Journal of Diabetes and Its Complications 37 (2023) 108629

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: www.elsevier.com/locate/jdiacomp

Insights from insulin resistance pathways: Therapeutic approaches against Alzheimer associated diabetes mellitus

Ayesha Fauzi [a], Ewen Se Thoe [a], Tang Yin Quan [a,b], Adeline Chia Yoke Yin [a,b,*]

[a] School of Biosciences, Faculty of Health & Medical Sciences, Taylor's University Lakeside Campus, 47500 Subang Jaya, Selangor Darul Ehsan, Malaysia
[b] Medical Advancement for Better Quality of Life Impact Lab, Taylor's University Lakeside Campus, 47500 Subang Jaya, Selangor Darul Ehsan, Malaysia

ARTICLE INFO

Keywords:
Type 3 diabetes mellitus
Diabetes
Alzheimer's disease
Biguanides
Metformin
Insulin secretagogues
Glimepiride
AdipoRON
GLP-1
DPP4

ABSTRACT

Alzheimer Associated Diabetes Mellitus, commonly known as Type 3 Diabetes Mellitus (T3DM) is a distinct subtype of diabetes with a pronounced association with Alzheimer's disease (AD). Insulin resistance serves as a pivotal link between these two conditions, leading to diminished insulin sensitivity, hyperglycemia, and impaired glucose uptake. The brain, a vital organ in AD context, is also significantly impacted by insulin resistance, resulting in energy deficits and neuronal damage, which are hallmark features of the neurodegenerative disorder.

To pave the way for potential therapeutic interventions targeting the insulin resistance pathway, it is crucial to comprehend the intricate pathophysiology of T3DM and identify the overlapped features between diabetes and AD. This comprehensive review article aims to explore various pathway such as AMPK, PPARγ, cAMP and P13K/Akt pathway as potential target for management of T3DM. Through the analysis of these complex mechanisms, our goal is to reveal their interdependencies and support the discovery of innovative therapeutic strategies.

The review extensively discusses several promising pharmaceutical candidates that have demonstrated dual drug action mechanisms, addressing both peripheral and cerebral insulin resistance observed in T3DM. These candidates hold significant promise for restoring insulin function and mitigating the detrimental effects of insulin resistance on the brain. The exploration of these therapeutic options contributes to the development of innovative interventions that alleviate the burden of T3DM and enhance patient care.

1. Background

Alzheimer's disease (AD) and diabetes are prevalent disorders that are increasingly common worldwide, especially among elderly individuals. Recent research has suggested a possible link between the two conditions. Some researchers use the term Type 3 Diabetes Mellitus (T3DM) to describe the theory that insulin resistance and insulin-like growth dysfunction in the brain may lead to Alzheimer's disease. T3DM is also known as 'diabetes of the brain' or 'brain diabetes' and is characterized by insulin resistance in the brain, leading to reduced

Abbreviations: β-cells, Beta cells; Aβ, Amyloid – beta; AD, Alzheimer's disease; AKT, Protein kinase B; AMPK, AMP-activated protein kinase; BACE1, Beta secretase 1; BBB, Blood brain barrier; cAMP, Cyclic adenosine monophosphate; CNS, Central nervous system; DPP-4, Dipeptidyl peptidase-4; eNOS, Endothelial NO synthase; ERK 1/2, Extracellular signal-regulated kinase 1/2; FBG, Fasting blood glucose; FoxO1, Forkhead box protein O1; FPG, Fasting plasma glucose; GIP, Glucose-dependent insulinotropic peptide; GITS, Glipizide gastrointestinal therapeutic system; GLP-1, Glucagon-like peptide 1; GLUT1, Glucose transporter 1; GLUT4, Glucose transporter 4; GPCR, G protein-coupled receptor; GSK3β, Glycogen synthase kinase-3; HbA1C, Glycosylated hemoglobin; HUVEC, Human umbilical vein endothelial cells; IGF1-R, Insulin like growth factor receptor 1; IGF2-R, Insulin like growth factor receptor 2; IKKb, Ikappab kinase; IL-1, Interleukin-1; IL-6, Interleukin-6; IR, Insulin resistance; IRS, Insulin receptor substrate; JNK, c-Jun N-terminal kinase; LKB1, Liver kinase B1; LPS, Lipopolysaccharide; MIP, Macrophage inflammatory protein; MR, Modified release; mTOR, Mammalian target of rapamycin; NADH, Nicotinamide adenine dinucleotide; NF-kβ, Nuclear Factor kappa b; NFT, Neurofibrillary tangles; NO, Nitric oxide; P13K, Phosphoinositide 3-kinase; PARP-1, Poly [ADP ribose] polymerase 1; PKA, Protein kinase A; PKCζ, Protein kinase Cζ; PP2A, Protein phosphatase 2 A; PPARg, Proliferator activated receptor-g; PPG, Preproglucagon; PTEN, Tensin homolog; RAS, Reticular activating system; ROS, Reactive oxygen species; STAT3, Signal transducer and activator transcription 3; SUR, Sulfonylurea receptor; T1DM, Type 1 Diabetes Mellitus; T2DM, Type 2 Diabetes Mellitus; T3DM, Type 3 Diabetes Mellitus; TNF-α, Tumor necrosis factor-α.

* Corresponding author at: School of Biosciences, Faculty of Health & Medical Sciences, Taylor's University Lakeside Campus, 47500 Subang Jaya, Selangor Darul Ehsan, Malaysia.
E-mail address: YokeYin.Chia@taylors.edu.my (A.C.Y. Yin).

https://doi.org/10.1016/j.jdiacomp.2023.108629
Received 11 July 2023; Received in revised form 3 September 2023; Accepted 15 October 2023
Available online 18 October 2023
1056-8727/

glucose uptake and utilization[1,2]. Studies indicate that T3DM is closely associated with aging and cognitive decline, with an increased risk of developing Alzheimer's disease and other form of dementia.[3,4]

In contrast, Type 2 Diabetes Mellitus (T2DM) is a well-established risk factor for AD, with patients are nearly twice as likely to suffer from dementia, particularly vascular dementia, occurring at a frequency of 2 to 2.5 times, while is 1.5 times more likely to occur.[5,6] The connection between T2DM and dementia is multifactorial and relatively complex. The main difference between T2DM and T3DM regarding AD is due to their underlying mechanism and extent of association. T3DM is believed to involved not only insulin resistance but also the impairment of brain insulin. It affects glucose metabolism and energy production, which contribute to AD pathology.[7,8] It is important to note that T3DM is not an officially recognised health condition and is not associated with any type of diabetes within its classification. Some researchers proposed the concept of T3DM as a subtype of diabetes that involves a neuroendocrine disorder contributing to the progression of T2DM to AD. The potential link between the two disease highlights the importance of further research as their increasing prevalence is a public health concern.

With this theory in mind, anti-diabetic drugs are presumed to mitigate AD-like pathology. Several modern pharmaceuticals medications, namely biguanides, insulin secretagogues, incretin-related drugs, and molecular receptor agonist are in the forefront for T3DM prevention and treatment due to their therapeutic roles.[9] The proposed etiologies include alterations in glucose metabolism, insulin signaling pathway, insulin resistance, inflammation, and oxidative stress. In this review, we will be examining the various potential therapeutic treatments along with their corresponding T3DM treatment.

2. Insulin resistance linking T3DM and AD

Peripheral insulin is an anabolic peptide hormone, crucial for glucose homeostasis and is routinely synthesized in the beta cells (β-cells) of islets of Langerhans in the pancreas in response to increased glucose level. In peripheral tissue, insulin is involved in glucose utilization, suppression of hepatic glucose production and transportation of glucose into cells. Glucose is a large hydrophilic molecule which requires a specific carrier to cross cell membranes, usually via sodium dependent-mechanism or carriers. It is also involved in cell growth, differentiation, and protein synthesis. Insulin resistance is defined as a state where target tissues are not able to respond to glucose concentration. It manifests at multiple levels of the insulin signaling pathway and its pathophysiology is complex and involves different mechanisms. Generally, insulin resistance for diabetes is due to genetic factors, inflammatory responses, mitochondrial dysfunction, and lipid metabolism. Due to the impaired glucose uptake and utilization in peripheral tissue, insulin resistance manifests in the form of hyperglycemia. In response, pancreas will overcompensate and release insulin, this however creates a harmful cycle as insulin hypersecretion stimulates insulin resistance and leads to progressive decline of β-cell mass and function.[10] In addition to its peripheral effects, insulin plays a vital role in the CNS.

In the normal brain, insulin signaling plays a crucial role in glucose uptake regulations and metabolism as a primary source of energy. Peripheral insulin uptake in the brain is via GLUT1 located on endothelial cells and astrocytes at blood brain barrier (BBB) while neurons and glial cells at brain parenchyma synthesize insulin de novo.[11] Both insulins however share similar molecular mechanisms and at least 25 % of glucose are used for maintenance of basal brain activities. In AD patients, hippocampus glucose metabolic rate is markedly reduced.[12] The brain is an insulin-sensitive organ due to high expression of insulin receptors (IR) and insulin-like growth factor receptors 1 and 2 (IGF1-R/IGF2-R) in various regions including cerebral cortex, hippocampus, olfactory bulb, and hypothalamus. Attachment of insulin to the receptors, triggers the molecular cascade which leads to activation of downstream signaling pathways such as P13K/AKT/mTOR which are important in glucose uptake, glycogen, and protein synthesis. However, in T3DM, insulin resistance disrupts this pathway, impairing its uptake and utilization. Epidemiological studies have shown association between glucose intolerance and insulin secretion impairment with higher risk of developing dementia or AD.[13]

Studying the pathway (Fig. 1), there is a convergence of the effects of insulin resistance in both diabetes and AD as both conditions disrupt the normal function of the insulin signaling pathway. In healthy cells, insulin binds to the insulin receptor substrate (IRS) and initiates the P13K/AKT pathway. This pathway inhibits GSK3β and FoxO1 while promoting mTOR activities. Inhibition of GSK3β causes an increase of glycogen synthesis and glucose uptake. However, in insulin resistance cells, insulin binding decreases, leading to reduced GSK3β inhibition. This in turn, inhibits glycogen synthase and reduces glucose transporter 4 (GLUT4) expression (facilitates uptake of glucose into cells) which resulted in hyperglycemia and inflammation in DM patients. In AD patients, this gives rise to increased hyperphosphorylated tau protein and eventual formation of NFT, greatly reducing Aβ clearance.

