zhao W, Chen H, Xu H, Moore E, Meiri N, Quon MJ, *et al.* Brain insulin receptors and spatial memory. Correlated changes in gene expression, tyrosine phosphorylation, and signaling molecules in the hippocampus of water maze trained rats. *J Biol Chem* 1999, 274: 34893–34902.
- [88] Dou JT, Chen M, Dufour F, Alkon DL, Zhao WQ. Insulin receptor signaling in long-term memory consolidation following spatial learning. *Learn Mem* 2005, 12: 646–655.
- [89] Kern W, Peters A, Fruehwald-Schultes B, Deininger E, Born J, Fehm HL. Improving influence of insulin on cognitive functions in humans. *Neuroendocrinology* 2001, 74: 270–280.
- [90] Craft S, Asthana S, Cook DG, Baker LD, Cherrier M, Purganan K, *et al.* Insulin dose-response effects on memory

- and plasma amyloid precursor protein in Alzheimer's disease: interactions with apolipoprotein E genotype. *Psychoneuroendocrinology* 2003, 28: 809–822.
- [91] Shemesh E, Rudich A, Harman-Boehm I, Cukierman-Yaffe T. Effect of intranasal insulin on cognitive function: a systematic review. *J Clin Endocrinol Metab* 2012, 97: 366–376.
- [92] Benedict C, Frey WH, 2nd, Schioth HB, Schultes B, Born J, Hallschmid M. Intranasal insulin as a therapeutic option in the treatment of cognitive impairments. *Exp Gerontol* 2011, 46: 112–115.
- [93] Chen Y, Liang Z, Tian Z, Blanchard J, Dai CL, Chalbot S, *et al.* Intracerebroventricular streptozotocin exacerbates Alzheimer-like changes of 3xTg-AD Mice. *Mol Neurobiol* 2014, 49(1): 547–562.
- [94] Schubert M, Brazil DP, Burks DJ, Kushner JA, Ye J, Flint CL, *et al.* Insulin receptor substrate-2 deficiency impairs brain growth and promotes tau phosphorylation. *J Neurosci* 2003, 23: 7084–7092.
- [95] Lee CC, Kuo YM, Huang CC, Hsu KS. Insulin rescues amyloid beta-induced impairment of hippocampal long-term potentiation. *Neurobiol Aging* 2009, 30: 377–387.
- [96] van der Heide LP, Kamal A, Artola A, Gispen WH, Ramakers GM. Insulin modulates hippocampal activity-dependent synaptic plasticity in a N-methyl-D-aspartate receptor and phosphatidylinositol-3-kinase-dependent manner. *J Neurochem* 2005, 94: 1158–1166.
- [97] Man HY, Lin JW, Ju WH, Ahmadian G, Liu L, Becker LE, *et al.* Regulation of AMPA receptor-mediated synaptic transmission by clathrin-dependent receptor internalization. *Neuron* 2000, 25: 649–662.
- [98] Christie JM, Wenthold RJ, Monaghan DT. Insulin causes a transient tyrosine phosphorylation of NR2A and NR2B NMDA receptor subunits in rat hippocampus. *J Neurochem* 1999, 72: 1523–1528.
- [99] Wan Q, Xiong ZG, Man HY, Ackerley CA, Braunton J, Lu WY, *et al.* Recruitment of functional GABA(A) receptors to postsynaptic domains by insulin. *Nature* 1997, 388: 686–690.
- [100] Skeberdis VA, Lan J, Zheng X, Zukin RS, Bennett MV. Insulin promotes rapid delivery of N-methyl-D-aspartate receptors to the cell surface by exocytosis. *Proc Natl Acad Sci U S A* 2001, 98: 3561–3566.
- [101] Kopf SR, Baratti CM. Effects of posttraining administration of insulin on retention of a habituation response in mice: participation of a central cholinergic mechanism. *Neurobiol Learn Mem* 1999, 71: 50–61.
- [102] Figlewicz DP, Szot P, Israel PA, Payne C, Dorsa DM. Insulin reduces norepinephrine transporter mRNA in vivo in rat locus coeruleus. *Brain Res* 1993, 602: 161–164.
- [103] Fishel MA, Watson GS, Montine TJ, Wang Q, Green PS, Kulstad JJ, *et al.* Hyperinsulinemia provokes synchronous increases in central inflammation and beta-amyloid in normal adults. *Arch Neurol* 2005, 62: 1539–1544.
- [104] Watson GS, Peskind ER, Asthana S, Purganan K, Wait C, Chapman D, *et al.* Insulin increases CSF Aβ42 levels in normal older adults. *Neurology* 2003, 60: 1899–1903.
- [105] Authier F, Posner BI, Bergeron JJ. Insulin-degrading enzyme. *Clin Invest Med* 1996, 19: 149–160.
- [106] Kurochkin IV, Goto S. Alzheimer's beta-amyloid peptide specifically interacts with and is degraded by insulin degrading enzyme. *FEBS Lett* 1994, 345: 33–37.
