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REVIEW ARTICLE

Role of insulin receptor substance-1 modulating PI3K/Akt insulin signaling pathway in Alzheimer's disease

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Abstract
Alzheimer's disease (AD) is a progressive neurodegenerative disease, also regarded as "type 3 diabetes" for the last few years because of the brain insulin resistance (IR) and dysregulation of insulin signaling in the brain, which can further promote pathological progression of AD. IRS-1/PI3K/Akt insulin signaling pathway disorder and its downstream cascade reaction are responsible for cognitive decline in the brain. In recent years, a growing number of studies has documented that dysregulation of insulin signaling is a key feature of AD and has crucial correlations with serine/tyrosine (Ser/Tyr) phosphorylation of insulin receptor substance-1(IRS-1). Phosphorylation of this protein has been identified as an important molecule involved in the process of amyloid-β (Aβ) deposition into senile plaques (SPs) and tau hyperphosphorylation into neurofibrillary tangles (NFTs). In this paper, we review the links between IRS-1 and the PI3K/Akt insulin signaling pathway, and highlight phosphorylated IRS-1 which negatively regulated by downstream effector of Akt such as mTOR, S6K, and JNK, among others in AD. Furthermore, anti-diabetic drugs including metformin, thiazolidinediones, and glucagon-like peptide-1 (GLP-1) analogue could modulate IRS-1 phosphorylation, brain IR, PI3K/Akt insulin signaling pathway, and other pathologic processes of AD. The above suggest that anti-diabetic drugs may be promising strategies for AD disease-modifying treatments.

Keywords Alzheimer's disease · Anti-diabetic drugs · Brain insulin resistance · IRS-1 · IRS-1 phosphorylation · PI3K/Akt insulin signaling pathway

Introduction

The number of individuals living with Alzheimer's disease (AD) is rapidly increasing, mainly as populations continue to age, which poses a growing problem for families and societies worldwide (Nichols et al. 2019). According to the World Alzheimer Report 2019, approximately over 50 million people worldwide are living with dementia and this number is projected to increase to 152 million by 2050 (Alzheimer's Disease International 2019). AD, one of the most pressing epidemics of our time, is a progressive, age-related neurodegenerative disease that is characterized clinically by cognitive deterioration, behavioral changes, memory loss, and executive function impairments. Pathologically, AD is characterized by neuropathologic hallmarks, amyloid-β (Aβ), which forms extracellular senile plaques (SPs), and intracellular neurofibrillary tangles (NFTs) consisting of aggregated hyperphosphorylated tau proteins, along with neuroinflammation, synaptic dysfunction, neuronal loss and dystrophy, among others (Arranz and De Strooper 2019; De Strooper and Karran 2016). Nevertheless, despite our understanding the advanced molecular pathogenesis of AD from the "amyloid cascade hypothesis" perspective, the prevention and/or clearance of Aβ plaques from the brain has failed to translate into effective therapies for AD patients and has not alleviated cognitive degeneration (Blanchard and Tsai 2019; Weller and Budson 2018). It has been suggested that underlying pathogenic mechanisms influence the modulation of the "amyloid cascade hypothesis".

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Over the past 2 decades, a growing body of research has revealed that dysregulation of insulin signaling and brain insulin resistance (IR) are associated with sporadic AD, and that both exert a fundamental role in the progression of AD pathogenesis (Akhtar et al. 2020a, b; Eric Steen et al. 2005; Ferreira et al. 2014; Spinelli et al. 2020; Talbot et al. 2012). Indeed, the insulin signaling pathway is central to neuronal survival, regulation of synapse number, dendritic plasticity, and glial functions (Chiu et al. 2008; McNay and Recknagel 2011; Van der Heide et al. 2005). In post-mortem AD brain tissue, insulin and insulin receptor expression is strikingly decreased, and alterations in downstream insulin signaling molecules are observed, including diminished IRS-1/2, IRS-associated PI3K, and p-Akt levels (Eric Steen et al. 2005; Moloney et al. 2010). Moreover, aberrantly distributed insulin receptor proteins are concentrated within neurons in AD (Moloney et al. 2010). In AD animal models using 3xTg-AD and Tg2576 mice, for example, brain IR has been observed along with perturbed brain levels of IRS-1, p-PI3K, p-Akt, and GSK-3β, among other proteins, which suggests an impaired insulin signaling pathway (Velazquez et al. 2017). Brain insulin receptor sensitivity and IRS-1/2 expression levels are reduced in association with increased levels of IRS-1 phosphorylation at Ser-312 ($pSer^{312}$-IRS-1) (Kleinridders 2016; Moloney et al. 2010); this suggests that brain IR is compromised in AD. Furthermore, Aβ42 is the main neurotoxic isoform composition of Aβ plaques, and defective insulin signaling drives the accumulation of $A\beta_{42}$ neurotoxic isoform but not $A\beta_{40}$ in the brain of APP/PS1 mice (Chua et al. 2012), the formation of hyperphosphorylated tau proteins and dystrophic neurites (Yarchoan et al. 2014), impairs hippocampal long-term potentiation (LTP) and learning (Grillo et al. 2015), and stimulates neuroinflammation and the accumulation of reactive oxygen species (de la Monte 2014).

Type 2 diabetes mellitus (T2DM) is a multifactorial disease characterized by IR, which is associated with disturbances in insulin signaling in cellular level, and has been demonstrated as a substantial risk factor for AD developing. Compared with the general population, individuals with T2DM have a more than 1.5 times greater risk of developing AD, especially in Eastern populations (Zhang et al. 2017). Besides, further clinical studies support a link between T2DM and AD (Beeri and Bendlin 2020). Results of some studies assessing the effect of anti-diabetic drugs involving metformin, thiazolidinediones, and glucagon-like peptide-1 (GLP-1) analogue on individuals diagnosed as mild cognitive impairment (MCI) or AD, in some extend, pose a notable cognitive benefit (Kellar and Craft 2020; Munoz-Jimenez et al. 2020; Rotermund et al. 2018). Above these suggesting that a considerable overlap in pathogenesis exists across these two conditions, AD and T2DM. This association may due in large part to dysregulation of insulin signaling pathway which mediates IR (Boccardi et al. 2019). Brain IR is simply defined as inactivated insulin signaling pathway, especially the IRS/PI3K/Akt pathway, which is crucial for maintaining synaptic plasticity and cognitive functions (Bedse et al. 2015; Boucher et al. 2014). IR, the linking mechanism between T2DM and AD, which potentiates the formation of Aβ plaques by reducing the degradation and clearance of Aβ, and especially impairs the downstream insulin signaling pathway PI3K/Akt, leading to enhanced production of Aβ and hyperphosphorylated tau in the brain with AD (Diehl et al. 2017; Zlokovic 2011) (Fig. 1). Furthermore, the impaired insulin signaling pathway PI3K/Akt downstream effectors involving mTOR, S6K, JNK, and GSK3, among others could elicit defect in energy metabolism, oxidative stress, neuroinflammation, mitochondrial dysfunction, and autophagy dysfunction (Boccardi et al. 2019; Chen et al. 2021; Khan et al. 2019) (Fig. 1). Results of experimental studies also suggested that anti-diabetic drugs might act in the brain to mitigate IR, modulate dysfunction of insulin signaling, and other mechanisms including Aβ deposition, tau hyperphosphorylation, neuroinflammation, and oxidative stress (Boccardi et al. 2019; Chen et al. 2021; Escribano et al. 2010; Khan et al. 2019). Given the important role of IR in the brain for learning and memory, it is essential to further understand the insulin signaling pathway that implicated in AD pathophysiology, as well as how its crucial molecule–insulin receptor substrate-1 (IRS-1) related to brain IR in AD.