Inhibition of FoxO1 is a regulatory mechanism for maintenance of blood glucose level by promoting glucose utilization and storage. It also regulates other cellular processes such as apoptosis, cell differentiation and oxidative stress. However, in insulin resistance cells, increased level of FoxO1 disrupts normal pathways leading to increased glycogenesis process resulting in hyperglycemia in diabetes. In AD, it reduces Aβ clearance by inhibiting the Aβ phagocytosis process. Accumulation of Aβ leads to inflammation, oxidative stress, and neuronal cell death. Another pathway that relies on insulin signaling is mTOR activation, responsible for protein synthesis and increased glucose uptake in normal healthy cells. In insulin resistance cells, there is an upregulation of mTOR causing lipid accumulation. This is associated with increased inflammation and oxidative stress, worsening diabetes. Similarly, upregulation of mTOR reduces autophagy of Aβ, causing accumulation of Aβ deposition that contributes to inflammation, oxidative stress and eventual neuronal cell death associated with AD.

Another pathway that is affected by insulin resistance is the RAS/ERK pathway. Normally, binding of insulin triggers phosphorylation of RAS which in turn, activates ERK1 and ERK2. This protein is responsible for regulation of glucose uptake and other cellular processes. However, the normal pathway is disrupted in insulin resistance, causing a reduction in GLUT4 which is important in glucose uptake, leading to inflammation and oxidative stress in DM. From the perspective of AD, this disruption increases tau hyperphosphorylation and NFT formation. In respect to inflammation, insulin modulates proinflammatory cytokines secretions.[15] IR trigger inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β, (IL-1β) and interleukin-6 (IL-6) which set off a chain reaction where the JNK pathway activates IKKb and NF-κb. Furthermore, the NF-κb pathway will trigger release of additional cytokines, further exacerbating the inflammatory response. These will cause decreased binding of insulin and IRS via JNK and STAT3 pathway. It is also important to note, in the context of insulin resistance, dysregulated GSK3β, FoxO1, mTORC1 and ERK1/2 leads to negative feedback mechanisms. These molecules will now inhibit the binding of insulin and IRS which further aggravates insulin resistance and contribute to the pathology. To conclude, insulin resistance disrupts several key pathways which are central to the development and progression of DM and AD, which is why it is fitting to refer to them as T3DM. Understanding the complex relationship and overlapping interactions is crucial for development of targeted therapies that benefit T3DM.

3. Potential therapeutic option

The pathogenesis of both T2DM and AD presents various potential therapeutic options. However, T3DM necessitates a treatment that address both conditions effectively. To achieve this goal, a focus on the distinct pathways implicated in insulin resistance holds promise.

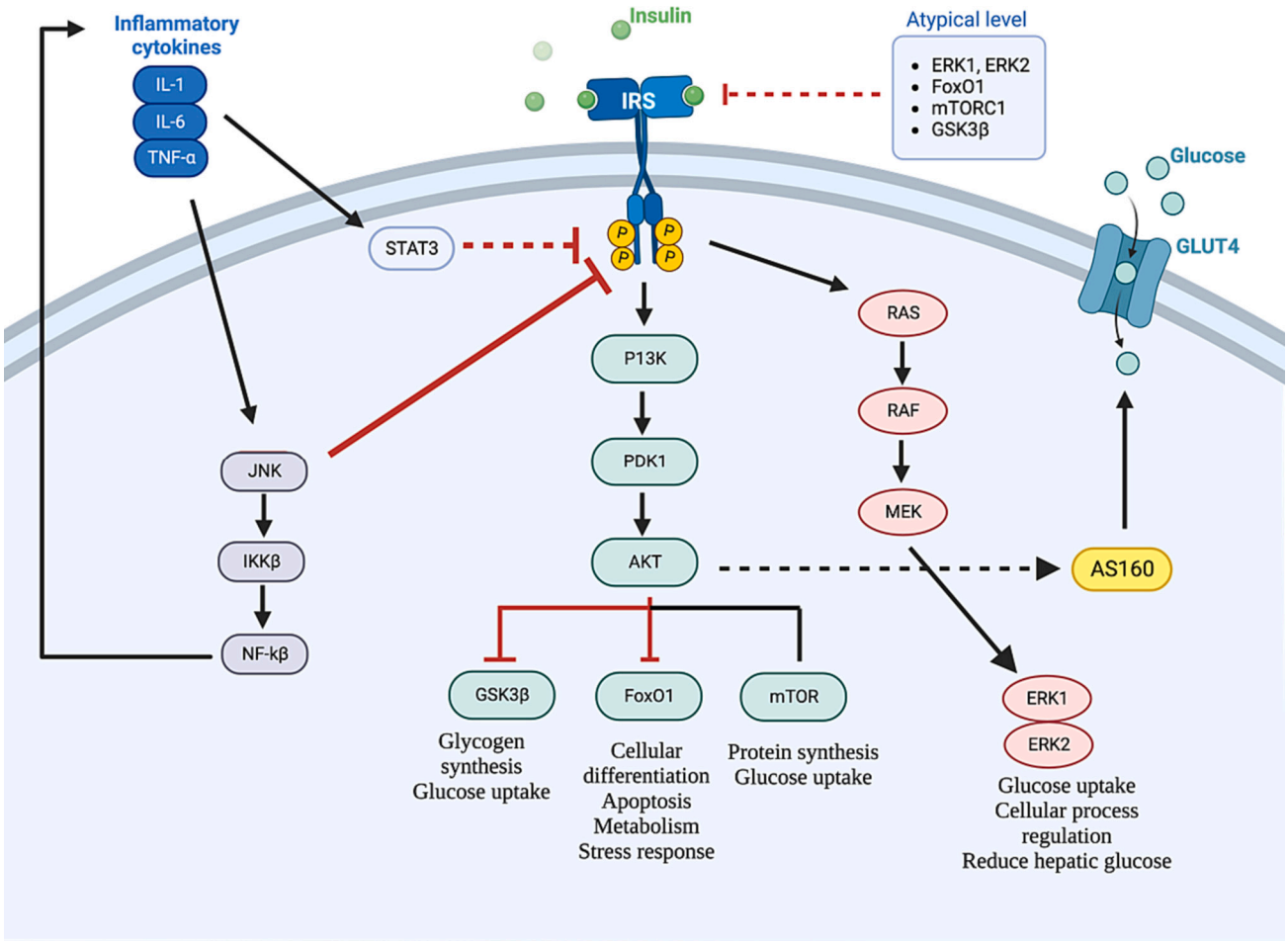

Fig. 1. Insulin signaling pathway overview in T3DM. Under normal conditions, binding of insulin to IRS triggers the P13K/PDK1/AKT activation which inhibits GSK-3B, FoxO1 and its downstream signaling but increases mTOR. However, in insulin resistance pathway, disruption of Insulin/IRS binding reduces the P13K/PDK1/AKT pathway which in turns cause an increase of GSK3B and FoxO1. This leads to manifestation of symptoms of hyperglycaemia and inflammation in diabetes patient and increased NFT and reduced AB clearance in AD. Disruption of the pathway also reduces glucose uptake due to the reduced level of AS160. Atypical level of proteins and increased inflammatory cytokines from disruption of the AKT pathway will further inhibit insulin/IRS mechanism. The figure was created by author based on[14] with additional information added.

Currently, the dual drug approach has emerged as a viable option for targeted treatment of T3DM, with promising outcomes. In the subsequent section, we will discuss the underlying mechanism and evidence supporting the effectiveness of this approach.

3.1. *AMPK pathway: a potential target for managing insulin resistance*

3.1.1. *Metformin dual drug action for T3DM*

AMP-activated protein kinase (AMPK) is a central regulator of energy homeostasis, widely known as 'metabolic sensors' and is vital in regulation of energy metabolism. AMPK is activated in response to various stimuli including cellular stress, exercise, and drugs such as metformin. AMPK activation leads to phosphorylation of GSK3β and the subsequent downregulation of glucogenic genes on the transcription level, resulting in decreased hepatic lipid accumulation and improved insulin sensitivity.[16] This section will focus on Metformin, a class of drugs named as biguanides, well-known for their antidiabetic properties and are commonly used as treatment for DM. In DM, metformin achieves its effect primarily via inhibition of Complex I activity of the electron transport chain in the mitochondria, which reduces the energetic costs associated with gluconeogenesis and contributes to a decrease in hepatic glucose production. Additionally, Complex I inhibition activates signaling kinase AMPK.

