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Targeting Insulin Resistance to Treat Cognitive Dysfunction

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Abstract

Dementia is a devastating disease associated with aging. Alzheimer's disease is the most common form of dementia, followed by vascular dementia. In addition to clinically diagnosed dementia, cognitive dysfunction has been reported in diabetic patients. Recent studies are now beginning to recognize type 2 diabetes mellitus, characterized by chronic hyperglycemia and insulin resistance, as a risk factor for Alzheimer's disease and other cognitive disorders. While studies on insulin action have remained traditionally in the domain of peripheral tissues, the detrimental effects of insulin resistance in the central nervous system on cognitive dysfunction are increasingly being reported by recent clinical and preclinical studies. The findings from these studies suggest that antidiabetic drugs have the potential to be used to treat dementia. In this review, we discuss the physiological functions of insulin in the brain, studies on the evaluation of cognitive function under conditions of insulin resistance, and reports on the beneficial actions of antidiabetic drugs in the brain. This review covers clinical studies as well as investigations in animal models and will further highlight the emerging link between insulin resistance and neurodegenerative disorders.

Keywords

Insulin resistance; Metabolic syndrome; Obesity; Diabetes; Dementia; Alzheimer's disease

Introduction

Chronic hyperglycemia, measured as glycosylated hemoglobin A1c (HbA1c), directly correlates with diabetic complications including peripheral neuropathy, retinopathy, nephropathy, and cardiovascular diseases. However, how diabetes affects brain function has not been a subject of serious investigation for a long time. With the increasing awareness and the availability of a vast array of antidiabetic medications, diabetic patients are living longer and in the process are at greater risk for aging-associated diseases, including dementia. This is evident from the increasing number of recent studies on cognitive function in

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diabetic patients. Studies on insulin action have primarily remained in the domain of peripheral diseases. Although insulin was known to regulate feeding behavior, it was generally considered that the brain is not a major target of insulin action. However, studies are beginning to recognize that insulin plays a role in cognition and neuroprotection. Brain function can be also affected indirectly by insulin action on peripheral tissues. For example, the circulating factors in obesity and diabetes can pass through blood brain barrier (BBB) and cause dysfunction of several brain cell types, including neurons, astrocytes and microglia. Insufficient metabolites may be also generated in the periphery for utilization in the brain in conditions of insulin resistance.

Insulin Signaling in the Brain

Insulin Transport across BBB

Insulin, produced and released by the pancreatic β cells, is known to act in the brain in addition to peripheral tissues. Insulin is readily transported across the BBB via a receptormediated process. However, it has been suggested that this transport pathway can be saturable given that the cerebrospinal fluid (CSF) insulin levels are non-linearly correlated with plasma insulin levels [1]. Levels of insulin in the brain vary dramatically, with hypothalamus and olfactory bulb having insulin concentrations higher than plasma insulin levels [2]. Ependymal cells and brain endothelial cells (BECs) that make up the BBB and blood-CSF barrier possess insulin-binding sites, allowing insulin to be transported across the BBB [3]. Insulin receptors (IR) on endothelial cells are likely to be essential for the transport of circulating insulin to its target tissues. Interestingly, using the same animal model in which the IR gene is deleted in endothelial cells, two studies came up with different findings on insulin transport across BBB. Konishi et al. (2017) reported that in response to systemic insulin stimulation, delayed insulin signaling was observed in skeletal muscle, hypothalamus, hippocampus and prefrontal cortex but not in liver or olfactory bulb [4]. The delay in insulin signaling in the hypothalamus resulted in increased food intake and obesity. However, employing kinetic methods, another study demonstrated that the endothelial IR gene is not required for insulin transport across the BBB [5]. Although the findings of these studies appear to contradict, one study [5] measured the transport of insulin directly whereas the other study [4] examined insulin action in the target tissue. In vitro transport models using purified BECs in monoculture or BECs co-cultured with astrocytes, found that the IR is responsible for physically transporting insulin across the BBB [6]. Decreased transport of insulin into brain has been observed in obese animals. The transport rate of insulin across the BBB is about half that in obese mice compared to lean mice [7]. Unlike obesity, diabetes mellitus was shown to increase BBB insulin transport and endothelial insulin binding [8]. Streptozotocin-induced diabetic mice were observed to have enhanced transport of insulin across the BBB and this was not attributed to altered levels of serum factors such as glucose or insulin. Thus, the transport of insulin across BBB is likely to involve multiple mechanisms.

Insulin Production in the Brain

The brain is also a source of insulin in addition to peripheral insulin getting transported across the BBB. Insulin was shown to be widely distributed in the human cadaveric brain

by radioimmunoassay [9]. Birch et al. (1984) later identified two forms of immunoreactive insulin in cultures of fetal mouse brain [10]. The major component resembled proinsulin which was converted by trypsin to the minor form, similar to pancreatic insulin. Deltour et al. (1993) examined the expression of proinsulin genes and detected proinsulin II mRNA in the mouse brain [11]. The authors suggested that insulin may act as a growth factor in the developing mouse brain. Similarly, another study examined the expression of Insulin I and II mRNA in multiple rat tissues and reported the presence of insulin II mRNA but not insulin I mRNA in the rat brain [12]. The same group later confirmed the presence of insulin mRNA in CA1 and CA3 regions of the hippocampus and in granule cell layer of the olfactory bulbs of the neonatal rabbit brain by in situ hybridization [13]. Another study identified the presence of insulin mRNA in both mouse and human brain samples [14]. In the post-mortem brain cortex of elderly and AD subjects, c-peptide and insulin concentrations were found to be directly correlated and decrease with aging [15]. These findings led the authors to conclude that, at least in part, cerebral insulin was a product of the brain itself. Neuronal cells derived from the hippocampus and olfactory bulb have been shown to produce insulin [16]. An interesting study demonstrated the presence of insulin mRNA in the GABAergic neurogliaform cells of rat brain, using single-cell quantitative RT-PCR [17]. Importantly, they also observed that the quantity of insulin II mRNA per cell was greater when the concentration of extracellular glucose was increased. The authors also demonstrated that the effects of locally generated insulin can be blocked with insulin receptor antagonist S961. Thus, there are sufficient experimental evidences to suggest that insulin is produced by the brain.