The most important representative of the IRS protein family (termed IRS1-6), IRS-1, is by definition one of the crucial molecules in the insulin signaling pathway that is involved in brain IR. It is appreciated that aberrant phosphorylation of IRS-1 is also extensively associated with brain IR in addition to with skeletal muscle, adipose tissue, and liver (Mullins et al. 2017a). Moreover, research on the relationship between brain insulin signaling and AD pathogenesis has shown that low levels of IRS-1 expression are associated with phosphorylated tau proteins and that aberrant hyperphosphorylation of IRS-1 is related to tau hyperphosphorylation (De Felice 2013; Moloney et al. 2010; Mullins et al. 2017a). One study recently revealed that AD brain atrophy is associated with IRS-1 expression, which indicates a positive relationship with IRS-1pan-Tyr phosphorylation and a negative relationship with $pSer^{312}$-IRS-1, in a spatial pattern (Mullins et al. 2017b). Overall, decreasing levels of IRS-1 and increasing levels of pSer-IRS-1 are convincing changes in insulin signaling pathway disorder, and accumulating evidence suggests that pSer-IRS-1 is an indicator of IR in both the peripheral and the brain (Hirosumi et al. 2002; Kleinridders 2016; Moloney et al. 2010; Talbot et al. 2012). In contrast to previous reviews (Akhtar and Sah 2020; Candeias et al. 2012; Daisuke et al. 2019; Dineley et al. 2014), here, we outline the insulin signaling

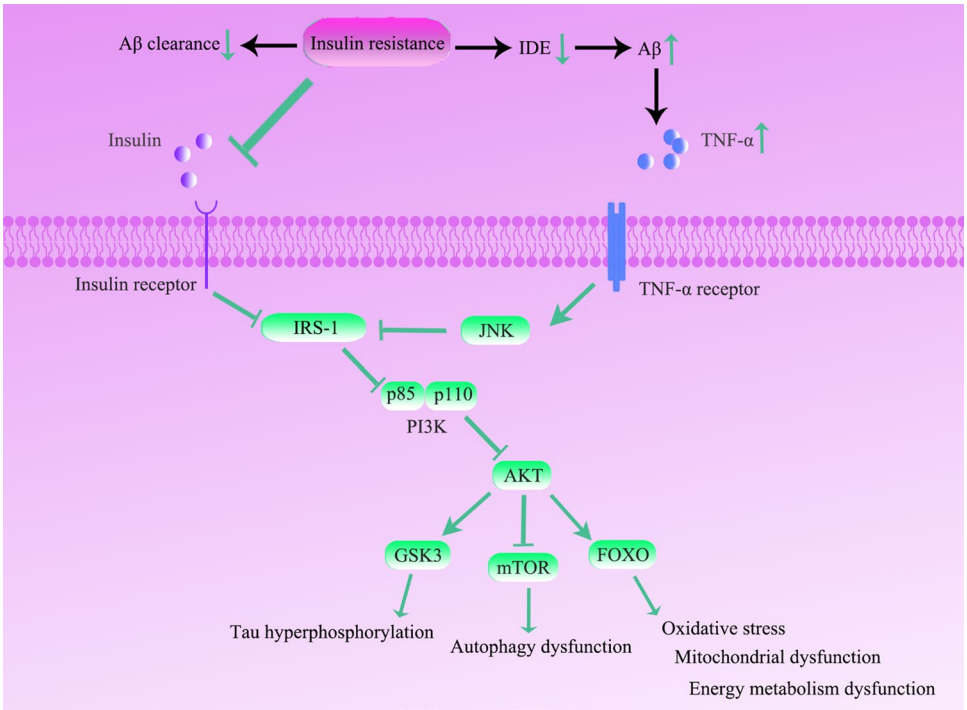

Fig. 1 Schematic representation of the shared mechanisms between AD and T2DM. IR could stimulate amyloid deposition by reducing the degradation of Aβ by IDE and clearance of Aβ by impairing BBB. Furthermore, IR makes insulin signaling pathway conduction abnormal, leading to PI3K/Akt signaling pathway and its downstream molecules dysfunction. The impaired insulin signaling pathway elicits oxidative stress, energy metabolism dysfunction, neuroinflammation, mitochondrial dysfunction, autophagy dysfunction, and neuronal death ultimately, all of which promote cognitive impairment in AD. *AD* Alzheimer's disease, *T2DM* Type 2 diabetes mellitus, *IR* Insulin resistance, *Aβ* amyloid-β peptide, *IDE* insulin-degrading enzyme, *BBB* blood–brain barrier

pathway crucial molecule, IRS-1, and highlight its actions with respect to PI3K/Akt insulin signaling pathway. We also summarize downstream effector of Akt involving mTOR, S6K, JNK, and GSK3 which could negatively regulate pSer-IRS-1 and how it affects hyperphosphorylated tau protein and Aβ plaques development in AD (Fig. 2), and the role of anti-diabetic drugs including metformin, thiazolidinediones, and GLP-1 analogue treating individuals with AD.

The molecular structure of IRS

IRS-1 and IRS-2 are widely distributed, and are the most well-characteristic protein among the IRS1-6; IRS-1 has a central role in the cerebral cortex and skeletal muscle, whereas IRS-2 is expressed primarily in the hypothalamus and liver (Arnold et al. 2018). The N terminus of IRS proteins contains pleckstrin-homology domains (PH domains) and phosphotyrosine-binding domains (PTB domains) that bind to the activated IR-β subunit. Near the C terminus tail of IRS proteins are as many as 20 tyrosine-phosphorylation binding sites for Src-homology-2 (SH2)-containing proteins (Shc), such as the regulatory subunit p85 PI3K and the adaptor molecule growth factor receptor-bound protein 2 (Grb2). These binding sites are also specific for SH2 domain-containing tyrosine phosphatase-2 (Shp2) proteins and for cytoplasmic tyrosine kinases (Fig. 3) (Copps and White 2012; Taniguchi et al. 2006). Shc activates the RAS-mitogen-activated protein kinase (MAPK) pathway, which activates extracellular signal-regulated kinase1/2 (ERK1/2); ERK1/2 in turn regulates cell proliferation, survival and gene transcription (Ferreira et al. 2014; Kleinridders et al. 2014). In contrast, phosphorylation at tyrosine sites in IRS mostly activates the phosphoinositide 3-kinase (PI3K)/Akt (also known as PKB) cascade, which largely mediates metabolism, protein/lipid/glycogen synthesis, glucose transport, and autophagy, among others processes (Arnold et al. 2018; Boucher et al. 2014). Besides, the PI3K/Akt insulin signaling pathway is implicated in promoting learning and memory, which occurs by regulating synaptic plasticity and improving memory consolidation (Chiang et al. 2010; Horwood et al. 2006), and thus, most of the discussion below focuses on the PI3K/Akt insulin signaling pathway regulating IRS-1 phosphorylation.