Metformin has also emerged as a potential therapeutic option for AD due to its ability to activate various signaling pathways and biological processes, specifically AMPK signaling. This makes it the ideal choice of treatment for T3DM. The AMPK pathway is heavily expressed in the brain and is involved in the regulation of neurodegenerative diseases.[17] Studies have shown it exert neuroprotective effects via reduced Aβ accumulation, decrease tau phosphorylation, improve spatial memory and increase neurogenesis in the brain.[18] Two randomized controlled study have been conducted revealing that the use of metformin, either as a monotherapy or in combination therapy with sulfonylurea (different class of DM drugs), can significantly reduce the risk of dementia in T2DM patients.[19,20]

Activation of the AMPK pathway by metformin reduces Aβ accumulation in the brain via combination of autophagy induction and reduction of β-site amyloid precursor protein cleaving enzyme-1 (BACE1) expression. Autophagy induction remove toxic cellular components such as Aβ, thereby reducing its accumulation in the brain while increased enzyme BACE1, increases the cleavage of the amyloid protein and the initiation of Aβ formation.[21] However, conflicting results have been reported for *APOE* ε4 carriers, where metformin may exacerbate negative effects on amyloid-beta metabolism and neurotoxicity and is associated with faster decline of cognitive function.[22,23] This may be attributed to upregulation of BACE1 activity, leading to an increase in Aβ peptide production.[24] In vivo studies have shown beneficial effect of metformin on Aβ reduction, which contrast to previous in vitro and ex

vivo studies.

Metformin impact on tau phosphorylation in AD has shown mixed results. In vitro and in vivo studies indicate a dose-dependent increase in autophagy and reduction in cognitive impairment and hyperphosphorylated tau proteins.[25,26] However conflicting results is observed in ApoE in vivo models,[27,28] likely due to involvement of other pathways such as mTOR/protein phosphatase 2A (PP2A) signaling pathway, presence of ApoE gene and also AKT phosphorylation and GSK-3β.[29] Further research is required to understand the complex interplay between these mechanisms and its impact on tau phosphorylation. Persistent neuroinflammation is a hallmark of AD, associated with the activation of Nuclear Factor kappa B (NF-κb) signaling pathway which is regulated by AMPK. NF-κb plays a vital role in regulating expression of pro-inflammatory cytokines and chemokines (Fig. 2). Metformin, an AMPK activator, reduces neuroinflammation by inhibiting NF-κb through three pathways: 1) suppression of inhibitory kappa B kinase (IKK), which regulates NF-κb 2) blocking AKT/NF-κb signaling pathway via activation of phosphatase and tensin homolog (PTEN), and 3) suppression of Poly [ADP ribose] polymerase 1 (PARP-1), down-regulating activation of pro-inflammatory pathways.[30] Animal studies show that suppression of NF-κb reduces expression of pro-inflammatory cytokines, including TNF-α, IL-1β and IL-6.[31,32] The discrepancy in

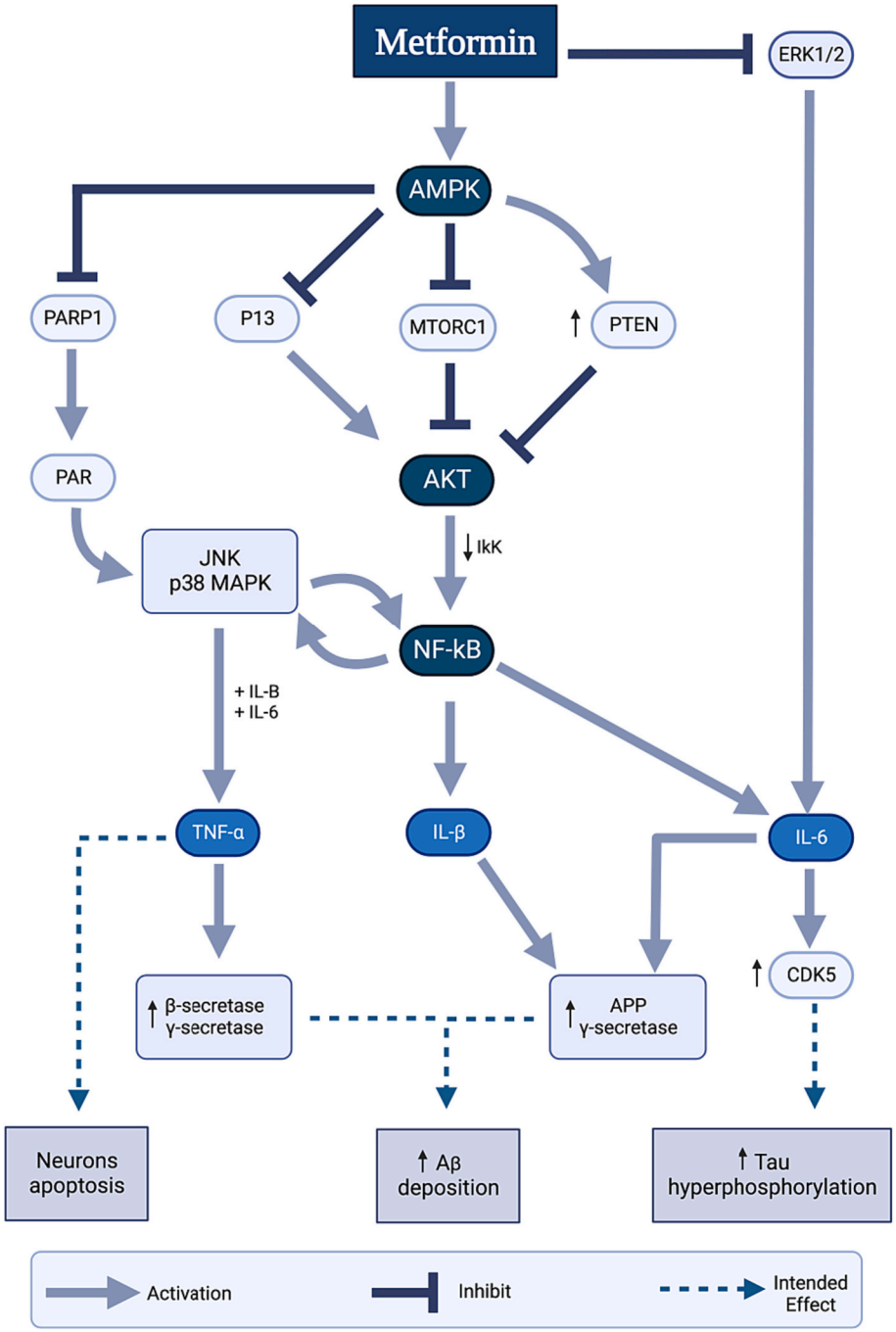

Fig. 2. Schematic diagram of metformin-activated AMPK pathway. Activation of AMPK triggers PTEN pathway which inhibits the activation of AKT that in turn inhibits NF-κB. AMPK activation also suppresses other pathways such as PARP1, P13, MTORC1 and ERK1/2 pathways which would activate NF-κB. Activation of NF-κB leads to the production of cytokines, TNF-α, IL-1β and IL-6 cytokines responsible for neuron apoptosis, increased Aβ deposition and tau hyperphosphorylation. The original figure is credited for the initial concept,[33] and the modifications made by the author included new information.

findings may be due to the complexity of the disease and different experimental systems used. Further research is needed to fully understand the mechanism of metformin's actions and its potential therapeutic effects, including optimal dosing and treatment duration. Nevertheless, it remains a potential treatment option for T3DM due to its ability to address insulin resistance.

3.1.2. Fundamental role of adiponectin and AdipoRon agonist triggers AMPK pathway

Adiponectin, also known as *AdipoQ, Acrp30* or *apM1*, is an adipocyte-secreted protein that possesses innate anti-inflammatory, anti-atherogenic, anti-adipogenic and anti-diabetic properties.[34–36] Adiponectin functions through their receptors, AdipoR1 and AdipoR2,[37] found throughout the body including skeletal muscle, osteoblasts, cardiomyocytes, pituitary gland, hepatocytes, adrenal gland, plasma, and cerebrospinal fluid.[38–44] Various studies have shown an inverse relationship between adiponectin levels and inflammation and insulin resistance.[45,46] Recently, adiponectin has also found to elicit antioxidant activity, which may improve cognitive deficit in aging-related neurological disorders.[47,48]

Extensive research has been conducted to increase its secretion, mainly via activation of its receptors and downstream signaling pathways. APPL1, a hydrophilic adaptor protein, is a crucial mediator that transmits signals from AdipoR1/R2 receptors to downstream signaling targets.[49] Its importance is supported via single nucleotide polymorphisms (SNPs) within the coding region that confer risks for T2DM onset.[50,51] Although lacking transmembrane regions, it possesses critical structural and functional domains, such as pleckstrin homology (PH) domain, phosphotyrosine binding (PTB) domain and coiled coils which facilitates its interaction with AdipoR1/R2 receptors.[52] Adiponectin signaling is initiated by extracellular domains of APPL1, which bind to both receptors domains, activating the interconnected molecular pathways that triggers metabolic effects.[53]

AdipoRon is a synthetic small-molecule agonist designed to mimic's adiponectin binding feature towards AdipoR1 and AdipoR2 receptors. Its main mechanism of action is to activate the AMPK pathway, thereby improving glucose intolerance, insulin resistance, and neuroinflammation.[54,55] Accordingly, binding of AdipoRon to AdipoR1/R2 receptors was noted to induce activation of intracellular CaMKKβ (Ca^{2+}/calmodulin-dependent protein kinase kinase-β)LKB1 (liver kinase B1)-AMPK/PPARα pathway.[56] In response to intracellular Ca^{2+} influx by AdipoRon, CaMKK phosphorylates Ser431 and Thr172 residue on LKB1 and AMP, respectively, where it then mediates the AMPK/PPARα expression to reduce high glucose-induced oxidative stress and reverse endothelial function deterioration in *db/db* mice models. AMPK phosphorylation was similarly shown to lower the renal injury score, apoptosis and inflammatory markers elicited by iopromide in Sprague-Dawley rats, helping to protect against contrast-induced nephropathy.[57] Several in vivo and ex vivo studies have examined the nephron- and neuro-protective potentials of AdipoRon. Interestingly, AdipoRon treatment was found to improve cognitive dysfunction and impaired neural stem cells proliferation in APP/PS1 transgenic mice through regulation of the AdipoR1/AMPK/CREB pathway.[58] The in vivo study further inferred that AdipoRon significantly ameliorated β-amyloid deposition and inhibited β-secretase 1 expression in both the cortex and hippocampus of AD mice. In another study, *db/db* mice reported considerable oxidative stress and tubular epithelial apoptosis in their kidneys, while AdipoRon administration via intragastric gavage attenuated these alterations by restoring the expression of AdipoR1 and phosphorylated AMPK.[59] In line with these findings, Balasubramanian et al. and his colleagues' in vivo studies showed upregulated PGC-1a protein expression indicating improved insulin sensitivity, skeletal muscle function and agility in aged mice fed with AdipoRon, depicting the viability of AdipoRon receptor agonism to influence skeletal muscle metabolism and tissue remodeling.[60] The benefits of AdipoRon is further apparent through the abrogation of LPS-induced activation of proinflammatory markers responsible for renal inflammation and injury in mice subjected to high-fat diet, cultured human podocytes and isolated human glomeruli.[61]