- [107] Qiu WQ, Walsh DM, Ye Z, Vekrellis K, Zhang J, Podlisny MB, *et al.* Insulin-degrading enzyme regulates extracellular levels of amyloid beta-protein by degradation. *J Biol Chem* 1998, 273: 32730–32738.
- [108] Farris W, Mansourian S, Chang Y, Lindsley L, Eckman EA, Frosch MP, *et al.* Insulin-degrading enzyme regulates the levels of insulin, amyloid beta-protein, and the beta-amyloid precursor protein intracellular domain in vivo. *Proc Natl Acad Sci U S A* 2003, 100: 4162–4167.
- [109] Zhao L, Teter B, Morihara T, Lim GP, Ambegaokar SS, Ubeda OJ, *et al.* Insulin-degrading enzyme as a downstream target of insulin receptor signaling cascade: implications for Alzheimer's disease intervention. *J Neurosci* 2004, 24: 11120–11126.
- [110] Perez A, Morelli L, Cresto JC, Castano EM. Degradation of soluble amyloid beta-peptides 1–40, 1–42, and the Dutch variant 1–40Q by insulin degrading enzyme from Alzheimer disease and control brains. *Neurochem Res* 2000, 25: 247–255.
- [111] Cook DG, Leverenz JB, McMillan PJ, Kulstad JJ, Erickson S, Roth RA, *et al.* Reduced hippocampal insulin-degrading enzyme in late-onset Alzheimer's disease is associated with the apolipoprotein E-ε4 allele. *Am J Pathol* 2003, 162: 313–319.
- [112] Zhao Z, Xiang Z, Haroutunian V, Buxbaum JD, Stetka B, Pasinetti GM. Insulin degrading enzyme activity selectively decreases in the hippocampal formation of cases at high risk to develop Alzheimer's disease. *Neurobiol Aging* 2007, 28: 824–830.
- [113] Bomfim TR, Forny-Germano L, Sathler LB, Brito-Moreira J, Houzel JC, Decker H, *et al.* An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer's disease-associated Aβ oligomers. *J Clin Invest* 2012, 122: 1339–1353.
- [114] Zhao WQ, De Felice FG, Fernandez S, Chen H, Lambert MP, Quon MJ, *et al.* Amyloid beta oligomers induce impairment of neuronal insulin receptors. *FASEB J* 2008, 22: 246–260.
- [115] De Felice FG, Vieira MN, Bomfim TR, Decker H, Velasco PT, Lambert MP, *et al.* Protection of synapses against Alzheimer's-linked toxins: insulin signaling prevents the

- pathogenic binding of A β oligomers. *Proc Natl Acad Sci U S A* 2009, 106: 1971–1976.
- [116] Iqbal K, Alonso AC, Gong CX, Khatoon S, Singh TJ, Grundke-Iqbal I. Mechanism of neurofibrillary degeneration in Alzheimer's disease. *Mol. Neurobiol.* 1994, 9: 119–123.
- [117] Lee VM, Goedert M, Trojanowski JQ. Neurodegenerative tauopathies. *Annu Rev Neurosci* 2001, 24: 1121–1159.
- [118] Iqbal K, Liu F, Gong CX, Grundke-Iqbal I. Tau in Alzheimer Disease and related Tauopathies. *Curr Alzheimer Res* 2010, 7: 656–664.
- [119] Hong M, Lee VM. Insulin and insulin-like growth factor-1 regulate tau phosphorylation in cultured human neurons. *J Biol Chem* 1997, 272: 19547–19553.
- [120] Schubert M, Gautam D, Surjo D, Ueki K, Baudler S, Schubert D, *et al.* Role for neuronal insulin resistance in neurodegenerative diseases. *Proc Natl Acad Sci U S A* 2004, 101: 3100–3105.
- [121] Takashima A. GSK-3 is essential in the pathogenesis of Alzheimer's disease. *J Alzheimers Dis* 2006, 9: 309–317.
- [122] Lesort M, Jope RS, Johnson GV. Insulin transiently increases tau phosphorylation: involvement of glycogen synthase kinase-3 β and Fyn tyrosine kinase. *J Neurochem* 1999, 72: 576–584.
- [123] Lesort M, Johnson GV. Insulin-like growth factor-1 and insulin mediate transient site-selective increases in tau phosphorylation in primary cortical neurons. *Neuroscience* 2000, 99: 305–316.
- [124] Li X, Lu F, Wang JZ, Gong CX. Concurrent alterations of O-GlcNAcylation and phosphorylation of tau in mouse brains during fasting. *Eur J Neurosci* 2006, 23: 2078–2086.
- [125] Liu F, Iqbal K, Grundke-Iqbal I, Hart GW, Gong CX. O-GlcNAcylation regulates phosphorylation of tau: a mechanism involved in Alzheimer's disease. *Proc Natl Acad Sci U S A* 2004, 101: 10804–10809.
- [126] Liu F, Shi J, Tanimukai H, Gu J, Gu J, Grundke-Iqbal I, *et al.* Reduced O-GlcNAcylation links lower brain glucose metabolism and tau pathology in Alzheimer's disease. *Brain* 2009, 132: 1820–1832.