Insulin Receptor Expression in the Brain

Havrankova et al. (1978) were the first to report the presence of IR in the rat brain, based on insulin binding studies [2]. A later study reported the autoradiographic localization of IR in rat brain by ^{125}I-labeled insulin binding experiments [18]. The insulin binding was shown to be prominent in the neocortex, accessory motor areas of the basal ganglia and the cerebellum. Further studies showed that IRs are abundantly distributed throughout the brain, especially in regions that regulate appetite (arcuate nucleus of the hypothalamus), cognitive function, autonomic activity, and olfaction (olfactory bulb) [19, 20]. They are also selectively distributed in the cerebral cortex and cerebellum. The presence of IR/A and IR/B, and the isoforms of IR have been demonstrated by in situ RT-PCR/FISH assay in neurons of adult human brain [21]. Expression of IR/IGF-IR hybrid receptor in neurons, astrocytes and microglia has been reported in mouse brain [22]. A study with fluorescently labeled insulin has shown that intranasally administered insulin reaches CNS targets and activates IR [23]. Thus, previous studies present sufficient experimental evidences to suggest that IR is expressed in the brain.

Insulin and Glucose Uptake in the Brain

It has been well established that insulin stimulates glucose uptake in peripheral tissues (Fig. 1), such as skeletal muscle and adipose tissue, through GLUT4, a glucose transporter [24]. However, studies suggest that insulin may not be involved in the cellular glucose uptake in the brain [25]. The majority of glucose uptake by the central nervous system (CNS) occurs via GLUT3 in neurons, GLUT1 in astrocytes, and GLUT5 in microglia

[26]. Insulin-insensitive GLUT2 is found in some cells in the hypothalamus. GLUT4 is largely limited to a few regions of the brain, including the olfactory bulb, hippocampus, hypothalamus, and other regions associated with motor movement in the cerebellum [27-29]. Deletion of GLUT4 from the CNS in mice (BG4KO) resulted in impaired glucose sensing and reduced glucose uptake in the brain [30]. In rats, GLUT4 is co-expressed with GLUT3 in the hippocampus, amygdala, basal forebrain, and, to lesser degrees, in the cerebellum and cerebral cortex [31]. All these regions are related to cognitive behaviors. GLUT4 has been suggested to play key role in hippocampal memory formation [32]. However, Talbot et al. (2012) reported that insulin had no effect on GLUT4 translocation to the membrane and was unable to induce cellular glucose uptake in neuronal cells [33]. Insulin and IGF-1 were found to synergistically stimulate the translocation of GLUT1 to the plasma membrane, promoting astrocytic glucose uptake [34]. Similarly, insulin may facilitate neuronal glucose uptake by translocation of GLUT3 to the cell membrane [35]. However, Gould et al. (1992) reported that GLUT3 mediated glucose uptake in the neurons of mice occurs independent of insulin action [36]. Therefore, previous studies on the regulation of glucose transport by insulin have reported mixed findings. It appears that insulin may not play a significant role in the uptake of glucose in the brain.

Insulin Action on Eating Behavior, Learning, and Memory

Hypothalamic insulin action is known to regulate eating behavior. Dodd et al. (2019) examined the effects of enhancing hypothalamic insulin sensitivity on feeding behavior in a mouse model [37]. Deletion of tyrosine phosphatases that downregulate insulin signaling resulted in restrained eating. Intranasal administration of inhibitors of tyrosine phosphatases also produced similar effects. In a 9-year follow-up study [38], the authors demonstrated that improving insulin sensitivity before lifestyle intervention results in enhanced reduction in visceral fat. It has been shown that either peripheral or intracerebroventricular administration of insulin leads to positive effects on learning and memory [39]. These improvements in cognition via insulin administration have also been shown to activate IR and its downstream signaling cascade [40]. A double-blind study investigated the effects of intranasal insulin administration for 8 weeks on memory, attention and mood in healthy subjects [41]. Improvement in delayed recall of words and signs of enhanced mood were observed in the absence of systemic side effects. The same group later tested the effects of a rapid acting insulin analog and reported better memory improvement in healthy subjects [42]. Insulin can also act as a neuroprotective agent by preventing neuronal apoptosis and by inhibiting of Aβ fibril formation [43]. A single dose of intranasal insulin was shown increase brain glucose metabolism as measured by FDG-PET and activated Akt in wild type mice [44]. Thus, previous studies have suggested a physiological role of insulin in the normal brain function.

Insulin Signaling and Alzheimer’s Disease

Insulin signaling and AD lesions have been shown to have a two-way relationship. While brain insulin resistance plays a role in Alzheimer’s pathogenesis, AD lesions also have deleterious effects on peripheral insulin signaling and glucose homeostasis, leading to a vicious cycle. Alzheimer’s patients are reported to have higher levels of insulin in the blood, a marker for peripheral insulin resistance, and decreased insulin in the

cerebrospinal fluid, compared to healthy controls [45]. Lower cerebral insulin levels and central insulin resistance are in part due to decreased insulin transport across the BBB and excessive amyloid accumulation [8]. In addition, the brains of AD patients have decreased levels of both insulin and insulin-like growth factors (IGF)-I and -II and reduced expression of IR mRNA, IRS-associated PI3K, and activated Akt [46]. The environment in the brain during neurodegenerative changes is not conducive to insulin signaling. For example, neuroinflammation is a key component of Alzheimer's pathogenesis [47, 48] and cytokines are known to interfere with insulin action [49]. Another causative factor in the neurodegenerative brain is oxidative stress which can also interfere with insulin action [50].

Furthermore, Aβ generated in the Alzheimer's brain is known to downregulate insulin signaling. For example, it has been demonstrated that neuronal IR signal transduction is sensitive to disruption by soluble Aβ oligomers [51]. A study examining IR binding, showed that both Aβ40 and Aβ42 peptides compete with insulin for IR binding, leading to reduced IR autophosphorylation [52]. Studies with cultured porcine brain capillary endothelial cells and 3XTg-AD mice show that Aβ causes lysosomal degradation of both IR and lipoprotein receptor-related protein-1, a target of insulin signaling at the BBB [53]. Neuronal response to insulin, as measured by evoked IR tyrosine autophosphorylation, was found to be greatly inhibited by soluble Aβ oligomers [51]. Insulin resistance, as shown by decreased Akt phosphorylation, was observed in neuroblastoma 2a cell line overexpressing human APP as a result of increased Aβ production [54].