In Alzheimer, the anti-inflammatory properties of AdipoRon have been extensively studied. The distribution of adiponectin and AdipoR1/R2 receptors in cortical neurons further substantiate their involvement in high cognitive processes such as memory and learning.[62] AdipoRon, which binds to these receptors, may be the gateway to counteracting these neurological deficits. AdipoRon treatment can improve synaptic markers, lowers neuroinflammation and Ab plaque burden in APP/PS1 mice, successfully eliminating Alzheimer's like pathologies by enhancing AMPK phosphorylation and potentiating insulin-signaling for neuronal cell survival.[63] Hence, AdipoRon insulin-sensitizing, anti-inflammatory and protective effects against metabolic disease makes it the ideal candidate for T3DM treatment. Further research is needed to understand the mechanism through which AdipoRon can improve insulin resistance in these conditions, but it holds significant potential as a therapeutic target for future drug development.

3.2. PPARγ agonist as target for insulin resistance in T3DM

3.2.1. Understanding PPARγ pathway and thiazolidinediones as a common agonist

Peroxisome proliferator – activated receptor gamma (PPARγ) is a nuclear receptor protein that functions as transcription factor. It is vital in regulation of lipid and glucose metabolism, as well as development and differentiation of adipose tissue. PPARγ is activated by ligands, including natural compounds like fatty acids and eicosanoids, as well as synthetic compounds like thiazolidinediones (TZDs). It will the bind to specific DNA where it either activates or repress the transcription of the target genes and specific transcriptional effects is highly dependent on the context of the cells and the ligands that binds it to the receptor. In adipocytes, PPARγ activation activates adipogenesis, lipid uptake and storage while in skeletal muscle and liver, its activation reduces insulin resistance and improvements of glucose metabolism. PPARγ activation in macrophages and immune cells leads to suppression of pro-inflammatory genes and promotion of anti-inflammatory genes making it beneficial in metabolic disease such as diabetes.

In Alzheimer, recent studies have shown that PPARγ may play a role in pathogenesis of AD. They are highly expressed in the brain especially in hippocampus and cortex which are associated with learning and memory. It is also said to be involved in regulation of neuronal differentiation, survival, and other pathways such as inflammatory and oxidative stress.[64] Its ability to reduce inflammation in peripheral and central nervous system is via inhibition of inflammatory gene expression. In AD, deposition of Aβ is associated with activation of microglial cells, leading to chronic inflammation and production of inflammatory mediators. PPARγ agonist have been found to suppress microglial cells and induce phagocytosis, increasing Aβ clearance.[65]

An example of PPARγ agonist is TZDs. TZDs is a class of drug that activates PPARγ and specifically target insulin resistance via intracellular metabolic pathways to enhance insulin action and increase insulin sensitivity in critical tissues such as adipose, muscle and liver cells. These include increasing adipogenesis, which helps to reduce circulating free fatty acids and triglycerides, both contributes to impairment of insulin signaling. TZDs also increase GLUT4 expression, the main transporters of insulin which enhances glucose uptake and inhibit gluconeogenesis in liver. In addition, they also reduce inflammation to improve insulin sensitivity and stimulate adiponectin release, which has insulin-sensitizing effects.[66] Upon analyzing the effects of TZDs in both diabetes and Alzheimer's disease separately, it is evident that they share a common mechanism of action in reducing insulin resistance. Given their effectiveness in regulating insulin sensitivity, TZDs hold great potential as a candidate for T3DM management. Further research in this area may lead to development of novel therapies.

3.2.2. Insulin secretagogues glimepiride: an overview of its multi-pathway mechanism in treating insulin resistance

Insulin secretagogues remain as one of the most commonly prescribed oral agents for diabetic patients. Generally, insulin secretagogues are categorized into two primary classes of drugs as follows: sulfonylureas and meglitinide analogues. For nearly five decades, sulfonylureas have been widely introduced for lowering blood glucose levels. Sulfonylureas works by binding to the sulfonylurea receptor (SUR) subunit of the ATP-sensitive potassium (KATP) channels present on surface membrane of β-cells. The binding promotes closure of the KATP channels and subsequent depolarization of the membrane and triggers insulin-containing granules exocytosis, subsequently increasing insulin circulation levels in the body.[67] Currently, first-generation (acetohexamide, chlorpropamide, tolazamide, tolbutamide) of sulfonylureas had been largely replaced by the second generation (glibenclamide, glipizide, gliclazide) and third generation (gliclazide modified release (MR), glipizide gastrointestinal therapeutic system (GITS), glimepiride due to increasing reports of reduced potency and adverse health complications such as dizziness, confusion, nervousness, hepatocellular and cholestatic injury associated with the former class of drugs [68–72]. The higher tolerability and safety profile exerted by second- and third-generation sulfonylureas had motivated researchers in conducting combinatorial therapies (administration of dual drug components) in the hope of discovering any possible synergistic activity.[73]

Recent studies had emphasized the synergistic effect of glimepiride co-treated with other drugs, as demonstrated in the better glycemic control of patients relative to glimepiride monotherapy. For instance, glimepiride/L-cartinine and glimepiride/metformin combination was shown to effectively improve several critical endpoints, such as the fasting and postprandial blood glucose, glycated hemoglobin, fasting insulin, extracellular part of insulin regulated aminopeptidase, homeostasis model assessment of insulin resistance, tumor necrosis factor-alpha [TNF-α], visfatin and lipid panel parameters.[74,75] Nonetheless, glimepiride alone has been found to possess therapeutic options beyond its ability to increase circulating insulin, which makes it beneficial in managing insulin resistance. This section will focus on Glimepiride as it is frequently utilized over other sulfonylureas due to its immense therapeutic benefits.

It has been established that high triglycerides levels can contribute to the dyslipidemia observed in insulin resistance, characterized by increased triglyceride levels, decreased HDL cholesterol and changes in LDL cholesterol composition.[76] One of glimepiride's mechanisms of action is long known to be associated with activation of PPARγ pathway, which improves insulin resistance by reducing triglyceride levels in the liver and adipose tissue of insulin-resistance individuals.[77] PPARγ activation in macrophages and immune cells also leads to suppression of pro-inflammatory genes and promotion of anti-inflammatory genes. One study suggested that glimepiride-induced 3 T3-L1 adipocyte differentiation is likely to be caused by PPARγ transcriptional activity.[78] Notably, glimepiride treatment provides significant protection against diabetes with vascular disease by enhancing the nitric oxide (NO) production and endothelial NO synthase (eNOS) expression of human umbilical vein endothelial cells (HUVEC).[79] There are also cumulative evidence describing the mechanism involving eNOS upregulation to phosphorylation on SER^{617} and SER^{1177} residues of AKT, which later inhibits TNFα-induced NF-kB activity.[80,81] It is expected that controlling TNF-α levels in adipocytes and peripheral tissues can alleviate reactive oxygen species (ROS) generation, which contributes to insulin resistance.[82]

In addition to its insulin-sensitizing properties, numerous studies have unraveled the anti-diabetic, anti-oxidative and anti-inflammatory activity of glimepiride through various routes, such as increasing plasma adiponectin output,[83] reducing release of glyceraldehyde-derived advanced glycation end (AGE) products[84], modulating the Jun N terminal kinase (JNK)/nuclear factor kappa B ($NF\text{-}_KB$) and PI3K/AKT pathways.[85] In AD, neuronal insulin resistance impairs glucose uptake in the CNS due to the inability of insulin to bind with insulin receptors specifically in the brain regions.[78,86,87] Interestingly, there is an important crosstalk between the neuroprotective potential of glimepiride and the agonistic activity on PPARγ.[88–91] In a report, the decrease in BACE1 mRNA level upon glimepiride highly suggests participation of PPARγ in suppressing BACE1 activity and clearing excessive Ab_{40}/Ab_{42}.[92]

3.3. cAMP pathway: incretin-related drugs targeting insulin resistance

Incretin-related drugs are a class of drugs that mimic the actions of the hormones known as incretins, which are released in response to food intake and play a vital role in glucose regulation. It is considered an antidiabetic medication and are routinely prescribed to patients as a second line of treatment or in tandem with other therapies as they can lower A1C levels and promote weight loss. Incretin-related drugs can be classified into two different groups, incretin mimetics (GLP-1) and incretin enhancers (DPP-4 inhibitors). In the context of Alzheimer's, incretin drugs are chosen due to the complex interplay between metabolic dysfunction and neurodegeneration from cAMP pathway.