IRS and the PI3K/Akt insulin signaling pathway

Insulin receptor is a tetramer protein composed of extracellular α subunits and transmembrane β subunits. Ligand such as insulin or insulin-like growth factors (IGF1) binds to insulin receptor α subunits that regulates the activity of intracellular tyrosine kinase on β subunits, and then insulin receptor undergoes a conformational change: the dimerization of intracellular β subunits. Subsequently, tyrosine autophosphorylation in the β subunits activates intrinsic tyrosine kinases and recruits intracellular effectors (mainly IRS-1 and IRS-2). The activated insulin receptor phosphorylates multiple tyrosine residues of IRS-1 or/and IRS-2, which elicits

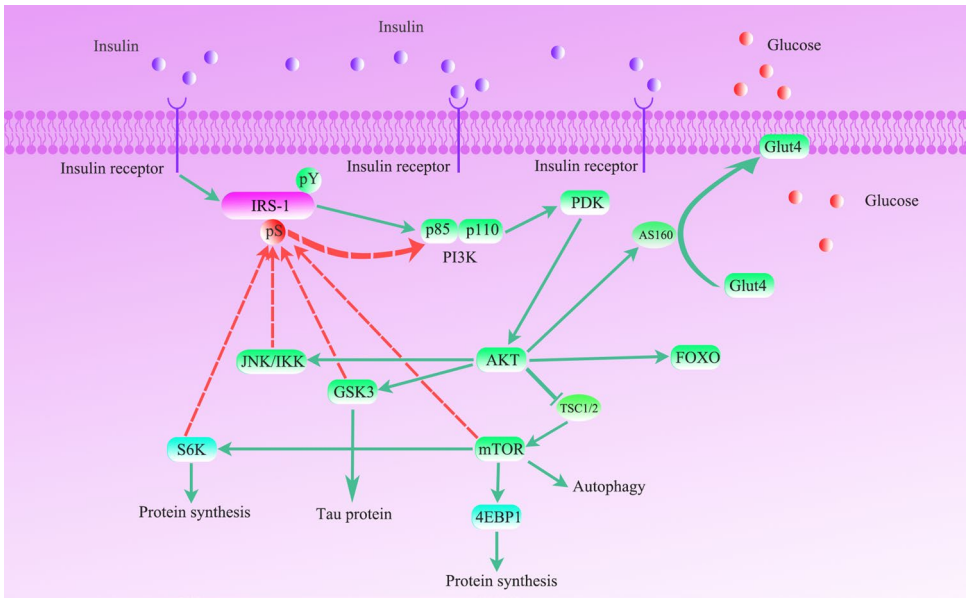

Fig. 2 The feedback regulation between IRS-1 phosphorylation and IRS-1/PI3K/Akt insulin signaling pathway in AD. Insulin binds to insulin receptor which stimulates autophosphorylation of itself and subsequently activates tyrosine residues of IRS-1 triggering cascade events. IRS-1 recruits and activates PI3K complex, which then phosphorylates and activates Akt. Activated Akt ultimately leads to the translocation of GLUT4 to the cell membrane for uptake of glucose into neurons. Akt-mediated activation of mTOR and the downstream targets of mTOR, like S6K and 4EBP1, serve to regulate protein synthesis, lipid synthesis and autophagy, among other processes. Phosphorylation of GSK3 by Akt inhibits the constitutive activity of this kinase. Activated Akt also can directly phosphorylate JNK/IKK. IR results in increased pSer-IRS-1 phosphorylation which further enhance PI3K/Akt signaling pathway and its downstream molecules dysfunction, leading to pathological process of AD involving hyperphosphorylated tau protein, Aβ plaques, autophagy dysfunction, glucose metabolism dysfunction, neuroinflammation, and oxidative stress. Dark green solid arrows represent activation upon insulin stimulation and blocked arrow shows inhibition. Red dotted arrows represent downstream molecules that can phosphorylate Ser residues in IRS-1 leading to inactivation of IRS-1/PI3K/Akt signaling pathway by feedback inhibition loop (Arnold et al. 2018; Stanley et al. 2016). *PI3K* phosphoinositide 3 kinase, *GLUT4* Glucose transporter 4, mT*O*R mammalian target of rapamycin, *TSC1*/2 tuberous sclerosis ½, *S6K* ribosomal protein S6 kinase, *4EBP1* 4E-binding protein 1, *GSK3* glycogen synthase kinase 3, *FOXO* fork-head family box O, *IKK* inhibitor of nuclear factor-κB kinase, *JNK* c-Jun-N-terminal kinase, *IR* insulin resistance, *AD* Alzheimer's disease, *Aβ* amyloid-β peptide

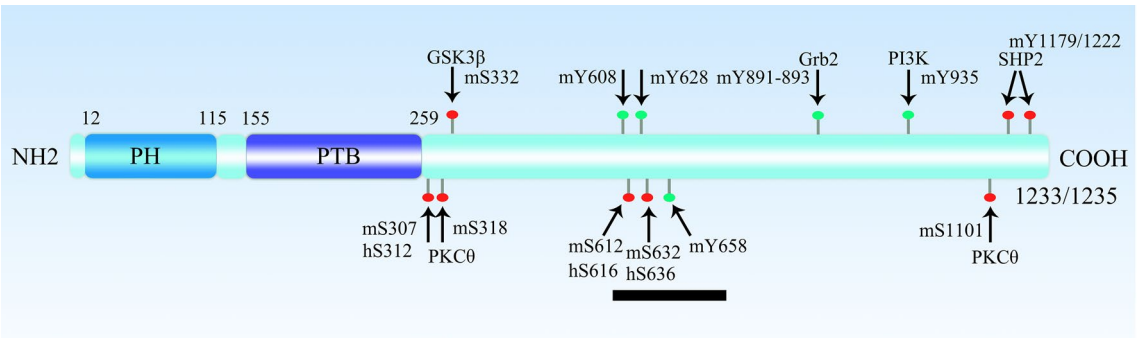

Fig. 3 A schematic representation of the IRS-1 protein in mice/rats (1233/1235 amino acid sequences) and human (1242). The IRS-1 sequence has 2 major functional structural regions near the N-terminus portion. A pleckstrin-homolog (PH) domain (light blue) spans between amino acids 12 and 115, and a phosphotyrosine-binding (PTB) domain (dark blue) between 155 and 259. The serine residues (S) and tyrosine residues (Y) are also shown. Red circles represent sites of negative regulation, whereas green circles represent sites of positive regulation. The black line shows a series of binding sites for PI3K kinase, and some black arrows indicate exact binding sites Y891-893 for Grb2 and Y1179/1222 for SHP2. More than one protein phosphorylates S307 site such as IKK, JNK, PKC θ, and S6K, S612 site such as Akt/PKB, ERK, and mTOR, and S632 site such as ERK and mTOR (Copps and White 2012; Gual et al. 2005; Taniguchi et al. 2006). *PI3K* phosphoinositide 3 kinase, *Grb2* growth factor receptor-bound protein-2, *SHP2* Src-homology-domain-containing tyrosine phosphatase-2, *GSK3β* glycogen synthase kinase 3β, *IKK* inhibitor of nuclear factor-κB kinase, *JNK* c-Jun-N-terminal kinase, *PKC θ* protein kinase C θ, *S6K* ribosomal protein S6 kinase, *mTOR* mammalian target of rapamycin