Aβ has been shown, by in vitro and in vivo studies, to induce hepatic insulin resistance via activation of JAK2/STAT3/SOCS-1 pathway [55, 56]. In a recent study, we have demonstrated that the brain insulin resistance observed in metabolic syndrome is further exacerbated by amyloid pathology in the brain of APP/PS1/Sirt3$^{-/-}$ mice, a comorbid Alzheimer's mouse model, generated in our lab [57]. In this study, we also observed peripheral insulin resistance as shown by hyperinsulinemia and glucose intolerance in APP/PS1 mice with amyloid pathology. Similarly, tau pathology can also impair insulin signaling. Hull et al. (2020) reported hyperglycemia in mice expressing human tau mutant ($PLB2_{Tau}$), suggesting a progressive diabetic phenotype [58]. Tau pathology has also been suggested to be a trigger for insulin resistance in the brain as well as peripheral tissues [59]. Thus, the two-way communications between AD lesions and insulin signaling can lead to a loop resulting in exacerbated cognitive dysfunction.

Apolipoprotein E4 and Insulin Signaling

The link between diabetes and amyloid pathology in AD has been shown to be stronger among carriers of the Apolipoprotein E4 (ApoE4) allele. ApoE4 was shown to interfere with insulin signaling in vivo in human ApoE4-targeted replacement mice [60] and this effect was further exacerbated following HFD feeding. In addition, the authors demonstrated, in cultured neurons, that ApoE4 interferes with IR trafficking by trapping it in the endosomes. Another study demonstrated that mice expressing human ApoE4 and human mutant APP are characterized by acceleration of cognitive deficits and impaired insulin signaling [61]. Conversely, insulin signaling was not affected in ApoE3/APP mice. The authors also demonstrated that insulin signaling is impaired in isolated hippocampal neurons

from ApoE4 mice, whereas neurons from ApoE3 mice show normal insulin response. The expressions of insulin network polypeptides were shown to be significantly less in the post-mortem samples of AD patients with the ApoE4 phenotype [62].

Insulin Resistance and Cognitive Dysfunction-Clinical Studies

Although limited information is available on the physiological actions of insulin in cognition, studies under conditions of insulin resistance strongly suggest a role for insulin in cognitive function. In this section, we have reviewed studies examining cognitive function under conditions of metabolic syndrome (MetS), type 2 diabetes, and obesity. All these conditions are characterized by insulin resistance. We have also included interactions of these conditions with AD.

Metabolic Syndrome (MetS)

MetS is the precondition for obesity, diabetes and cardiovascular disease. It is characterized by hypertension, insulin resistance, hypertriglyceridemia, low HDL-cholesterol and central obesity. MetS is highly prevalent in developed countries with one in three adults having at least three of these risk factors. A 15-year long-term study that examined the relationship between metabolic syndrome and cognitive decline in 1759 elderly women observed that patients with all five components of MetS were three to four times more likely to develop cognitive dysfunction than those with no risk factors [63]. Employing the category fluency test (CFT) to determine cognitive ability, this study found that higher fasting plasma glucose levels are associated with poorer CFT scores. Insulin resistance, as determined by the Homeostatic Model Assessment for insulin Resistance (HOMA-IR) index, was also associated with increased cognitive dysfunction. A clinical study aimed at understanding the impact of variation in MetS status and risk of dementia found that individuals whose metabolic condition worsened over the 5-year study had a significantly greater chance of developing dementia [64]. Another clinical study with over four million participants investigated the relationship between changes in MetS status over a 2-year period and occurrence of dementia [65]. Specifically, this study observed that hyperglycemia and hypertension were impactful in raising the risk of dementia. Another study examined the associations between individual components of MetS and the risk for dementia and AD [66]. The authors found a significant linear relationship between decrease in cognitive scores with increased number of MetS risk factors. Among the components of MetS, hyperglycemia showed maximum effects on cognitive decline, followed by hypertension.

MetS has also been shown to be a risk factor for AD. For example, a clinical study observed significantly more cognitive decline among AD patients with MetS [67]. Vascular endothelial dysfunction and insulin resistance were characteristic features of AD patients with coexisting MetS in this study. A Finnish population-based study reported that midlife insulin resistance is an independent risk factor for brain amyloid accumulation 15 years later [68]. This association was observed in carriers as well as noncarriers of the ApoE4 allele. However, a recent meta-analysis of nine longitudinal studies reported that there was no significant association between MetS and the occurrence of AD, although MetS increased the likelihood of developing VaD and the risk of mild cognitive impairment

(MCI) progressing to dementia [69]. Thus, the association between MetS and AD may be contentious.

Type 2 Diabetes

Several clinical studies have reported that cognitive performance is affected by type 2 diabetes. A study involving nearly seven thousand older male and females reported that the presence of type 2 diabetes is associated with poor performance in cognitive tests [70]. Diabetic patients with good glycemic control, as shown by HbA1c levels under 53 mmol/mol, did significantly better in cognitive performance than those with higher HbA1c levels. This study also found that both increased body mass index (BMI) and duration of diabetes were directly linked with worse cognitive performance. Similarly, a meta-analysis of twelve studies in sixty-eight hundred patients examined the impact of diabetes in the progression of MCI to dementia [71]. The authors observed that having diabetes for five or more years had a 40–60% increased risk for dementia than those recently diagnosed. Diabetic patients, taking statins and oral hypoglycemic agents, were at reduced risk of developing dementia. A recent meta-analysis of twenty-four studies revealed that the presence of diabetes, obesity, hypertension, hypercholesterolemia in mid-life were associated with development of dementia in late life [72]. Conversely, lifestyle changes including exercise and consumption of a healthy diet in mid-life were associated with lowered risk of dementia. Pekkala et al. (2020) examined the association between markers of type 2 diabetes with amyloid accumulation in the brain using PiB PET scans [73]. They observed a correlation of amyloid status with insulin resistance index (HOMA-IR), but not with HbA1c levels. A recent study has reported that brain insulin resistance in Down syndrome (DS) patients can trigger early onset AD [74]. In this study, the authors examined proteins belonging to the insulin signaling pathway in post-mortem brain samples of DS patients before and after the development of AD. They observed markers of dysregulated insulin signaling, especially before the onset of AD pathology, suggesting that brain insulin resistance in DS may contribute to cognitive impairment.