3.3.1. GLP-1 key hormone in glucose regulation

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are two gastrointestinal hormones that are vital in glucose regulation and insulin secretion as they are responsible for 50–70 % of insulinotropic effect. L-cells excrete GLP-1 while GIP is released by K-cells both located in the small intestine in response to nutrient ingestion. GIP physiological roles are closely related to GLP-1 and are often referred to as the 'sister' incretin hormone. GLP-1 binds to the G protein-coupled receptor (GPCR) located on the surface of pancreatic b-cells. This causes a conformational change and associated G-protein activation. G proteins will then bind and stimulate adenylyl cyclase, which catalyze the conversion of ATP to cyclic adenosine monophosphate, cAMP.[89,90] As an intracellular second messenger, cAMP dissociates its regulatory subunit from catalytic subunit and binds to protein kinase A (PKA). The binding of PKA activates the phosphorylation of several downstream targets, and specifically, the insulin-containing granules. Phosphorylation of insulin-containing granules triggers their exocytosis by causing them to fuse with plasma membrane and releases insulin into the bloodstream.[91] The mechanism of cAMP activation is illustrated in Fig. 3 below.

GLP-1 receptor agonist (also refer to GLP-1 analogues) mimics the function of GLP-1 hormone via binding and activation of the GLP-1 receptors. When it binds to the surface of the receptor on pancreatic β-cells, it activates cyclic adenosine monophosphate (cAMP) cycle. Consequently, patients with diabetes on a GLP-1 agonist regime benefit from increased insulin levels because of GLP-1 agonist regime. Recently, the usage of GLP-1 analogues for AD patients has been gaining traction mainly due to its ability to modulate various cellular processes in the brain. In the CNS, GLP-1 is produced within the hypothalamic nuclei where it expresses pre-proglucagon (PPG) that encodes for precursor molecules processed to yield GLP-1 and other peptides.[94] Its receptors are widely distributed in key brain regions implicated in memory, learning and emotional processing such as the hippocampus, amygdala, and prefrontal cortex. It is also possible that receptors activation is by circulating periphery GLP-1.[95] Activation triggers a multitude of cellular processes relevant to AD, such as neuronal survival, synaptic plasticity, and inflammation.[96] GLP-1 protection of neuronal cells is achieved by lowering oxidative stress, inflammation, and Aβ accumulation via the cAMP/PKA pathway.[97] Liraglutide (GLP-1 receptor agonist available in the market) used in pilot study are shown to maintain glucose utilization and neuronal activity of patients, prevent disease progression and reduce cognitive impairment via reduction of neuronal loss.[98–100] GIP analogues showed neuroprotective effects (reduced synaptic loss and increase synapse plasticity) in APP/PSI mouse model of AD with reduced amyloid plaque load (reduced oxidative stress and DNA damage) indicating similar properties as GLP-1 analogues.[101]

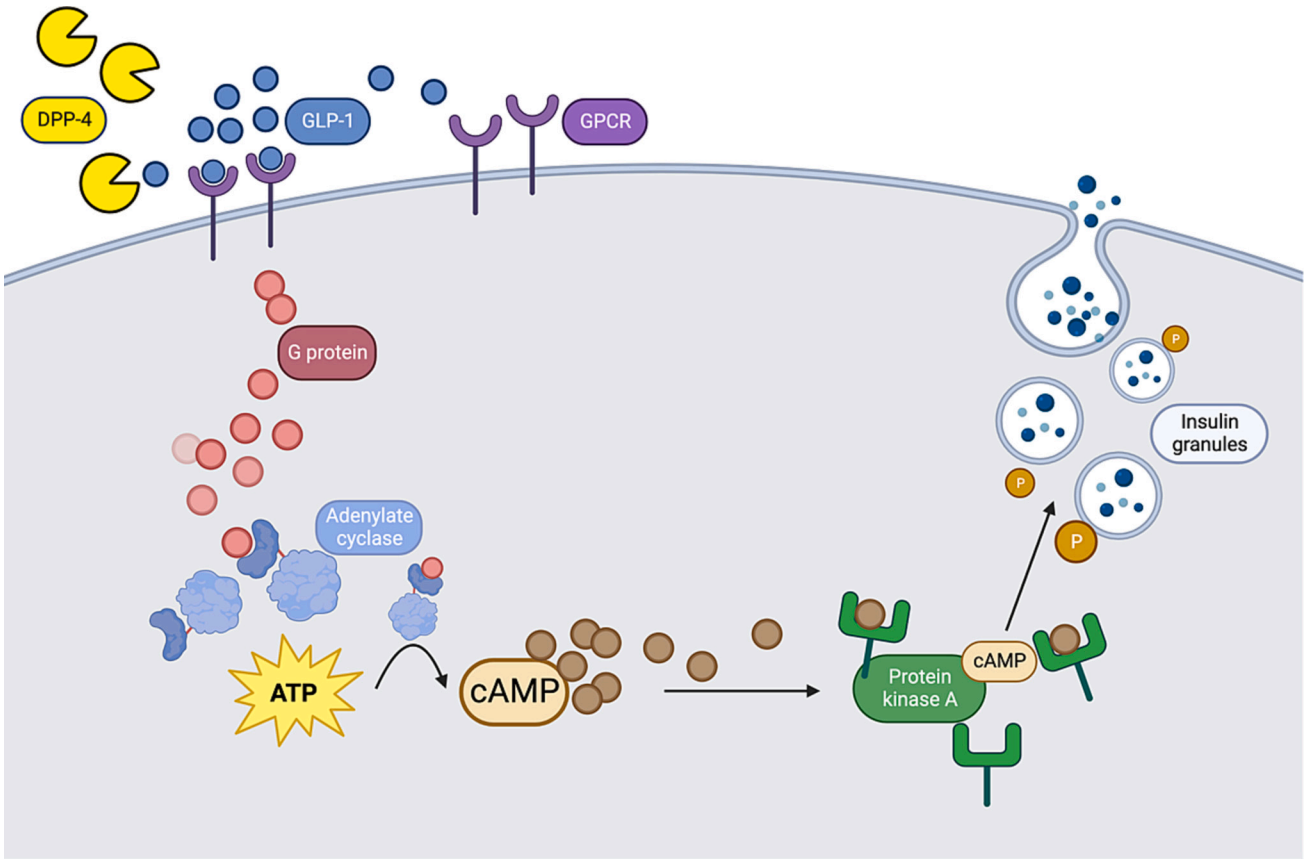

Fig. 3. Illustration of mechanism of action of GLP-1. GLP-1 binds to the GPCR receptors on the surface of the alpha pancreatic cells and releases G proteins and activates a cascade of signaling pathways. Attachment of G proteins to adenylate cyclase increases intracellular cAMP levels. The increased cAMP levels trigger phosphorylation process of insulin-containing granules, activating exocytosis process and the release of insulin into the bloodstream. The degradation of GLP-1 is initiated by attachment of DPP-4 enzymes. Original figure modified from existing figure.[93]

3.3.2. *DPP-4 overcoming the limitations of GLP-1*

GLP-1 has a short half-life thereby limiting its reaction duration as it is rapidly degraded by dipeptidyl peptidase-4 (DPP-4) enzymes. Serine exopeptidase, DPP4 cleaves N-terminal dipeptides, with higher sensitivity if alanine or proline as the second amino acid. GLP-1 specifically has alanine as its second amino acid and is cleaved from GLP-$1_{7–36}$ to GLP-$1_{9–36}$, rending it inactive.[102] Hence, the usage of DPP-4 inhibitors as a GLP-1 receptor agonist has been proposed to address this limitation. It mainly exerts its effect by attaching itself to DPP-4 enzyme making it unable to digest GLP-1 hormone. This in turns leads to increased insulin secretion and improved glucose control which is why it is commonly used as diabetes treatment. Extended half-life of GLP-1 has been shown to benefit diabetic patients with or without AD cognitive function especially in APOE carriers.[23] Common DPP-4 inhibitors are linagliptin, saxagliptin, and vildagliptin.

In vitro study using linagliptin indicates reduced Aβ-mediated cytotoxicity and mitochondrial dysfunction, improving insulin signaling.[103] In vitro study using rats with oral linagliptin improves both cognitive and motor functions.[104] Clinical evidence also indicates that treatment of DPP-4 inhibitors demonstrates 46 % decrease of AD development in elderly T2DM patients.[105] From the evidence, the usage of incretin mimetics is an ideal option that should be evaluated further as its involvement in cAMP pathway directly via GLP-1 or indirectly via DPP4 is vital in the mechanism of insulin resistance.

3.4. *P13-Akt pathway: convergence of insulin resistance*

In peripheral tissues, insulin initiates the P13K-Akt pathway through IRS binding and tyrosine phosphorylation. This activates P13K, leading to Akt complex phosphorylation, which triggers GLUT4 translocation to the cell membrane, enabling glucose uptake and reducing blood glucose levels. In the brain, GLUT1 is expressed in endothelial cells and astrocytes, while neurons express GLUT3; GLUT4 is minimally expressed in specific brain regions.[106] The PI3K-Akt pathway plays a pivotal role in both diabetes and Alzheimer's disease. In the brain specifically, it is involved in various cellular processes such as neuronal function, synaptic plasticity, metabolism, and neurodegeneration. Disruptions in the PI3K-Akt pathway are evident through diminished phosphorylation and overall levels of components within the cascade.[107] These alterations align with AD hallmarks and tau pathology progression. This highlights the pathway's potential as a therapeutic target in insulin resistance.