IRS-1 or/and IRS-2 self-activation leading to the recruitment and activation of the lipid kinase PI3K complex. Notably, IRS plays a pivotal switch in insulin signaling pathway, the phosphorylation of IRS-1 on serine (Ser) residues can inhibit IRS-1 activity, resulting in insulin resistance (Yarchoan et al. 2014). PI3K phosphorylates 3 phosphoinositide dependent protein kinase (PDK1), which then directly phosphorylates and activates threonine (Thr) residues in Akt; this initiates the PI3K/Akt insulin signaling pathway, and consequently, triggers many downstream effects (Chatterjee and Mudher 2018; Diehl et al. 2017).

Glucose transporter 4 (GLUT4) mainly expressed in neurons in hippocampus and cortex, and it is often co-expressed with GLUT3 (Apelt et al. 1999). GLUT4 functions primarily to uptake glucose into some neurons, muscle and adipose cells for energy (Fernando et al. 2008); Akt phosphorylates AS160, the 160 kDa substrate of Akt, which consequently induces the translocation of GLUT-4 to the cell membrane. Results of patients with AD demonstrated that downregulation of GLUT1 and GLUT3 proteins are detected in cerebral cortex and hippocampus (Liu et al. 2008; Mooradian et al. 1997; Yan et al. 2020). The downregulation of GLUT1 and GLUT3 proteins as an early pathogenetic mechanism of AD aggravate the deposition of Aβ and hyperphosphorylation of tau (Zhu et al. 2014). Glycogen synthase kinase 3β (GSK3β) is also mediated by Akt, which inhibits its constitutive activity through serine phosphorylation. GSK3β also plays a vital role in the regulation of microtubule-associated proteins including tau, which can form NFTs, one of the features of AD (Pardeshi et al. 2017; Stanley et al. 2016). Activated Akt also phosphorylates tuberous sclerosis 1/2 (TSC1/2) protein, which ultimately activates the mammalian target of rapamycin (mTOR) and its downstream factors ribosomal protein S6 kinase (S6K) and 4E-binding protein 1 (4EBP1); this in turn modulates protein synthesis. Additionally, inhibitor of nuclear factor-κB kinase (IKK) and c-Jun N-terminal kinase (JNK) are also directly activated by Akt kinase, as well as fork-head family box O (FOXO) transcription factors, which can regulate mitochondrial function (Fernandez and Torres-Aleman 2012). More importantly, several kinases, S6K, JNK, mTOR and GSK3 themselves, for example, permit the inhibition of IRS-1 activity through the negative feedback regulation of IRS-1 site-specific serine phosphorylation, thus contributing to inactivation of the insulin signaling pathway (Fig. 2) (Copps and White 2012).

IRS-1 phosphorylation in AD

The tail regions of IRS proteins are enriched in Ser/Thr/Tyr residues, and multiple phosphorylations of IRS Ser/Thr/Tyr residues regulate IRS function, which further influences downstream molecules such as IRS-1/PI3K/Akt insulin signaling either positively or negatively. It has been previously demonstrated that the phosphorylation pattern of IRS-1 dictates signal capacity, as well as its capacity to bind to receptors (Gual et al. 2005), which suggests that aberrant IRS-1 phosphorylation at tyrosine and serine residues may evoke a pathologic state of insulin receptor; this is associated with the IRS-1/PI3K/Akt insulin signaling pathway (Copps and White 2012; Hancer et al. 2014; Herschkovitz et al. 2007; Samuel and Shulman 2012). Indeed, phosphorylation of IRS-1 at tyrosine residues contributes to signaling functions, whereas phosphorylation at serine residues inhibits the dissociation of IRS-1 from the insulin receptor and diminishes tyrosine phosphorylation, which results in insulin signaling dysregulation (White 2003). Homeostasis between tyrosine and serine residues phosphorylation in IRS-1 is therefore important in the IRS-1/PI3K/Akt insulin signaling pathway.

In neural-derived blood exosomes from preclinical subjects (asymptomatic amyloidosis subjects who are cognitively intact at 1–10 years before their diagnosis of AD) or AD patients, the total IRS-1 level is decreased to a lesser extent compared with the extent of phosphorylation of pan-Tyr in IRS-1, which is significantly diminished (Kapogiannis et al. 2015). In contrast, the $pSer^{312}$-IRS-1 level is apparently increased; the IR index means the ratio of pSer312-IRS-1 to P-pan-Tyr-IRS-1 in preclinical subjects or AD patients that is also higher than that in age- and gender-matched control (Kapogiannis et al. 2015). On the other hand, because IRS-1 phosphorylation or IR index could predict the development of AD up to 10 years prior to clinical onset, and some suggest, in some extend, IRS-1 phosphorylation or IR index may serve as biomarkers of AD (Kapogiannis et al. 2015). The levels of $pSer^{612}$-IRS-1 and $pSer^{636}$-IRS-1, which play a pivotal role in IR, are significantly elevated. This has been demonstrated in the brains of AD transgenic mice (APP/PS1 mice) as well as in the brains of individuals with AD with increased levels of $pSer^{616}$-IRS-1and $pSer^{636/639}$-IRS-1, and this phosphorylation pattern is positively associated with Aβ oligomer levels (Bomfim et al. 2012; Mao et al. 2016; Talbot et al. 2012). Increased IRS-1 phosphorylation in serine sites ultimately lead to IRS-1 inhibition, which has been shown in the brains of AD transgenic mice, in that IRS-1 phosphorylation at serine residues may disrupt the IRS-1/PI3K/Akt insulin signaling pathway and further accelerate AD progression (Bomfim et al. 2012). In hippocampal neurons stimulated by Aβ oligomers, the $pSer^{307}$-IRS-1 and $pSer^{312/616}$-IRS-1 levels are prominently elevated, whereas IRS-1 phosphorylation at tyrosine-465($pTyr^{465}$-IRS-1) is inhibited, which triggers defective brain insulin signaling (Bomfim et al. 2012). Chenodeoxycholic acid (CDCA) lowers $pSer^{307}$-IRS-1 levels and increases Akt activation and GLUT4 levels, which helps mitigate IR in the hippocampus (Bazzari et al. 2019). Taken together, IRS-1 phosphorylation at tyrosine and serine

residues is crucial to the IRS-1/PI3K/Akt insulin signaling pathway in AD pathology and to the negative feedback control process. Importantly, the IRS-1 downstream components mTOR, S6K, GSK3, IKK and JNK, play a negative regulatory role in IRS-1 Ser/Tyr phosphorylation, and the detailed phosphorylation site is presented in Table 1.