Obesity

Obesity has been shown to cause cognitive dysfunction independent of type 2 diabetes. For example, Whitmer et al. (2008) reported that abdominal obesity alone has a direct correlation with the risk of developing dementia [75]. Several studies have suggested that obesity in midlife causes cognitive decline later in life [76-78]. An Australian study projected that by decreasing mid-life obesity by 20%, dementia in old age could be lowered by 10% [79]. However, late-age obesity may be protective against AD. For example, a study utilizing over twelve million patient data from a Korean health database found that obese subjects who were aged sixty or more had a lower risk of developing dementia and AD than non-obese subjects [80]. Higher incidence of dementia was observed among elderly underweight patients when compared to normal weight and obese patients, although this study did observe other components of MetS to be associated with higher dementia risk, especially vascular dementia. Overall, previous studies have suggested that subjects who developed mid-life obesity are significantly more likely to develop cognitive dysfunction than those who developed late-life obesity. While overt hyperglycemia is not commonly seen in obese individuals, compared to diabetic patients, hypertriglyceridemia is a common

feature of both conditions. A study with radiolabeled triglycerides has shown that they can cross the BBB and play a role in brain leptin and insulin resistance [81]. A review characterizing the role of non-esterified fatty acids in developing dementia describe how they are able to the cross the BBB, leading to neuronal dysfunction and toxic effects in different brain cell types [82].

Cognitive Dysfunction in Genetic Animal Models of Insulin Resistance

Zucker Diabetic Fatty Rat

The CNS effect of insulin resistance is also suggested by studies in several genetic models of obesity and diabetes. Zucker diabetic fatty (ZDF) rats are a model for type 2 diabetes. These rats are characterized by obesity, hyperinsulinemia, and hypertriglyceridemia. Obese Zucker rats were found to show impaired performance in a hippocampal-dependent learning and memory test [83]. There was also reduced association of insulin sensitive GLUT4 in the plasma membrane of the hippocampus, although there was no change in the total GLUT4 and insulin receptor expression. Another study reported reduction in the number of BBB insulin receptors in these rats [84]. Because these receptors are involved in the transport of insulin across BBB, this may account for a decrease in CSF insulin levels previously observed in these rats. Impairments in the cerebral cholinergic system were observed in ZDF rats, as shown by increased choline acetyltransferase and decreased acetylcholinesterase activities [85]. These rats were also found to have impaired mitochondrial function, increased ROS production and redox homeostasis complications, and reduced ATP content in the brain [86]. Figlewicz et al. (1985) reported a decrease in insulin binding in the olfactory bulb in the obese rats when compared to the lean controls [87]. However, insulin binding in cerebral cortex and hippocampus were comparable in both groups. A PET-[18F]FDG study reported the lack of acute metabolic flexibility in brain glucose disposal of Zucker diabetic rats as a result of chronic overexposure to glucose [88]. Another study observed astrogliosis in the cortex and hippocampal regions of obese Zucker rats [89]. Increased production of ROS and nitric oxide (NO), along with reduced ATP synthesis, were observed in the brain of Zucker diabetic rats [86]. We have reported significant increases in the expression of genes related to the pathways of oxidative stress and inflammation, as well as defective CREB phosphorylation, resulting in reduced levels of CREB target proteins including Bcl-2, BDNF, and BIRC3 in the brain of ZDF rats [90].

db/db Mouse

Another model for type 2 diabetes is the leptin receptor-deficient db/db mouse. Impaired spatial memory, as measured by the Morris water maze test (MWMT), was observed in db/db mice [91]. A study using NMR-based metabolomic approach reported that cognitive decline in db/db mice correlated with region-specific changes in brain metabolism [92]. Specifically, the authors observed an increase in anaerobic glycolysis and a decrease in tricarboxylic acid (TCA) pathway. Another study examined the domains of executive function in db/db mice, and showed impaired cognitive flexibility in the Morris water maze reversal phase [93]. Studies have also shown that db/db mice are more susceptible to injury in stroke models. For example, distal middle cerebral occlusion (dMCAO)-induced ischemic stroke caused massive BBB leakage in db/db mice, compared to lean controls [94].

When rFGF21 was administered 6 h after stroke, all abnormal changes were significantly reversed, including PPAR DNA-binding activity and mRNA levels of tight junction proteins. Another study observed increased mortality in db/db mice, compared to lean controls, after hypoxic/ischemic (H/I) insult [95]. This study attributed increased infiltration of neutrophils into the brain as the probable cause of increased mortality because depletion of circulating neutrophils resulted in smaller infarct size.

ob/ob Mouse

Leptin plays a critical role in energy homeostasis. Mice deficient in leptin (ob/ob) develop obesity and insulin resistance without overt fasting hyperglycemia. Studies have examined changes in the CNS of this model. A study reported tau hyperphosphorylation at multiple epitopes in the brain of ob/ob mice [96]. The authors suggest impaired thermoregulation due to hypothermia as a potential cause for the findings because normothermia restored the tau phosphorylation to control levels. Long-term potentiation (LTP) in the lateral nucleus of the amygdala was increased in the ob/ob mouse brain, suggesting that emotional state may be affected by diabetes [97]. Spatial memory impairment was observed in ob/ob mice compared to lean controls following chronic unpredictable mild stress [98]. This observation was accompanied by higher levels of proinflammatory cytokines and low levels of antiinflammatory cytokines. Takeda et al. (2010) generated a novel comorbid mouse model by crossing ob/ob mice with Alzheimer's transgenic mice (APP23) [99]. Diabetes exacerbated cognitive dysfunction in this model without an increase in amyloid deposition in the brain. There was also increased cerebrovascular inflammation and amyloid angiopathy. Interestingly, these mice showed accelerated diabetic phenotype, compared to ob/ob mice, suggesting that amyloid pathology can aggravate diabetes as well. Aβ1-42 was shown to decrease the lifespan of ob/ob mice, following the cross of ob/ob mice with $App^{NL\text{-}F/wt}$ knock-in mice [100].