3.4.1. *Intranasal insulin*

Due to the critical effect of P13k-Akt disruptions, other novel therapeutic avenues become imperative. One promising approach is via administration of insulin directly using intranasal delivery, it is non-invasive and can bypass the BBB to provide a sufficient systemic drug delivery process. Insulin distribution uses the direct bloodstream connection from the nasal cavity, bypassing hepatic first-pass metabolism which is beneficial for diabetic patient. BBB is composed of endothelial cells and tight junctions and segregates it from the bloodstream, while facilitating selective molecular exchange. It actively regulates the entry and exit of substances and functions as a receptor-laden interface for hormonal signaling, including insulin. While small molecules passively permeate if it's under 400 Da with few hydrogen bonds, larger molecules require active transport. Insulin, with a molecular weight of 5808 Da, necessitates active transport due to its size.[108]

Intranasal insulin is preferable than other administration method

due to its non-invasive nature and ease of usage. In animal study, current employed methodologies are of direct central nervous system administration using intracerebroventicular (ICV) injection or microdialysis which is highly invasive. Human studies on the other hand uses systemic insulin administration, although not an as invasive, it can lead to hypoglycemia-induced cognitive impairment and activate stress axes affecting brain function. It is also harder to distinguish direct brain effects from peripheral pathway-mediated effects. However, with intranasal insulin there are limitation as it is only applicable to high water solubility content with short retention time. Different formulation or carrier are tested in tandem with this treatment. Hence, usage of intranasal as an insulin administration method to study its affect for brain insulin resistance is the best current therapeutic option for P13-Akt pathway.

In rat model of Parkinson's disease, administration of intranasal insulin improves Akt/GSK3β pathway related to insulin signaling, without impacting blood glucose level. This makes it suitable for individuals with both diabetes and Alzheimer's disease.[109] Similar effects were also seen in brain insulin resistance mice model, where restoration of learning and memory functions, improved neurogenesis in the hippocampus, elevated brain insulin levels, and enhanced activation of the IRS-1-PI3K-Akt-GSK3β insulin signaling pathway is observed.[110] In humans, different concentrations of insulin were tested and 40 IU given daily in a short trial showed improved memory composite.[111] In another study, regular treatment was linked to maintained or increased volumes in AD-vulnerable brain regions and an improved CSF biomarker profile, suggesting potential modification of both AD pathological processes and symptoms.[112] However, in a recent study of a randomized clinical trial involving 289 adults with mild cognitive impairment or Alzheimer's disease dementia, the use of intranasal insulin treatment did not yield cognitive or functional advantages speculated due to complications arising from the intranasal delivery device. These findings underscore the necessity for additional research using intranasal delivery devices known to elevate insulin levels within the central nervous system.

In conclusion, the insulin-PI3K-Akt signaling pathway plays a crucial role in both T2D and AD. Impaired insulin-PI3K-Akt signaling is observed in the AD brain and is associated with amyloid-β and tau pathologies. Lifestyle factors that contribute to insulin resistance, such as physical inactivity and a Western diet, may increase the risk of developing AD. Enhancing PI3K-Akt signaling through intranasal insulin treatment shows promise in improving cognitive function in AD. Further research is needed to fully understand the molecular mechanisms underlying the relationship between T2D and AD and to develop effective therapeutic strategies targeting the insulin-PI3K-Akt pathway.

4. Conclusion

In summary, the heterogeneity and complexity of T3DM and its close association to AD made it challenging to identify the causative mechanisms responsible for disease progression, thereby hindering the development of effective treatments. However, research has identified key signaling pathway linking both diseases, opening potential therapeutic avenues that improve insulin resistance and glucose control. This review has explored several pharmaceutical medications, including metformin, glimepiride, TZDs, AdipoRon, GLP-1 receptor agonists, DPP-4 inhibitors and intranasal insulin as potential therapeutic options for T3DM.

While positive outcomes have been observed in some studies, inconsistencies across various studies have been reported, likely due to the multifactorial nature of T3DM and the influence of external environmental factors. To improve the reliability and validity of drug efficacy, more randomized and double-blind studies are needed, along with standardization of protocols and larger sample size. A multifaceted T3DM therapeutic approach that combines different treatment may hold promises for future exploration.

Hence, identifying novel therapeutics targets that address the metabolic dysregulation and insulin resistance is essential for developing effective treatments for T3DM. Further research is needed to fully understand the mechanism of these targets and their potential for clinical application. These findings underscore the importance of considering the interplay between the metabolic dysregulation and neurodegeneration when developing new treatments for T3DM.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Funding

This work is supported by the Malaysia Ministry of Higher Education (MOHE) Fundamental Research Grant Scheme (FRGS/1/2019/SKK08/TAYLOR/02/4).

CRediT authorship contribution statement

AF and EST conceived the idea for the review article, conducted the literature search and selection of relevant articles. All authors reviewed published articles and contributed to the manuscript. AF edited the manuscript. TYQ and ACYY provided critical feedback and revision to the manuscript. All authors contributed to the final manuscript preparation, read, and approved the final version for submission.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Adeline Chia Yoke Yin reports financial support was provided by Malaysia Ministry of Higher Education.

Data availability

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Acknowledgement

Figures are created with BioRender.com.

References

1 Huang J, Huang N, Mao Q, Shi J, Qiu Y. Natural bioactive compounds in Alzheimer's disease: from the perspective of type 3 diabetes mellitus. *Front Aging Neurosci*. 2023:15.
2 Shen Z, Li Z-Y, Yu M-T, Tan K-L, Chen S. Metabolic perspective of astrocyte dysfunction in Alzheimer's disease and type 2 diabetes brains. *Biomed Pharmacother*. 2023;158, 114206.
3 Kubis-Kubiak A, Rorbach-Dolata A, Piwowar A. Crucial players in Alzheimer's disease and diabetes mellitus: friends or foes? *Mech Ageing Dev*. 2019;181:7–21.
4 Tamarai K, Bhatti JS, Reddy PH. Molecular and cellular bases of diabetes: focus on type 2 diabetes mouse model-TallyHo. *Biochim Biophys Acta Mol basis Dis*. 2019; 1865:2276–2284.
5 Ott A, Stolk R, van Harskamp F, Pols H, Hofman A, Breteler M. Diabetes mellitus and the risk of dementia: the Rotterdam study. *Neurology*. 1999;53:1937.
6 Gudala K, Bansal D, Schifano F, Bhansali A. Diabetes mellitus and risk of dementia: a meta-analysis of prospective observational studies. *J Diabetes Invest*. 2013;4: 640–650.
7 Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science*. 2002;297:353–356.
8 Jayaraman A, Pike CJ. Alzheimer's disease and type 2 diabetes: multiple mechanisms contribute to interactions. *Curr Diab Rep*. 2014;14:1–9.
9 Rizvi SMD, Shaikh S, Waseem SMA, et al. Role of anti-diabetic drugs as therapeutic agents in Alzheimer's disease. *EXCLI J*. 2015;14:684.
10 Hudish LI, Reusch JE, Sussel L. β Cell dysfunction during progression of metabolic syndrome to type 2 diabetes. *J Clin Invest*. 2019;129:4001–4008.