mTOR and S6K

mTOR, a major downstream effector of IRS-1/PI3K/Akt insulin signaling, acts as two functional complexes, mTORC1 and mTORC2, which are implicated in the regulation of protein and lipid synthesis, mitochondrial function, insulin signaling, and autophagy (Butterfield and Halliwell 2019). Research indicates that IRS-1 tyrosine phosphorylation increases when the PI3K/Akt/mTOR pathway is suppressed by PI3K inhibition, Akt or mTOR inhibition, whereas phosphorylation of IRS-1 at $Ser^{302, 307, 318}$ decreases (Hancer et al. 2014). mTOR enhances the phosphorylation of serine residues in IRS-1. Moreover, aberrant mTOR activation could further exacerbate brain IR in both AD and MCI patients after induction with Aβ monomers and/or soluble oligomers through phosphorylation of S6K proteins, a downstream target of mTOR; this includes an approximate twofold increase in advanced phosphorylation of the IRS-1 inhibitory Ser residue (Ser^{307}) by a negative feedback process (Tramutola et al. 2015). Moreover, activated mTOR signaling contributes to the buildup of SPs and NFTs, two hallmarks of AD neuropathology, through inhibition of autophagy as well as activation of downstream targets S6K and 4EBP1, which contribute to hyperphosphorylation of tau proteins (Di Domenico et al. 2018; Tramutola et al. 2015).

S6K, a critical signaling molecule in IR development, is a downstream target of mTOR that also induces IR by mediating IRS-1 Ser^{1101} phosphorylation (Tremblay et al. 2007). Another study indicated that activating mTORC1/S6K leads to increased IRS-1 Ser^{636} phosphorylation and diminished IRS-1 tyrosine phosphorylation, which are part of a feedback inhibition loop of insulin signaling (Gao et al. 2015). In SH-SY5Y cells, biliverdin reductase A inactivation is concomitant with increased p-mTOR and IRS-1 Ser^{307} phosphorylation levels; this is also observed in 3xTg AD mice, which suggests that elevated levels of p-mTOR parallels either IR or impaired biliverdin reductase A (Barone et al. 2016). On the contrary, hyperactivation of the mTORC1/S6K pathway instigates aberrant IRS-1 serine phosphorylation and degradation, which disrupts insulin signaling (Shah et al. 2004). Overall, in MCI and AD brains, this is a negative feedback mechanism by which overactivated mTOR induces IRS-1 serine residue phosphorylation to promote IRS-1 inactivation, which halts the normal activation of downstream targets in the insulin signaling pathway (Gupta and Dey 2012; Perluigi et al. 2015; Tramutola et al. 2015).

JNK/IKK

JNK, a serine/threonine protein kinase, inhibits insulin signaling by regulating phosphorylated IRS, and growing evidence indicates the role of elevated p-JNK in the induction of IRS-1 serine phosphorylation in AD brains (Zick 2005). Moreover, one study that investigated post-mortem brain tissues and cerebrospinal fluid (CSF) samples from AD patients showed that increased JNK and p-JNK levels are associated with $A\beta_{42}$ levels, which reflects the degree of cognitive decline (Gourmaud et al. 2015). Aβ peptide forms abnormal plaques due to its abnormal aggregation, which can promote the release of tumor necrosis factor-α (TNF-α), a proinflammatory factor, by activating microglial cells; subsequently, this results in elevated levels of TNF-α that can activate the JNK and/or IKK signaling pathways (Park and Bowers 2010; Ribe and Lovestone 2016). Aβ triggers IRS-1 serine phosphorylation via JNK activation by TNF-α, which ultimately leads to the dysfunction of insulin signaling.

A technique revealing the interaction between IRS proteins and insulin receptor/insulin-like growth factor receptor demonstrated that, by altering the interaction kinetics between IRS and insulin receptor, JNK phosphorylates serine residues of IRS, which contributes to IR (Lanzerstorfer

Table 1 PI3K/Akt downstream components play a negative regulatory role in IRS-1 phosphorylation

Downstream components	IRS phosphorylation	References
mTOR	Increased phosphorylation of serine site 302, 307, 318 and decreased phosphorylation of tyrosine site	Tramutola et al. (2015)
S6K	Increased phosphorylation of serine site 307, 636, 1101 and decreased phosphorylation of tyrosine site	Barone et al. (2016), Gao et al. (2015) and Tremblay et al. (2007)
IKK/JNK	Increased phosphorylation of serine site 307, 318, 616, 612 and decreased phosphorylation of tyrosine site	Yoon et al. (2012) and Zhang et al. (2016)
GSK3	Increased phosphorylation of serine site 332 and decreased phosphorylation of tyrosine site	Eldar-Finkelman and Krebs (1997) and Liberman and Eldar-Finkelman (2005)

et al. 2015). In addition, JNK/TNF-α is activated by Aβ oligomers, leading to the phosphorylation of multiple serine residues within IRS-1 and the physiologic inhibition of IRS-1tyrosine phosphorylation, which also contributes to IR in primary hippocampal neurons and AD transgenic mouse models (Bomfim et al. 2012). Further research in vivo demonstrated that intracerebroventricular injection of Aβ oligomers causes IRS-1 serine phosphorylation and JNK activation in cynomolgus monkeys hippocampi (Bomfim et al. 2012). On the contrary, as Aβ oligomers enhance JNK pathway activation, IRS-1Ser^{616} phosphorylation and Tau Ser^{422} phosphorylation are increased (Yoon et al. 2012). Additionally, Aβ oligomers induce endoplasmic reticulum stress (ERS), which interferes with insulin signaling by JNK-dependent IRS-1 serine phosphorylation in AD pathogenesis (Zhang et al. 2016). Moreover, IRS-1 Ser^{307,318,612} phosphorylation is enhanced and accompanied by increased tau Thr^{181} hyperphosphorylation (Zhang et al. 2016). Those findings are concordant with those in previous studies (Ma et al. 2009). Furthermore, inhibition of JNK activation can diminish SPs formation and hyperphosphorylation of tau proteins and is thus able to mitigate cognitive deficits (Zhang et al. 2016; Zhou et al. 2015). Therefore, JNK could modulate IRS-1 Ser/Tyr phosphorylation by elevating TNF-α levels or by ERS, which interferes with insulin signaling and contributes to inactivation of IRS-1/PI3K/Akt downstream molecules through the feedback mechanism.