Goto-Kakizaki Rat

The Goto-Kakizaki (GK) rat is a non-obese and genetic type 2 diabetic model generated by repeated selective breeding of glucose intolerant Wistar rats. Brain energy metabolism was investigated by 13C magnetic resonance spectroscopy in GK rats following 13C glucose administration [101]. GK rats displayed lower rates of brain glutamate synthesis and glutamate-glutamine cycle and TCA cycle rates in neurons. However, the TCA cycle rate was higher in astrocytes, suggesting impairment of glutamate-glutamine cycle between neurons and astrocytes. Higher susceptibility to lipid peroxidation, as assessed by formation of malondialdehyde (MDA) and TBARS, was observed in the brain as compared to liver of GK rats [102]. The mitochondria isolated from the brain of these diabetic rats were also more susceptible to oxidative damage in vitro. Impaired glycogen synthesis in the hippocampus and hypothalamus of GK rats was demonstrated by magnetic resonance spectroscopy [103]. Diabetes also caused a significant reduction in the glucose transport rate as well as the cerebral metabolic rate of glucose. Another study reported that brain mitochondrial dysfunction observed in the GK rats is further exacerbated by aging [104]. In addition, isolated brain mitochondria, were more prone to injury following exposure to Aβ in vitro. Lasting cognitive impairment was observed in GK rats following the induction of ischemia [105]. Markers of neurodegeneration were also observed in these diabetic rats.

Similarly, another study reported cognitive dysfunction in GK rats along with decreased activation of CREB [106]. Increased p-tau and Aβ levels were observed in the brain of aged GK rats along with decreased synaptic protein levels [107].

Effects of Antidiabetic Drugs on Cognitive Function

Diabetic patients are living longer because of the availability of a vast array of antidiabetic medications. Studies with antidiabetic drugs have generally focused on diabetic complications including neuropathy, nephropathy, retinopathy and cardiovascular diseases. Recent studies are beginning to examine the cognitive dysfunction as well. As chronic hyperglycemia in diabetes plays a key role in causing cognitive dysfunction, treatment with antidiabetic drugs that improve glycemic control is expected to improve cognitive function (Fig. 2). It is also possible that some of these drugs could have independent beneficial effects in the brain and slow down cognitive decline. In this section, we review the findings from previous reports on the assessment of cognitive function with various antidiabetic treatments. We have excluded sulfonylureas because they may produce hypoglycemic episodes [108] which can affect cognitive function.

Intranasal Insulin

Although insulin action in the brain can be improved by peripheral administration of insulin, this approach is limited by its hypoglycemic effects. Diabetic patients receiving insulin peripherally may experience hypoglycemic episodes along with increased risk of dementia [109]. Intranasal (IN) insulin administration on the other hand has shown promise as an effective treatment option to facilitate insulin action in the brain. IN insulin is non-invasive and delivers insulin to the brain parenchyma quickly and effectively. Cerebral levels of insulin are significantly higher following IN administration than after intra venous administration. Several studies have taken this approach and reported significant improvement in cognitive function. For example, Avgerinos et al. (2018) analyzed seven studies with 293 patients that tested the effectiveness of IN insulin in improving cognitive function and observed positive effects in patients with dementia or MCI [110]. These effects appear to be limited to patients with the ApoE4 allele. This study also describes how ApoE4 (−) patients had improved results based on the authors' primary memory composite score, while ApoE4 (+) patients had worse outcomes. A randomized controlled trial of over one hundred MCI and AD patients found amelioration of delayed memory following IN treatment [111]. However, another study reported significant improvements in verbal working memory and visuospatial working memory following IN insulin administration, regardless of ApoE4 allele status [112]. A study in patients with MCI reported that low dose IN insulin improved cognitive function which had a positive correlation with insulin signaling mediators in plasma neuronal-enriched extracellular vesicles [113]. There are also negative reports on the lack of insulin action in cognition. A recent phase 2/3 multisite randomized clinical trial with 289 participants found no cognitive or functional benefits associated with IN insulin treatment over a 12-month period [114]. Participants in this trial included adults aged 55 to 85 years with a diagnosis of amnestic MCI or AD, a score of 20 or higher on the Mini-Mental State Examination (MMSE) and a clinical dementia rating of 0.5 or 1.0.

The effectiveness of IN insulin is further supported by studies in preclinical models. The effects of IN insulin was examined by a study in 9-month-old 3xTg-AD mice, a mouse model with both amyloid and tau pathologies [115]. The authors observed restoration of brain insulin signaling, increased synaptic proteins, reduced Aβ levels, and inhibition of microglia activation in mice, leading to reduced inflammation. Ruegsegger et al. (2019) demonstrated how insulin reduction in the brain contributes to cognitive impairment, upregulation of proteins involved in Tau phosphorylation and neurodegeneration in streptozotocin-induced diabetic mice [116]. IN insulin administration in these mice resulted in enhanced mitochondrial ATP production and cognitive function. A study in wild type mice showed that peripheral administration of insulin modulates the trafficking of Aβ across BBB [117]. The authors also demonstrated in an in vitro model of the BBB that insulin is able to regulate the luminal uptake of Aβ. Traumatic brain injury (TBI) being a risk factor for AD, Franklin et al. (2019) examined insulin responsiveness in isolated hippocampal synaptosomes after TBI injury in a rat model [118]. They observed that insulin is able to block LTP inhibition by Aβ and tau oligomers and that its effect is lost in TBI rats.

Metformin

Metformin, a widely used oral hypoglycemic drug for the treatment of diabetes, acts by increasing glucose utilization in the peripheral tissues and by reducing hepatic glucose output. Several clinical studies have assessed the impact of this drug on cognitive dysfunction. Hsu et al. (2011) observed that metformin treatment significantly reduced the risk of dementia in type 2 diabetic patients aged fifty and older, after controlling for cerebrovascular disease [119]. In addition, when metformin was given in combination with sulfonylureas, the risk of dementia was reduced by 35% over an 8-year period [119]. The Sydney Memory and Aging Study has recently reported decreased incidence of dementia in older diabetic patients treated with metformin [120]. In this prospective observational study, community-dwelling 70–90-year-old participants without dementia were followed for 6 years. Among them, diabetic patients receiving metformin had slower cognitive decline compared to diabetic patients without metformin treatment. However, a U.K. clinical study found long-term chronic use of metformin associated with an increased risk of developing AD, while long-term use of other drugs including sulfonylureas, thiazolidinediones, or insulin were found to have no effect on the risk of dementia [121]. Thus, clinical studies have reported mixed findings on the effectiveness of this drug in improving cognitive function.