11 Devaskar SU, Giddings SJ, Rajakumar PA, Carnaghi LR, Menon RK, Zahm DS. Insulin gene expression and insulin synthesis in mammalian neuronal cells. *J Biol Chem*. 1994;269:8445–8454.
12 Kyrtata N, Emsley HC, Sparasci O, Parkes LM, Dickie BR. A systematic review of glucose transport alterations in Alzheimer's disease. *Front Neurosci*. 2021;15, 626636.
13 Ohara T, Doi Y, Ninomiya T, et al. Glucose tolerance status and risk of dementia in the community: the Hisayama study. *Neurology*. 2011;77:1126–1134.
14 Kumar M, Nath S, Prasad HK, Sharma G, Li Y. MicroRNAs: a new ray of hope for diabetes mellitus. *Protein Cell*. 2012;3:726–738.
15 Ferreira LS, Fernandes CS, Vieira MN, De Felice FG. Insulin resistance in Alzheimer's disease. *Front Neurosci*. 2018:830.
16 LaMoia TE, Shulman GI. Cellular and molecular mechanisms of metformin action. *Endocr Rev*. 2021;42:77–96.
17 Du L-L, Chai D-M, Zhao L-N, et al. AMPK activation ameliorates Alzheimer's disease-like pathology and spatial memory impairment in a streptozotocin-induced Alzheimer's disease model in rats. *J Alzheimers Dis*. 2015;43:775–784.
18 Poor SR, Ettcheto M, Cano A, et al. Metformin a potential pharmacological strategy in late onset Alzheimer's disease treatment. *Pharmaceuticals*. 2021;14:890.
19 Ye F, Luo Y-J, Xiao J, Yu N-W, Yi G. Impact of insulin sensitizers on the incidence of dementia: a meta-analysis. *Dement Geriatr Cogn Disord*. 2016;41:251–260.
20 Zhou J-B, Tang X, Han M, Yang J, Simó R. Impact of antidiabetic agents on dementia risk: a Bayesian network meta-analysis. *Metabolism*. 2020;109, 154265.
21 Hettich MM, Matthes F, Ryan DP, et al. The anti-diabetic drug metformin reduces BACE1 protein level by interfering with the MID1 complex. *PloS One*. 2014;9, e102420.
22 Moore EM, Mander AG, Ames D, et al. Increased risk of cognitive impairment in patients with diabetes is associated with metformin. *Diabetes Care*. 2013;36:2981–2987.
23 Wu CY, Ouk M, Wong YY, et al. Relationships between memory decline and the use of metformin or DPP4 inhibitors in people with type 2 diabetes with normal cognition or Alzheimer's disease, and the role APOE carrier status. *Alzheimers Dement*. 2020;16:1663–1673.
24 Chen Y, Zhou K, Wang R, et al. Antidiabetic drug metformin (GlucophageR) increases biogenesis of Alzheimer's amyloid peptides via up-regulating BACE1 transcription. *Proc Natl Acad Sci*. 2009;106:3907–3912.
25 Chen J-L, Luo C, Pu D, et al. Metformin attenuates diabetes-induced tau hyperphosphorylation in vitro and in vivo by enhancing autophagic clearance. *Exp Neurol*. 2019;311:44–56.
26 Chen Y, Zhao S, Fan Z, et al. Metformin attenuates plaque-associated tau pathology and reduces amyloid-β burden in APP/PS1 mice. *Alzheimer's Res Ther*. 2021;13:1–13.
27 Zhang J, Lin Y, Dai X, Fang W, Wu X, Chen X. Metformin treatment improves the spatial memory of aged mice in an APOE genotype–dependent manner. *FASEB J*. 2019;33:7748–7757.
28 Kuhla A, Brichmann E, Rühlmann C, Thiele R, Meuth L, Vollmar B. Metformin therapy aggravates neurodegenerative processes in ApoE−/−mice. *J Alzheimers Dis*. 2019;68:1415–1427.
29 Liao W, Xu J, Li B, Ruan Y, Li T, Liu J. Deciphering the roles of metformin in Alzheimer's disease: a snapshot. *Front Pharmacol*. 2022;12:4123.
30 Sanati M, Aminyavari S, Afshari AR, Sahebkar A. Mechanistic insight into the role of metformin in Alzheimer's disease. *Life Sci*. 2022;120299.
31 Oliveira WH, Nunes AK, França MER, et al. Effects of metformin on inflammation and short-term memory in streptozotocin-induced diabetic mice. *Brain Res*. 2016;1644:149–160.
32 Saffari PM, Alijanpour S, Takzaree N, et al. Metformin loaded phosphatidylserine nanoliposomes improve memory deficit and reduce neuroinflammation in streptozotocin-induced Alzheimer's disease model. *Life Sci*. 2020;255, 117861.
33 Li M, Li X, Zhang H, Lu Y. Molecular mechanisms of metformin for diabetes and cancer treatment. *Front Physiol*. 2018;9:1039.
34 Yanai H, Yoshida H. Beneficial effects of adiponectin on glucose and lipid metabolism and atherosclerotic progression: mechanisms and perspectives. *Int J Mol Sci*. 2019;20:1190.
35 La Russa D, Marrone A, Mandalà M, Macirella R, Pellegrino D. Antioxidant/anti-inflammatory effects of caloric restriction in an aged and obese rat model: the role of adiponectin. *Biomedicines*. 2020;8:532.
36 Matsuda M, Shimomura I. Roles of adiponectin and oxidative stress in obesity-associated metabolic and cardiovascular diseases. *Rev Endocr Metab Disord*. 2014;15:1–10.
37 Yamauchi T, Kamon J, Ito Y, et al. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. *Nature*. 2003;423:762–769.
38 AlM D, Jonas J-C, Bauche IB, Cornu O, Brichard SM. Induction of adiponectin in skeletal muscle by inflammatory cytokines: in vivo and in vitro studies. *Endocrinology*. 2004;145:5589–5597.
39 Berner HS, Lyngstadaas SP, Spahr A, et al. Adiponectin and its receptors are expressed in bone-forming cells. *Bone*. 2004;35:842–849.
40 Piñeiro R, Iglesias MJ, Gallego R, et al. Adiponectin is synthesized and secreted by human and murine cardiomyocytes. *FEBS Lett*. 2005;579:5163–5169.
41 Rodriguez-Pacheco F, Martinez-Fuentes AJ, Tovar S, et al. Regulation of pituitary cell function by adiponectin. *Endocrinology*. 2007;148:401–410.
42 Ma H, Gomez V, Lu L, Yang X, Wu X, Xiao SY. Expression of adiponectin and its receptors in livers of morbidly obese patients with non-alcoholic fatty liver disease. *J Gastroenterol Hepatol*. 2009;24:233–237.
43 Paschke L, Zemleduch T, Rucinski M, Ziolkowska A, Szyszka M, Malendowicz LK. Adiponectin and adiponectin receptor system in the rat adrenal gland: ontogenetic and physiologic regulation, and its involvement in regulating adrenocortical growth and steroidogenesis. *Peptides*. 2010;31:1715–1724.
44 Une K, Takei Y, Tomita N, et al. Adiponectin in plasma and cerebrospinal fluid in MCI and Alzheimer's disease. *Eur J Neurol*. 2011;18:1006–1009.
45 Acar EM, Ilter N, Elbeg S. *Association of Leptin, Resistin, and High-Molecular-Weight Adiponectin Levels with Psoriasis Area and Severity Index Scores, Obesity, and Insulin Resistance in Psoriasis Patients*. 2019.
46 Pandey GK, Vadivel S, Raghavan S, Mohan V, Balasubramanyam M, Gokulakrishnan K. High molecular weight adiponectin reduces glucolipotoxicity-induced inflammation and improves lipid metabolism and insulin sensitivity via APPL1-AMPK-GLUT4 regulation in 3T3-L1 adipocytes. *Atherosclerosis*. 2019;288:67–75.
47 Rizzo MR, Fasano R, Paolisso G. Adiponectin and cognitive decline. *Int J Mol Sci*. 2020;21:2010.
48 Kim JY, Barua S, Jeong YJ, Lee JE. Adiponectin: the potential regulator and therapeutic target of obesity and Alzheimer's disease. *Int J Mol Sci*. 2020;21:6419.
49 Deepa SS, Dong LQ. APPL1: role in adiponectin signaling and beyond. *Am J Physiol Endocrinol Metab*. 2009;296:E22–E36.
50 Prudente S, Jungtrakoon P, Marucci A, et al. Loss-of-function mutations in APPL1 in familial diabetes mellitus. *Am J Hum Genet*. 2015;97:177–185.
51 Fang Q-C, Jia W-P, Gao F, et al. Association of variants in APPL1 gene with body fat and its distribution in Chinese patients with type 2 diabetic mellitus. *Zhonghua Yi Xue Za Zhi*. 2008;88:369–373.
52 Mitsuuchi Y, Johnson SW, Sonoda G, Tanno S, Golemis EA, Testa JR. Identification of a chromosome 3p14. 3-21.1 gene, APPL, encoding an adaptor molecule that interacts with the oncoprotein-serine/threonine kinase AKT2. *Oncogene*. 1999;18:4891–4898.
53 Mao X, Kikani CK, Riojas RA, et al. APPL1 binds to adiponectin receptors and mediates adiponectin signalling and function. *Nat Cell Biol*. 2006;8:516–523.
54 Zheng J, Sun Z, Liang F, et al. AdipoRon attenuates neuroinflammation after intracerebral hemorrhage through AdipoR1-AMPK pathway. *Neuroscience*. 2019;412:116–130.
55 Iwabu M, Okada-Iwabu M, Tanabe H, et al. AdipoR agonist increases insulin sensitivity and exercise endurance in AdipoR-humanized mice. *Commun Biol*. 2021;4:45.
56 Kim Y, Lim JH, Kim MY, et al. The adiponectin receptor agonist AdipoRon ameliorates diabetic nephropathy in a model of type 2 diabetes. *J Am Soc Nephrol*. 2018;29:1108.
57 Gu D, Shi Y, Gong Z, et al. AdipoRon, an adiponectin receptor agonist, protects contrast-induced nephropathy by suppressing oxidative stress and inflammation via activation of the AMPK pathway. *Clin Exp Nephrol*. 2020;24:989–998.
58 Liu B, Liu J, Wang J-g, Liu C-L, Yan H-j. AdipoRon improves cognitive dysfunction of Alzheimer's disease and rescues impaired neural stem cell proliferation through AdipoR1/AMPK pathway. *Exp Neurol*. 2020;327, 113249.
59 Xiong S, Han Y, Gao P, Zhao H, Jiang N, Sun L. AdipoRon protects against tubular injury in diabetic nephropathy by inhibiting endoplasmic reticulum stress. *Oxid Med Cell Longev*. 2020;2020:1–15.
60 Balasubramanian P, Schaar AE, Gustafson GE, et al. Adiponectin receptor agonist AdipoRon improves skeletal muscle function in aged mice. *Elife*. 2022;11, e71282.
61 Lindfors S, Polianskyte-Prause Z, Bouslama R, et al. Adiponectin receptor agonist AdipoRon ameliorates renal inflammation in diet-induced obese mice and endotoxin-treated human glomeruli ex vivo. *Diabetologia*. 2021;64:1866–1879.
62 Thundyil J, Pavlovski D, Sobey CG, Arumugam TV. Adiponectin receptor signalling in the brain. *Br J Pharmacol*. 2012;165:313–327.
63 Khandelwal M, Manglani K, Upadhyay P, Azad M, Gupta S. AdipoRon induces AMPK activation and ameliorates Alzheimer's like pathologies and associated cognitive impairment in APP/PS1 mice. *Neurobiol Dis*. 2022;174, 105876.
64 Quinn C, Hamilton P, Lockhart C, McVeigh G. Thiazolidinediones: effects on insulin resistance and the cardiovascular system. *Br J Pharmacol*. 2008;153:636–645.
65 Khan MA, Alam Q, Haque A, et al. Current progress on peroxisome proliferator-activated receptor gamma agonist as an emerging therapeutic approach for the treatment of Alzheimer's disease: an update. *Curr Neuropharmacol*. 2019;17:232–246.
66 Jiang Q, Heneka M, Landreth GE. The role of peroxisome proliferator-activated receptor-γ (PPARγ) in Alzheimer's disease: therapeutic implications. *CNS Drugs*. 2008;22:1–14.
67 Seino S, Sugawara K, Yokoi N, Takahashi H. β-Cell signalling and insulin secretagogues: a path for improved diabetes therapy. *Diabetes Obes Metab*. 2017;19:22–29.
68 Hoofnagle JH. LiverTox: a website on drug-induced liver injury. In: *Drug-induced liver disease*. Elsevier; 2013:725–732.
69 Harrower AD. Comparative tolerability of sulphonylureas in diabetes mellitus. *Drug Saf*. 2000;22:313–320.
70 Kalra S, Bahendeka S, Sahay R, et al. Consensus recommendations on sulfonylurea and sulfonylurea combinations in the management of type 2 diabetes mellitus–International Task Force. *Indian J Endocrinol Metab*. 2018;22:132.
71 Sola D, Rossi L, Schianca GPC, et al. State of the art paper sulfonylureas and their use in clinical practice. *Arch Med Sci*. 2015;11:840–848.
72. Diseases NIoDaDaK. *LiverTox: clinical and research information on drug-induced liver injury: National Institute of Diabetes and Digestive and Kidney Diseases*. 2012.
73 Hemmingsen B, Sonne DP, Metzendorf MI, Richter B. Insulin secretagogues for prevention or delay of type 2 diabetes mellitus and its associated complications in persons at increased risk for the development of type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2016;10.