Akt/GSK3

GSK3 refers to two isoforms, GSK3α and GSK3β, and is a multifunctional serine/threonine kinase that, when phosphorylated, exerts its effects through Akt. GSK3 regulates microtubule-associated proteins and the phosphorylation and buildup of tau proteins through the IRS-1/PI3K/Akt pathway (Arnold et al. 2018; Hanger et al. 1992). GSK3 activity is diminished through the phosphorylation of Ser^{9} in the GSK3β N-terminal as well as by phosphorylation of Ser^{21} in GSK3α. In AD pathogenesis, brain IR evokes GSK3β overactivation, which partly exacerbates tau hyperphosphorylation (includes misfolded tau and fibril aggregation) (Bhat et al. 2003). In autopsied frontal cortex brain tissue from AD patients, decreased levels of IRS-1, p-Akt, and p-GSK3β (Ser^{9}) have been observed, which suggests that GSK3β activity is increased and results in tau phosphorylation; GSK3β expression also colocalizes with NFTs (Liu et al. 2011). It has been documented that overexpression of GSK3 in AD results in diminished LTP induction, which leads to learning and memory deficits that present early in AD (Salcedo-Tello et al. 2011). Additionally, activated GSK3 triggers IRS-1 serine phosphorylation and suppresses phosphorylation of tyrosine residues within IRS-1, which indicates that a role for GSK3 is the promotion of IR; this in turn leads to IRS-1/PI3K/Akt insulin signaling deficiency (Eldar-Finkelman and Krebs 1997). GSK3, as the first identified physiological target of PI3K/Akt, is overactivated on account of aberrant IRS-1/PI3K/Akt insulin signaling, which results in tau hyperphosphorylation and LTP inhibition (Dubey et al. 2020; Liu et al. 2011; Salcedo-Tello et al. 2011). This leads to diminished synaptic plasticity, which suggests a crucial role for GSK3 in AD pathogenesis (Jaworski et al. 2019).

Therapeutic approaches to brain IR/insulin signal pathway in AD

Results of epidemiologic, clinical and experimental compellingly support a link between T2DM and AD that bear interrelated disease mechanisms involving insulin resistance and dysfunction of insulin signaling, and moreover antidiabetic drugs could modify the pathological and clinical progression of AD and improve cognition in some extend (Munoz-Jimenez et al. 2020; Rotermund et al. 2018; Yarchoan and Arnold 2014). Abnormal Ser/Tyr phosphorylation of IRS-1 is observed in the brain and neural-derived exosomes extracted from the blood of AD patients, and notably, is related to brain atrophy, all of which indicate a correlation between abnormal Ser/Tyr phosphorylation of IRS-1 and cognitive dysfunction (Kapogiannis et al. 2015; Mullins et al. 2017b; Rahman et al. 2019). Research on AD patients documented that the deposition of Aβ promotes Ser phosphorylation of IRS-1, which further elicits the impairment of downstream insulin signaling pathway, leading to brain IR, and these processes in turn further expedite Aβ accumulation and tau hyperphosphorylation (Mullins et al. 2017a; Talbot et al. 2012). Antidiabetic drugs involving sulfonylureas, metformin, thiazolidinediones, and GLP-1 analogues improve brain IR, impaired insulin signaling, neuroinflammation, oxidative stress, Aβ accumulation, tau hyperphosphorylation and other pathological processes in AD experimental and clinical research (Table 2). Despite the controversial findings of clinical studies, a number of literature and several compelling hypotheses still suggest that antidiabetic therapies hold potential as treatments for dementia (Bendlin 2019). We mainly summarize the effects of metformin, thiazolidinediones, and GLP-1 analogues on AD from experimental and clinical studies, and discussed below.

Metformin is a biguanide derivative that could increase insulin sensitivity and glucose uptake in individuals with T2DM, and also can cross the blood brain barrier (BBB) and has an impact on the brain biochemical pathways (Chaudhari et al. 2020; Pasquale et al. 2016). One study showed that metformin exerts a beneficial effect on both Aβ and tau

Table 2 Summary of representative preclinical and clinical studies on the efficacy of anti-diabetic drugs in AD

GLP-1 drugs	Proposed mechanism of action	Study design	References
Metformin	Reduction in plaque-associated tau pathology and Aβ burden	APP/PS1 mice	Chen et al. (2021)
Metformin	Improve in learning and memory ability; reduction in oxidative stress and neuroinflammation; ameliorate Aβ pathology by insulin-degrading enzyme	APP/PS1 mice	Lu et al. (2020)
Metformin	Enhancement of excitatory synaptic transmission onto hippocampal CA1 pyramidal neurons	In vitro acute hippocampal slices	Chen et al. (2020)
Metformin	Improve in learning and memory ability; decrease in Aβ and tau aggregation	SAMP8 mice	Farr et al. (2019)
Metformin	Restore the antioxidant status; activation of autophagy; reduction in inflammation	Naturally aged and accelerated senescence rats	Garg et al. (2017)
Metformin	Accelerate in glycolytic lactate production	Cultured primary cerebellar granule Neurons	Blumrich and Dringen (2019)
Metformin	Mitigation in Aβ-induced apoptosis through the suppression of JNK/MAPK signaling pathway	Cultured hippocampal neurons	Chen et al. (2016a, b)
Metformin	Amelioration in neuronal insulin resistance and Alzheimer's-like changes	In vitro neuronal cell line Neuro-2a	Gupta et al. (2011)
Metformin	Improve in executive functioning; no significant changes in cerebral blood flow	Randomized placebo-controlled crossover study	Aaron et al. (2017)
Metformin	Change in total recall of the Selective Reminding Test; no significant changes in glucose uptake in the brain	A pilot randomized placebo controlled clinical trial	Luchsinger et al. (2016)
Rosiglitazone	Augmentation in PPARγ and ERK/MAPK activity; restore neural network	Tg2576 mice	Denner et al. (2012)
Rosiglitazone	Improve in memory deficits; reduction in Aβ levels, Aβ plaque deposition, tau aggregation, and the expression of proinflammatory markers; promotion in phagocytic ability of microglia	Alzheimer's transgenic mice	Escribano et al. (2010)
Rosiglitazone	Improve Aβ neurotoxin induced electrophysiological alterations	Primary cultured hippocampal pyramidal neurons	Bahrami et al. (2019)
Rosiglitazone	Activation in ERK and recruitment of PPARγ to pERK during memory consolidation	Tg2567 mice	Jahrling et al. (2014)
Rosiglitazone	Increase in brain glucose metabolism	Multi-center randomized clinical trial	Tzimopoulou et al. (2010)
Rosiglitazone	Improve in plasma Aβ levels; exhibit better delayed recall and selective attention	Placebo-controlled, double-blind, parallel-group pilot study	Watson et al. (2005)
Rosiglitazone	No significant changes in cognition or global function	Double-blind, randomized, placebo-controlled study	Gold et al. (2010) and Harrington et al. (2011)
Pioglitazone	Improve in metabolic profiles in cerebellum, cortex, and hippocampus	Tg2676 mice	Wong et al. (2020)
Pioglitazone	Restore the energy metabolism and antioxidative capacity; lower in Aβ levels	APP/PS1 mice	Chang et al. (2019)
Pioglitazone	Improve in memory deficit; protection against oxidative stress and apoptotic action; reduction in inflammation	Intracerebroventricular injection of $A\beta_{42}$ in rats	Prakash and Kumar (2014)
Pioglitazone	Improve in contextual memory deficits; increase in anti-inflammatory M2 state microglia and Aβ clearance	APP/PS1 mice	Mandrekar-Colucci et al. (2012)

Table 2 (continued)