SGLT2 Inhibitors

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a new class of antidiabetic drugs. They act by increasing glucose excretion in the urine by inhibition of the reabsorption of glucose in renal tubules. Empagliflozin and dapagliflozin are such drugs, currently being used in the treatment of diabetic patients. The effect of empagliflozin administration has been tested in APP/PS1/db/db mice, a model with AD and diabetes [122]. The authors observed a decrease of neuronal loss and senile plaque burden in the brain of treated mice, along with amelioration of cognitive deficits. Glycemic control with empagliflozin was shown to prevent cognitive impairment and amelioration of cardiovascular injury in db/db mice following 10 weeks of treatment [123]. Another study reported improved brain

mitochondrial function and prevention of cognitive decline in high-fat diet (HFD)-fed rats after treatment with dapagliflozin [124]. This SGLT2 inhibitor ameliorated mitochondrial dysfunction, peripheral insulin resistance, inflammation, and neuronal apoptosis in treated rats. The effects of SGLT2 inhibitions on the CNS are likely to be secondary to glucose lowering effects.

Thiazolidinediones

Thiazolidinediones, another class of oral hypoglycemic drugs, act as agonists of PPAR-ɣ and promote insulin responsiveness in type 2 diabetic patients. They improve the sensitivity of adipose tissue and skeletal muscles towards insulin and inhibit hepatic gluconeogenesis [125]. Both clinical and preclinical animal model studies suggest beneficial effects of these drugs in improving cognition. Rosiglitazone and pioglitazone belong to the thiazolidinedione class of drugs.

Rosiglitazone

Rosiglitazone has been shown to improve cognitive function by several clinical studies. For example, a randomized double-blind trial of rosiglitazone demonstrated cognitive function improvement in early-stage AD patients who did not carry the ApoE4 allele [126]. Similarly, a six-month randomized controlled trial in MCI and AD patients observed that rosiglitazone-treated subjects maintained memory function and demonstrated better delayed recall and selective attention, while placebo-assigned subjects showed anticipated memory decline [127]. A study in older diabetic patients with MCI tested the effects of diabetes drugs over a 36-week period [128]. Several neuropsychological tests, including MMSE, Rey Verbal Auditory learning and Trail Making Tests were performed. Patients receiving both metformin and rosiglitazone showed stable results with all the tests, while groups on diet control and on metformin alone showed declining performance in one of the tests, suggesting that rosiglitazone may have positive effects on cognitive function. However, a few other studies found no significant improvement in cognitive function, following rosiglitazone treatment in patients with mild to moderate AD [129, 121].

An interesting study examined the effects of rosiglitazone treatment for 1 month in different age groups of Tg2576 mice, a transgenic Alzheimer's mouse model [130]. Both peripheral gluco-regulatory status and cognitive function were assessed. Based on the results, the authors concluded that rosiglitazone-mediated reversal of associative learning and memory deficits is independent of its glucose lowering effects. Rosiglitazone was found to reduce Aβ burden in the brain by improving the phagocytic activity of microglia in an Alzheimer's transgenic mouse model expressing human mutant APP [131]. Impaired recognition and spatial memory were also rescued in the treated mice. Neuronal insulin resistance, induced by a three-month HFD, in rats was reversed by rosiglitazone [132]. Insulin-induced long-term depression was significantly improved, and increased brain mitochondrial ROS production was attenuated in this study. Pathan et al. (2008) reported rosiglitazone's ability to attenuate cognitive dysfunction and metabolic dysregulation induced by 5 weeks of HFD consumption in rats [133]. Rosiglitazone administration also stimulated mitochondrial biogenesis in the mouse brain by inducing both mitochondrial DNA and estrogen-stimulated related receptor alpha mRNA, a key regulator of this process [134].

Pioglitazone

The effects of pioglitazone on cognitive function have been reported by studies in animal models. Pioglitazone improved learning on the active avoidance task and decreased β-amyloid deposition and tau pathology in 10-month-old triple transgenic mice (3xTg-AD) [135]. Gene microarray analysis of hippocampal tissue revealed that this TZD drug facilitated estrogenic processes. In a study on aged mice expressing human mutant APP (APPSwe,Ind), pioglitazone was administered for 6–8 weeks [136]. While pioglitazone did not improve spatial memory or reduce Aβ levels significantly, it attenuated astroglial activation, reduced oxidative stress, and completely normalized cerebral blood flow. Proteomic analysis of surgically isolated cerebral arteries from 3-month-old APP transgenic mice revealed that nearly 200 cerebrovascular proteins were abnormally expressed [137]. Pioglitazone administration rescued a third of these proteins and they were mostly associated with oxidative stress, promotion of cerebrovascular vasocontractile tone, and vascular compliance. Papadopoulos et al. (2013) tested the effects of pioglitazone in bitransgenic A/T mice that overexpress a human APP mutant (APPSwe,Ind) and constitutively active TGF-β1 [138]. Pioglitazone treatment normalized metabolic and vascular functions and reduced hippocampal microglial activation but did not rescue spatial learning and memory deficits in the MWMT. Another study showed that the sera from AD patients induced apoptosis of human umbilical vein endothelial cells which was prevented by preincubation with pioglitazone [139]. Poor BBB permeability of pioglitazone has been suggested to be an obstrucle for its therapeutic potential in AD. However, Chang et al. (2015) have demonstrated that the levels of pioglitazone in brain tissue can be significantly increased by inhibition of P-glycoprotein (P-gp) [140]. Pioglitazone was also investigated for its stereoselectivity and the concentration of (+) pioglitazone was 46.6% higher than (−) pioglitazone in brain tissue and 67.7% lower than (−) pioglitazone in plasma. Mice that were given pure (+) pioglitazone had 76% higher brain exposure levels than mice given an equivalent dose of racemic pioglitazone. Therefore, P-gp may act as a stereoselective barrier for pioglitazone brain penetration and pure (+)-pioglitazone may result in higher levels of brain exposure to pioglitazone. Pioglitazone has been tested in other models of cognitive dysfunction. For example, pioglitazone rescued impaired cognitive function, as observed by the MWMT in a rat controlled cortical impact model of TBI [141]. In addition, pioglitazone ameliorated several neuropathological aspects including activation of microglia. Long-term fructose-drinking in rats caused insulin resistance, oxidative stress, and cognitive deficit, and pioglitazone treatment significantly reduced insulin resistance and the levels of ROS in the hippocampus and cerebral cortex [142]. Pioglitazone also improved learning and memory functions partially, as observed by the MWMT.