74 El-Sheikh HM, El-Haggar SM, Elbedewy TA. Comparative study to evaluate the effect of l-carnitine plus glimepiride versus glimepiride alone on insulin resistance in type 2 diabetic patients. *Diabetes Metab Syndr Clin Res Rev*. 2019;13:167–173.
75 Yu HM, Kim SJ, Chun SW, et al. A comparison study on efficacy, insulin sensitivity and safety of glimepiride/metformin fixed dose combination versus glimepiride single therapy on type 2 diabetes mellitus patients with basal insulin therapy. *Diabetes Res Clin Pract*. 2019;155, 107796.
76 Savage DB, Petersen KF, Shulman GI. Disordered lipid metabolism and the pathogenesis of insulin resistance. *Physiol Rev*. 2007;87:507–520.
77 Lee KW, Ku YH, Kim M, Ahn BY, Chung SS, Park KS. Effects of sulfonylureas on peroxisome proliferator-activated receptor γ activity and on glucose uptake by thiazolidinediones. *Diabetes Metab J*. 2011;35:340–347.
78 Ruiz HH, Chi T, Shin AC, et al. Increased susceptibility to metabolic dysregulation in a mouse model of Alzheimer's disease is associated with impaired hypothalamic insulin signaling and elevated BCAA levels. *Alzheimers Dement*. 2016;12:851–861.
79 Jojima T, Suzuki K, Hirama N, Uchida K, Hattori Y. Glimepiride upregulates eNOS activity and inhibits cytokine-induced NF-κB activation through a phosphoinoside 3-kinase–Akt-dependent pathway. *Diabetes Obes Metab*. 2009;11:143–149.
80 Ueba H, Kuroki M, Hashimoto S, et al. Glimepiride induces nitric oxide production in human coronary artery endothelial cells via a PI3-kinase-Akt dependent pathway. *Atherosclerosis*. 2005;183:35–39.
81 Salani B, Repetto S, Cordera R, Maggi D. Glimepiride activates eNOS with a mechanism Akt but not caveolin-1 dependent. *Biochem Biophys Res Commun*. 2005; 335:832–835.
82 Akash MSH, Rehman K, Liaqat A. Tumor necrosis factor-alpha: role in development of insulin resistance and pathogenesis of type 2 diabetes mellitus. *J Cell Biochem*. 2018;119:105–110.
83 Emini-Sadiku M, Car N, Begolli L, Blaslov K, Haliti E, Bahtiri E. The differential influence of glimepiride and glibenclamide on insulin resistance and adiponectin levels in patients with type 2 diabetes. *Endocr J*. 2019;66:915–921.
84 Bansal S, Burman A, Tripathi AK. Advanced glycation end products: key mediator and therapeutic target of cardiovascular complications in diabetes. *World J Diabetes*. 2023;14:1146–1162.
85 ElMahdy MK, Zaki MO, Al-Karmalawy AA, Abdo W, Alnasser SM, Antar SA. Glimepiride ameliorates renal toxicity induced by cadmium in mice: modulation of Jun N terminal kinase (JNK)/nuclear factor kappa B (NF-κB) and phosphatidylinositol 3-kinases (PI3K)/protein kinase (AKT) pathways. *Life Sci*. 2022;311, 121184.
86 Mielke JG, Taghibiglou C, Liu L, et al. A biochemical and functional characterization of diet-induced brain insulin resistance. *J Neurochem*. 2005;93: 1568–1578.
87 Arnold SE, Arvanitakis Z, Macauley-Rambach SL, et al. Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. *Nat Rev Neurol*. 2018;14:168–181.
88 Fukuen S, Iwaki M, Yasui A, Makishima M, Matsuda M, Shimomura I. Sulfonylurea agents exhibit peroxisome proliferator-activated receptor γ agonistic activity. *J Biol Chem*. 2005;280:23653–23659.
89 Tomas A, Jones B, Leech C. New insights into beta-cell GLP-1 receptor and cAMP signaling. *J Mol Biol*. 2020;432:1347–1366.
90 Ishikawa Y, Homcy CJ. The adenylyl cyclases as integrators of transmembrane signal transduction. *Circ Res*. 1997;80:297–304.
91 Cantini G, Mannucci E, Luconi M. Perspectives in GLP-1 research: new targets, new receptors. *Trends Endocrinol Metab*. 2016;27:427–438.
92 Liu F, Wang Y, Yan M, Zhang L, Pang T, Liao H. Glimepiride attenuates Aβ production via suppressing BACE1 activity in cortical neurons. *Neurosci Lett*. 2013; 557:90–94.
93 Vangoitsenhoven R, Mathieu C, Van der Schueren B. GLP1 and cancer: friend or foe? *Endocr Relat Cancer*. 2012;19:F77.
94 Baggio LL, Drucker DJ. Glucagon-like peptide-1 receptors in the brain: controlling food intake and body weight. *J Clin Invest*. 2014;124:4223–4226.
95 Daniels D, Mietlicki-Baase EG. Glucagon-like peptide 1 in the brain: where is it coming from, where is it going? *Diabetes*. 2019;68:15–17.
96 Veber DF, Johnson SR, Cheng H-Y, Smith BR, Ward KW, Kopple KD. Molecular properties that influence the oral bioavailability of drug candidates. *J Med Chem*. 2002;45:2615–2623.
97 Xie Y, Zheng J, Li S, et al. GLP-1 improves the neuronal supportive ability of astrocytes in Alzheimer's disease by regulating mitochondrial dysfunction via the cAMP/PKA pathway. *Biochem Pharmacol*. 2021;188, 114578.
98 Gejl M, Gjedde A, Egefjord L, et al. In Alzheimer's disease, 6-month treatment with GLP-1 analog prevents decline of brain glucose metabolism: randomized, placebo-controlled, double-blind clinical trial. *Front Aging Neurosci*. 2016:108.
99 Watson KT, Wroolie TE, Tong G, et al. Neural correlates of liraglutide effects in persons at risk for Alzheimer's disease. *Behav Brain Res*. 2019;356:271–278.
100 Femminella GD, Frangou E, Love SB, et al. Evaluating the effects of the novel GLP-1 analogue liraglutide in Alzheimer's disease: study protocol for a randomised controlled trial (ELAD study). *Trials*. 2019;20:1–10.
101 Hölscher C. Protective properties of GLP-1 and associated peptide hormones in neurodegenerative disorders. *Br J Pharmacol*. 2022;179:695–714.
102 Omar B, Ahrén B. Pleiotropic mechanisms for the glucose-lowering action of DPP-4 inhibitors. *Diabetes*. 2014;63:2196–2202.
103 Kornelius E, Lin CL, Chang HH, et al. DPP-4 inhibitor linagliptin attenuates Aβ-induced cytotoxicity through activation of AMPK in neuronal cells. *CNS Neurosci Ther*. 2015;21:549–557.
104 Siddiqui N, Ali J, Parvez S, Najmi AK, Akhtar M. Neuroprotective role of DPP-4 inhibitor Linagliptin against neurodegeneration, neuronal insulin resistance and neuroinflammation induced by intracerebroventricular streptozotocin in rat model of Alzheimer's disease. *Neurochem Res*. 2023:1–17.
105 Sim AY, Barua S, Kim JY, Lee Y-h, Lee JE. Role of DPP-4 and SGLT2 inhibitors connected to Alzheimer disease in type 2 diabetes mellitus. *Front Neurosci*. 2021;15, 708547.
106 Vannucci SJ, Koehler-Stec EM, Li K, Reynolds TH, Clark R, Simpson IA. GLUT4 glucose transporter expression in rodent brain: effect of diabetes. *Brain Res*. 1998; 797:1–11.
107 Gabbouj S, Ryhänen S, Marttinen M, et al. Altered insulin signaling in Alzheimer's disease brain–special emphasis on PI3K-Akt pathway. *Front Neurosci*. 2019;13:629.
108 Hallschmid M. Intranasal insulin for Alzheimer's disease. *CNS Drugs*. 2021;35: 21–37.
109 Yang L, Zhang X, Li S, et al. Intranasal insulin ameliorates cognitive impairment in a rat model of Parkinson's disease through Akt/GSK3β signaling pathway. *Life Sci*. 2020;259, 118159.
110 Lv H, Tang L, Guo C, et al. Intranasal insulin administration may be highly effective in improving cognitive function in mice with cognitive dysfunction by reversing brain insulin resistance. *Cogn Neurodyn*. 2020;14:323–338.
111 Claxton A, Baker LD, Hanson A, et al. Long-acting intranasal insulin detemir improves cognition for adults with mild cognitive impairment or early-stage Alzheimer's disease dementia. *J Alzheimers Dis*. 2015;44:897–906.
112 Craft S, Claxton A, Baker LD, et al. Effects of regular and long-acting insulin on cognition and Alzheimer's disease biomarkers: a pilot clinical trial. *J Alzheimers Dis*. 2017;57:1325–1334.