GLP-1 drugs	Proposed mechanism of action	Study design	References
Pioglitazone	Reduction in hippocampal Aβ and tau deposition; enhancement in short- and long-term plasticity; decrease in glutamatergic and lipid metabolic/cholesterol dependent processes	3xTg-AD mice	Searcy et al. (2012)
Pioglitazone	Improve in regional cerebral blood flow; exhibit cognitive and functional improvements	Randomized, open-controlled clinical trial	Sato et al. (2011)
Pioglitazone	Improve in insulin resistance	A pilot study	Hildreth et al. (2015)
Liraglutide	Improve in memory impairment and synaptic loss; reduction in Aβ plaque and soluble oligomers; alleviation in neuroinflammation and microglial activation	APP/PS1 mice	McClean and Holscher (2014) and McClean et al. (2011)
Liraglutide	Improve in memory impairment	Senescence-accelerated prone 8 (SAMP8) mice	Hansen et al. (2015)
Liraglutide	Improve in memory formation and synaptic plasticity; reduction in Aβ plaque load and inflammation	APP/PS1 mice	McClean et al. (2015)
Liraglutide	Amelioration in learning and memory impairment and tau hyperphosphorylation	$A\beta_{42}$ induced mice	Qi et al. (2016)
Liraglutide	Prevention in chronic ER stress, autophagy impairments and apoptotic signaling	Thapsigargin-induced SH-SY5Y cells	Panagaki et al. (2017)
Liraglutide	Improve in memory impairment; increase in brain insulin receptors and synapses	Aβ oligomer induced mice; hippocampal neuronal cultures; Aβ oligomer induced non-human primates model	Batista et al. (2018)
Liraglutide	Reduction in $A\beta_{42}$ generation; enhance in autophagy	APPswe/SH-SY5Y cells	Kong et al. (2020)
Liraglutide	Protection against oxidative/nitrosative stress; reduction in inflammation	3xTg-AD mice	Duarte et al. (2020)
Liraglutide	Improve in phosphorylation status of insulin signal transduction; suppression of tau hyperphosphorylation and Aβ accumulation	Insulin-induced SH-SY5Y cells	Jantrapirom et al. (2020)
Liraglutide	Inhibition of neuronal apoptosis; activation of the PI3K/Akt signaling pathway	Aβ-induced SH-SY5Y	Liu et al. (2016)
Liraglutide	Prevention in brain glucose metabolism decline	Randomized, placebo-controlled, double-blind clinical trial	Gejl et al. (2016)
Liraglutide	Increase in blood–brain glucose transfer	Randomized clinical trial	Gejl et al. (2017)
Exenatide	Improve in axonal transport; prevention increased $pSer^{636}$-IRS-1 and decreased $pTyr^{465}$-IRS-1 levels	Oligomer-induced hippocampal neuronal cultures; Intracerebroventricular (ICV) injection of Aβ oligomer in cynomolgus monkeys	Bomfim et al. (2012)
Exenatide	Decrease in $pSer^{636}$-IRS-1, $pSer^{312}$-IRS-1, and p-JNK levels; reduction in amyloid deposition and soluble Aβ levels; improve in spatial memory and memory retention	APP/PS1 mice	Bomfim et al. (2012)
Exenatide	Improve in cognitive performance and hippocampal neuronal viability; suppression of inflammation response; increase in cholinergic activity	ICV injection of streptozotocin (STZ) in rats	Solmaz et al. (2015)
Exenatide	Prevention of cognitive decline, $A\beta_{42}$ deposition and synapse damage; improve in mitochondrial dysfunction	5 × FAD mice	An et al. (2019)
Exenatide	Enhancement of long-term memory; activation of the BDNF-TrkB neurotrophic axis; protection against apoptosis	Wide-type mice of mid-life brain ageing	Bomba et al. (2018)

Table 2 (continued)

GLP-1 drugs	Proposed mechanism of action	Study design	References
Exenatide	Switching metabolism from aerobic to anaerobic glycolysis; increase in production of lactate	PS1-KI AD model mice	Bomba et al. (2013)
Exenatide	Improve in learning and memory; rescue in long-term potentiation	Intra-hippocampal injection of $A\beta_{42}$ in rats	Wang et al. (2016)
Exenatide	Protection in neuronal survival signaling pathway; prevention of apoptosis action	$A\beta_{42}$ oligomer-induced PC12 cell	Chen et al. (2016)
Exenatide	Improve in spatial learning and memory impairments; decrease in the expression of Bax and cleaved Caspase-3	$A\beta_{42}$ induced rats	Jia et al. (2016)
Exenatide	Improve in memory deficits; reduction in Aβ levels; mitigation in mitochondrial toxicity through the PI3K/Akt-mediated pathway	$A\beta_{42}$ induced rats	Garabadu and Verma (2019)
Exenatide	Reduction in plasma neuronal extracellular vesicles (EV) Aβ42 level	Double-blind randomized placebo-controlled clinical trial	Mullins et al. (2019)

pathologies in APP/PS1 mice (Chen et al. 2021). Findings from the study showed that metformin ameliorated microglial autophagy impairment, promoted the phagocytosis of pathological Aβ and tau proteins, and then limited the propagation of Aβ and tau aggregates in dystrophic neurites surrounding Aβ plaques. Additionally, metformin increased the protein levels of p-AMPK and insulin-degrading enzyme (IDE) in the brain of APP/PS1 mice, restored the antioxidant status, reduced the neuroinflammation, thus improving the cognitive decline (DiTacchio et al. 2015; Garg et al. 2017; Lu et al. 2020). In vitro, metformin is neuroprotective against Aβ-induced cytotoxicity and can enhance excitatory synaptic transmission in hippocampal CA1 neurons, increase glycolytic lactate production, and improve neuronal insulin resistance (Blumrich and Dringen 2019; Chen et al. 2016a, b; Chen et al. 2020; Gupta et al. 2011). However, results of other studies indicate that metformin exerts paradoxical effects on tau pathology, possibly leading to increased tau aggregation, and metformin induce mitochondrial dysfunction and promote the aggregation of toxic amyloid pre-fibrillar in brain cortex region (Barini et al. 2016; Pasquale et al. 2016). Results from clinical studies should that long-term treatment with metformin may decrease the risk of cognitive decline in individuals with T2DM (Hsu et al. 2011; Tze et al. 2014). Notably, however, the results of another study suggested that individuals with T2DM treated with metformin for a long-term had a slightly higher risk of developing AD than the T2DM patients treating with sulfonylureas or thiazolidinediones (Imfeld et al. 2012). Besides, in a pilot randomized placebo controlled clinical trial comparing placebo individuals, metformin improves total recall of the selective reminding test (SRT) in amnestic mild cognitive impairment patients (Luchsinger et al. 2016). Results of the other randomized placebo-controlled crossover study suggest that metformin was associated with improved executive functioning, and trends suggested improvement in learning/memory and attention in AD (Aaron et al. 2017). Overall, the results from experimental and clinical studies assessing the effect of metformin on cognitive decline and AD are mostly promising, and the further study, such as a 2-year metformin clinical trial (ClinicalTrials.gov NCT04098666) results should be expected (Munoz-Jimenez et al. 2020).

Thiazolidinediones, also known as glitazones, that include rosiglitazone and pioglitazone, are peroxisome proliferator-activated receptor gamma (PPARγ) agonists. Recent progress indicated that PPARγ agonists could modulated different cellular targets in AD and improve cognitive impairments. Results of several experimental studies indicated that rosiglitazone could promote the phagocytic ability of microglia, reduce the expression of proinflammatory factors, decrease Aβ and tau pathology in the brain of AD transgenic mice, and restore neural networks compromised by AD (Denner et al. 2012; Escribano et al. 2010).