GLP-1 Based Therapies

Glucagon-like peptide-1 (GLP-1), secreted by the intestinal L-cells in response to food, acts on pancreatic β cells to stimulate insulin. GLP-1 action is transient because it is rapidly degraded by dipeptidyl peptidase-4 (DPP-4) [143]. To further enhance GLP-1 action, two types of drugs are being used currently in the treatment of diabetes. DPP-4 inhibitors can be given orally to sustain endogenous GLP-1 levels, whereas DPP-4-resistant GLP-1 analogs need to be injected. The GLP-1 receptor has been shown to be expressed in tissues other than pancreatic β cells including the brain [144]. We have reported the expression of

GLP-1 receptors in differentiated human neuroprogenitor cells [145]. Abbas et al. (2009) examined the cognitive function in GLP-1 receptor knockout mice using several behavioral tests [146]. $Glp1r^{-/-}$ mice were found to have impaired cognitive function, based on water maze and novel object recognition tasks, compared to wild type mice. LTP in CA1 area of the hippocampus was also severely impaired in $Glp\text{-}1^{-/-}$ mice. Findings of this study and previous reports suggest a physiological role for GLP-1 in neuronal function and some forms of memory formation. Because GLP-1 can pass through BBB, diabetic patients treated with GLP-1-based drugs are likely to have beneficial actions in the CNS in addition to glycemic control.

GLP-1 Analogs

Exenatide/Exendin-4

Li et al. (2010) examined the effects of exendin-4 treatment in 3xTgAD mice with streptozotocin (STZ)-induced diabetes [147]. Exendin-4 decreased HbA1c levels and brain Aβ levels, suggesting its potential therapeutic value in patients with AD and diabetes. Exendin-4 also mitigated the toxicity of Aβ and oxidative challenge in mouse primary neuronal cultures and in SH-SY5Y cells in a concentration-dependent manner. Administration of exenatide for 16 weeks in 5XFAD mice resulted in normalization of mitochondrial dynamics and prevention of cognitive decline [148]. In addition, the drug alleviated $A\beta_{1-42}$ deposition and synapse damage in the hippocampus of this mouse model of AD. Li et al. (2016) examined the neuroprotective effects of GLP-1 receptor agonists, exendin-4 and liraglutide in db/db mice following middle cerebral artery occlusion (MCAO) injury [149]. The MCAO injury decreased cerebral microcirculation, but this was reversed by the administration of exendin-4 or liraglutide. The mechanism involved was suggested to be through elevation of endothelial NOS levels. Another study reported that blast TBI-induced neurodegeneration and memory deficits were ameliorated by subcutaneous administration of exendin-4 [150]. Similarly, exendin-4 also improved cognitive function, as assessed by the MWMT in a fluid percussion injury rat model [151]. Exendin-4 has been shown to exert neuroprotective effects when administered to HFD-induced insulin-resistant mice [152]. These treated mice showed improved hippocampal synaptic plasticity and cognitive function. A potential mechanism of direct action of exenatide in the brain was suggested by Bomba et al. (2018), who examined its effects in wild type mice [153]. Following a two-month treatment, exenatide promoted the activation of the BDNF-TrkB neurotrophic axis and inhibited apoptosis by decreasing p75NTR-mediated signaling. We have reported the neuroprotective effects of exendin-4 in cultured human neural stem cell-derived neurons [145]. Exendin-4 decreased Aβ-induced neuronal apoptosis through a mechanism involving the activation of the neuroprotective transcription factor CREB and induction of BDNF promoter activity in a CREB-dependent manner. Furthermore, withdrawal of neurotrophins in the neuronal culture led to the loss of neuronal phenotype of differentiated neuroprogenitor cells but this was prevented by exposure to exendin-4.

Liraglutide

A pilot study found that T2DM patients who were administered liraglutide performed better in short term memory and memory composition scores than patients who had

controlled blood glucose levels by diet and exercise, suggesting that liraglutide action on cognitive function is not secondary to glycemic control [154]. A recent study found that obese individuals with T2DM given liraglutide or exenatide for 3 months had significantly improved Montreal Cognitive Assessment (MoCA) scores, olfactory test total scores, and olfactory brain activation [155]. A double-blinded study used fMRI brain scans to demonstrate reduced brain activity and connectivity between brain regions in placebo-assigned middleaged subjects over the course of 1 year, whereas this negative association was not present in those given liraglutide [156]. A 26-week randomized, placebo-controlled, double-blind study with AD patients concluded that liraglutide treatment was able to prevent the decline of cerebral glucose metabolism. The authors, however, were not able to find significant differences in Aβ deposition or cognitive measures between liraglutide-treated and placebo groups [157]. Another study analyzed the benefits of 28-day liraglutide treatment in 10-month-old 3xTg-AD female mice [158]. Liraglutide reduced cortical $A\beta_{1-42}$ levels and partially attenuated brain oxidative/nitrosative stress. Liraglutide was shown to prevent memory impairment and synapse loss in the hippocampi of 7-month-old APP/PS1 mice following 8 weeks of treatment [159]. In addition, there were significant reductions in β-amyloid plaque deposition and activated microglia numbers in the brain of these mice. In a later study, the same group tested the effects of liraglutide treatment for 2 months in aged APP/PS1 mice [160]. The GLP-1 analog improved spatial memory and reduced amyloid plaque load. In addition, long-term potentiation was significantly enhanced, along with increased synapse numbers in the hippocampus and cortex. Another study examined the effects of liraglutide in a non-human primate model of AD, following infusion of Aβ oligomers into the lateral cerebral ventricle [161]. Loss of synapses and memory impairment by this infusion were partially reversed by liraglutide administration. However, long-term liraglutide administration was found to have no significant impact on β-Amyloid plaque load, as assessed in two AD mouse models expressing “London” (hAPPLon/PS1A246E) and “Swedish” (hAPPSwe/PS1ΔE9) mutants of APP along with co-expression of distinct PS1 variants [162]. Administration of liraglutide to HFD-fed mice [163] or ob/ob mice [164] resulted in significantly improved cognitive function and hippocampal synaptic plasticity, as a result of the preservation of neurogenesis and neuronal survival.