- [127] Gong CX, Liu F, Grundke-Iqbal I, Iqbal K. Impaired brain glucose metabolism leads to Alzheimer neurofibrillary degeneration through a decrease in tau O-GlcNAcylation. *J Alzheimers Dis* 2006, 9: 1–12.
- [128] Gong CX, Liu F, Iqbal K. O-GlcNAc cycling modulates neurodegeneration. *Proc Natl Acad Sci U S A* 2012, 109: 17319–17320.
- [129] Nemoto T, Yanagita T, Satoh S, Maruta T, Kanai T, Murakami M, *et al.* Insulin-induced neurite-like process outgrowth: acceleration of tau protein synthesis via a phosphoinositide 3-kinase–mammalian target of rapamycin pathway. *Neurochem Int* 2011, 59: 880–888.
- [130] McEwen BS, Reagan LP. Glucose transporter expression in the central nervous system: relationship to synaptic function. *Eur J Pharmacol* 2004, 490: 13–24.
- [131] Schubert D. Glucose metabolism and Alzheimer's disease. *Ageing Res Rev* 2005, 4: 240–257.
- [132] Dwyer DS, Vannucci SJ, Simpson IA. Expression, regulation, and functional role of glucose transporters (GLUTs) in brain. *Int Rev Neurobiol* 2002, 51: 159–188.
- [133] Pankratz SL, Tan EY, Fine Y, Mercurio AM, Shaw LM. Insulin receptor substrate-2 regulates aerobic glycolysis in mouse mammary tumor cells via glucose transporter 1. *J Biol Chem* 2009, 284: 2031–2037.
- [134] Ferreira IA, Mocking AI, Urbanus RT, Varlack S, Wnuk M, Akkerman JW. Glucose uptake via glucose transporter 3 by human platelets is regulated by protein kinase B. *J Biol Chem* 2005, 280: 32625–32633.
- [135] Watson GS, Craft S. Modulation of memory by insulin and glucose: neuropsychological observations in Alzheimer's disease. *Eur J Pharmacol* 2004, 490: 97–113.
- [136] Baker LD, Cross DJ, Minoshima S, Belongia D, Watson GS, Craft S. Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. *Arch Neurol* 2011, 68: 51–57.
- [137] Emmanuel Y, Cochlin LE, Tyler DJ, de Jager CA, David Smith A, Clarke K. Human hippocampal energy metabolism is impaired during cognitive activity in a lipid infusion model of insulin resistance. *Brain Behav* 2013, 3: 134–144.
- [138] Grillo CA, Piroli GG, Hendry RM, Reagan LP. Insulin-stimulated translocation of GLUT4 to the plasma membrane in rat hippocampus is PI3-kinase dependent. *Brain Res* 2009, 1296: 35–45.
- [139] Lochhead JJ, Thorne RG. Intranasal delivery of biologics to the central nervous system. *Adv Drug Deliv Rev* 2012, 64: 614–628.
- [140] Benedict C, Hallschmid M, Hatke A, Schultes B, Fehm HL, Born J, *et al.* Intranasal insulin improves memory in humans. *Psychoneuroendocrinology* 2004, 29: 1326–1334.
- [141] Benedict C, Hallschmid M, Schmitz K, Schultes B, Ratter F, Fehm HL, *et al.* Intranasal insulin improves memory in humans: superiority of insulin aspart. *Neuropsychopharmacology* 2007, 32: 239–243.
- [142] Watson GS, Cholerton BA, Reger MA, Baker LD, Plymate SR, Asthana S, *et al.* Preserved cognition in patients with early Alzheimer disease and amnesic mild cognitive impairment during treatment with rosiglitazone: a preliminary study. *Am J Geriatr Psychiatry* 2005, 13: 950–958.
- [143] Harrington C, Sawchak S, Chiang C, Davies J, Donovan C, Saunders AM, *et al.* Rosiglitazone does not improve cognition or global function when used as adjunctive therapy to AChE

- inhibitors in mild-to-moderate Alzheimer's disease: two phase 3 studies. *Curr Alzheimer Res* 2011, 8: 592–606.
- [144] Gold M, Alderton C, Zvartau-Hind M, Egginton S, Saunders AM, Irizarry M, *et al.* Rosiglitazone monotherapy in mild-to-moderate Alzheimer's disease: results from a randomized, double-blind, placebo-controlled phase III study. *Dement Geriatr Cogn Disord* 2010, 30: 131–146.
- [145] de la Monte SM. Brain insulin resistance and deficiency as therapeutic targets in Alzheimer's disease. *Curr Alzheimer Res* 2012, 9: 35–66.
- [146] Yang Y, Zhang J, Ma D, Zhang M, Hu S, Shao S, *et al.* Subcutaneous administration of liraglutide ameliorates Alzheimer-associated tau hyperphosphorylation in rats with type 2 diabetes. *J Alzheimers Dis* 2013, 37: 637–648.