Pioglitazone also reversed behavioral deficits in AD model mice by decreasing hippocampal Aβ and tau proteins deposits, enhancing short- and long-term plasticity, attenuating neuroinflammation, activating phosphorylated ERK (p-ERK) during memory consolidation (Jahrling et al. 2014; Mandrekar-Colucci et al. 2012; Searcy et al. 2012). Furthermore, pioglitazone successfully reverts metabolic dysfunction in cortex, restore the energy metabolism, lower Aβ levels and deposition in AD model mice (Chang et al. 2019; Wong et al. 2020). Besides, the initial clinical results with rosiglitazone for AD patients were positive influence, but the later clinical trials evidence from larger patient groups and from the systematic review and meta-analysis are insufficient to support the use of rosiglitazone in MCI and AD patients to improve cognitive performance (Liu et al. 2015; Risner et al. 2006; Tzimopoulou et al. 2010; Watson et al. 2005). Moreover, rosiglitazone only has a neutral effect on the risk of dementia in T2DM, and individual patient level data suggest that treated with rosiglitazone is associated with a potential risk of cardiovascular disease (Tseng 2019; Wallach et al. 2020) risk. By contrast, pioglitazone seems to be promising therapeutic approach to AD patients. Results of clinical trials showed that pioglitazone improves memory and cognitive performance in mild AD patients, reduces dementia risk in patients with T2DM, and indicated the greatest efficacy compared to placebo (Cao et al. 2018; Cheng et al. 2016; Sato et al. 2011; Tseng 2018). However, the another several studies also demonstrated that pioglitazone has no beneficial effect on cognitive performance in patients with AD or MCI (Geldmacher et al. 2011; Hildreth et al. 2015). Overall, the controversial effects on MCI or AD patients exerted by thiazolidinediones are worthy of more investigation, and the possible explanations for the difference results of the research could be the unblind selection of patients, the small samples, the status of ApoE4(−/+), and the brain bioavailability of the drugs (Chang et al. 2015; Hildreth et al. 2015; Iketani et al. 2018). Thus, the efficacy of thiazolidinediones as a disease-modifying drug on individuals with MCI or/and AD needs to be further confirmed by rigorous well-designed with large-scale randomized controlled trials.

GLP-1 analogue, such as liraglutide and exenatide (synthetic form of exendin-4) facilitate insulin signaling, and can cross the BBB reaching the brain to target GLP-1 receptors, which alleviate brain IR and insulin signaling pathway disorders, decrease the levels of hippocampal pSer-IRS-1 in AD model mice, thus improving cognitive dysfunction (Bomfim et al. 2012; Hunter and Hölscher 2012; Salameh et al. 2020; Talbot and Wang 2014). Liraglutide could improve learning and memory impairments in AD models by decreasing Aβ plaque load and modulating tau hyperphosphorylation, as well as regulating brain IR, PI3K/Akt pathway and insulin signal transduction (Batista et al. 2018; Jantrapirom et al. 2020; Liu et al. 2016; Qi et al. 2016). Exenatide administration prevented cognitive decline through alleviating Aβ deposition, tau hyperphosphorylation, improving brain glucose metabolism, mitigating mitochondrial toxicity by PI3K/Akt-mediated pathway as well as regulating IRS-1 phosphorylation (An et al. 2019; Bomba et al. 2013; Bomfim et al. 2012; Garabadu and Verma 2019). Overall, the in vivo and in vitro studies of GLP-1 analogues treating AD demonstrate an effect of this treatment on amyloid and tau pathologies as well as brain IR, abnormal insulin signaling pathway, oxidative stress, synaptic plasticity, apoptosis, and other core neuronal functions (Hansen et al. 2015; Liu et al. 2016; McClean et al. 2015; McClean et al. 2011; Perry et al. 2002, 2003; Qi et al. 2016). The multiple mechanism of action of liraglutide and exenatide for the treatment or prevention of AD progression are detailed presented in Table 2. Indeed, treatment with liraglutide or exenatide has consistently been associated with improvements in cognition and memory in preclinical model of AD.

Several more recent studies indicated that GLP-1 analogues such as liraglutide and exenatide, are potential candidate for AD disease-modifying treatment (Ballard et al. 2020; Talbot 2014). A randomized, placebo-controlled, double-blind clinical study in individuals with AD indicated that, compared with placebo, liraglutide treatment prevented the decline of glucose metabolism in the brain, which is associated with cognitive degeneration and synaptic dysfunction, and declining brain glucose metabolism often indicate dysfunction in brain activities (Gejl et al. 2016). Further research indicated that the underlying mechanism for this effect was an increased blood–brain glucose transport at the BBB (Gejl et al. 2017). Besides, a double-blind randomized placebo-controlled study which included only 21 participants, indicated that exenatide could lower plasma neuronal extracellular vesicles (EV) $A\beta_{42}$ level, a biomarker in clinical trials in AD, and, however, only marginally improve cognitive outcomes in AD patients (Mullins et al. 2019). Given the very limited power of this study, early termination, small sample size as well as at a single-center study, these observations may underpowered and cannot be meaningfully interpreted (Ballard et al. 2020; Mullins et al. 2019). Clinical trial of Parkinson's disease (PD) treatment with exenatide demonstrated that, compared with the control group, exenatide improved motor function and cognitive measures in individuals with PD, which was identified as potential disease-modifying treatment in neurodegenerative disease (Athauda et al. 2017; Aviles-Olmos et al. 2013). Thus, these results of GLP-1 analogues are promising and provide increasing evidence that these drugs are potential for the treatment of AD, and the further results of Evaluating Liraglutide in Alzheimer's disease (ELAD) trial are eagerly awaited (Femminella et al. 2019).

Conclusion

In recent years, cumulative studies have elucidated that brain IR, which is a crucial pathological feature of AD, is associates with cognitive dysfunction, Aβ plaques, hyperphosphorylated tau protein and impaired cerebral glucose metabolism. Here, we highlight a key molecule in brain IR, IRS-1, which is phosphorylated at Ser/Tyr residues and is related to neuropathologic hallmarks of AD such as Aβ plaques and hyperphosphorylated tau proteins, and we present their potential mechanisms. In conclusion, dysregulation of IRS-1 Ser/Tyr phosphorylation could exacerbate disturbances in the IRS-1/PI3K/Akt insulin signaling pathway and the pathway's interaction with mTOR, S6K, JNK/IKK and Akt/GSK3, among others. Anti-diabetic drugs could modulate the insulin signaling pathway, brain IR and other pathological process of AD, which provide a potential strategy for AD disease-modifying treatments, and future studies will contribute to the precise mechanism of Ser/Tyr phosphorylation in IRS-1 in the regulation of IRS-1/PI3K/Akt insulin signaling pathway in AD.

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Author contributions MCZ designed and wrote the manuscript. PWW critically reviewed the manuscript and did the required editing and supervision.

Declarations

Conflict of interest The authors declare that they have no conflict of interest in the preparation of manuscript.

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