Dulaglutide and Lixisenatide

The effect of dulaglutide on cognitive function was investigated by the Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial [165]. Patients’ cognitive function was assessed at baseline and during follow-up using the MoCA and Digit Symbol Substitution Test (DSST) in this randomized, double-blind placebo-controlled trial at 371 sites in 24 countries. This trial reported that treatment with dulaglutide reduces cognitive impairment in people with type 2 diabetes by 14%. Lixisenatide, another GLP-1 analog, was shown to reduce amyloid plaque deposition, neurofibrillary tangle formation and neuroinflammation in the brain of aged APP/PS1/tau mice, following 2 months of treatment [166]. The authors suggested the activation of PKA-CREB signaling as a possible mechanism. Similarly, this GLP-1 analog reduced amyloid plaque load, prevented the loss of synapses, and improved performance in novel object recognition tasks in APP/PS1 mice after 10 weeks of treatment [167]. Overall, Lixisenatide was equally effective at a lower dose compared to liraglutide in some of the parameters measured. Lixisenatide was shown to

reduce peripheral insulin resistance, improve recognition memory, and boost the number of hippocampal dentate gyrus neurons in HFD-fed mice [168].

New GLP-1 Analogs

Some studies have suggested that dual GLP-1/gastric inhibitory peptide (GIP) receptor agonists may be better options for the treatment of AD [169]. A recent study found that DA5-CH, a novel dual GLP-1/GIP receptor agonist, reverses working memory and spatial memory impairments in an intracerebroventricular STZ-induced insulin desensitization AD rat model [170]. The authors observed that DA5-CH can cross the BBB at a rate comparable to other GLP-1 receptor agonists and DA5-CH treatment reduces tau^{S396} phosphorylation in the hippocampus significantly. The drug also alleviated hippocampal mitochondrial stress and increased the expression of synapse-related proteins in the hippocampal region, further highlighting the neuroprotective effects of DA5-CH. Cao et al. (2018) tested the neuroprotective effects of DA5-CH in the APP/PS1 transgenic mouse model [171]. DA5-CH reduced hippocampal amyloid senile plaques and phosphorylated tau protein levels and activated the PI3K/Akt signaling pathway. The treatment also resulted in improved working memory and long-term spatial memory. A novel triagonist of GLP-1, GIP and glucagon was tested in the 3xTg mouse model of AD [172]. Following a 30-day treatment in 7-month-old AD mice, the authors observed improved long-term spatial memory in the MWMT and improved working memory in a Y-maze task. The triagonist also alleviated the suppression of LTP in the CA1 region of the hippocampus, upregulated the hippocampal levels of ^{S133} p-CREB, ^{T286} p-CAMKII, and ^{S9} p-GSK3β in 3xTg-AD mice and significantly reduced hippocampal pathological damages, including Aβ and phosphorylated tau aggregates. Similarly, a study reported the neuroprotective effects of another triple receptor agonist in the APP/PS1 transgenic mouse model [173]. Decreases were observed in β-amyloid deposition and markers of neuroinflammation and oxidative stress in the brain of the treated AD mice, leading to reversal of memory deficits. The agonist also decreased the levels of the mitochondrial pro-apoptotic BAX, enhanced the anti-apoptotic Bcl-2 and increased the levels of BDNF, resulting in increased levels of synaptophysin.

DPP-4 Inhibitors

DPP-4 inhibitors are another class of drugs under incretin therapies. These drugs act by sustaining the levels of endogenous GLP-1 through inhibition of DPP-4. A large number of DPP-4 inhibitors, including sitagliptin, vildagliptin, alogliptin and linagliptin are currently being used in the treatment of diabetes. A recent network meta-analysis and meta-analysis with over 1.2 million patients analyzed seven antidiabetic agents across twenty-two studies and their impact on the risk of dementia in T2DM patients [174]. The analysis included several drugs including metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, glucosidase inhibitors, benzoic acid derivatives, and insulin, but did not include GLP-1 analogs or SGLT-2 inhibitors due to lack of relevant data. Results of the study indicated that DPP-4 inhibitors and metformin provide a protective effect against the risk of developing dementia, while those treated with insulin had the highest risk for dementia. Overall, DPP-4 inhibitors provided the most significant protective effect among all the antidiabetic agents and were the most effective drug to prevent dementia, followed by metformin and thiazolidinedione.

Sitagliptin

A recent study with nearly fifteen thousand T2DM patients in Taiwan found that patients given DPP-4 inhibitors, such as sitagliptin, are less likely to develop dementia, especially vascular dementia, compared to the placebo group [175]. However, this trend was notably absent for the risk of developing AD. Another study reported that 6-month sitagliptin therapy improves cognitive function, based on MMSE scores, in older diabetic patients with and without AD [176]. The effect of sitagliptin on cognitive function has been tested in animal models. A recent study reported improved performance in the MWMT by APP/PS1 mice after oral administration of sitagliptin for 8 weeks [177]. In addition, treated APP/PS1 mice had significantly reduced amyloid plaque deposition, elevated spine density, and increased protein levels of BDNF in the brain. Sitagliptin was shown to improve insulin sensitivity, reduce inflammation and reverse memory impairment in high-fat-fed mice [178]. Similarly, another study found that, in HFD-induced insulin-resistant rats, DPP-4 inhibitors, vildagliptin or sitagliptin administered individually, decreased oxidative stress levels and improved brain mitochondrial dysfunction in the brain [179]. Tsai et al. (2015) tested CNS effects of sitagliptin in a mouse model of chronic cerebral hypoperfusion, induced by bilateral carotid artery stenosis [180]. Sitagliptin suppressed white matter lesions, microglial activation, and astrocytosis. Furthermore, there was protection against cognitive impairment and a decrease of inflammatory markers.

Vildagliptin

A retrospective longitudinal clinical trial found that vildagliptin administration for 6 months led to better performance in the copying subdomain of the MMSE in patients with T2DM [181]. Another retrospective longitudinal study found that older patients with both T2DM and MCI had reduced glucose level fluctuations and improved cognitive functioning within 2 years of vildagliptin therapy [182]. Six-month administration of vildagliptin with metformin showed protective effects, with better HbA1c control and prevented MMSE score reduction in diabetic elderly patients compared to metformin-only treated patients [183]. Treatments with both vildagliptin and pioglitazone were shown to restore dendritic spines in CA1 hippocampus that were reduced by HFD in rats [184]. Vildagliptin has been also shown to restore neuronal IR phosphorylation, IRS-1 phosphorylation, and Akt phosphorylation, all indicators of insulin signaling, to normal levels in HFD-fed rats [185]. STZ-induced diabetic mice treated with vildagliptin for 8 weeks showed reversal of diabetes-induced memory and learning impairment [186]. In addition, vildagliptin significantly increased the expression of BDNF and SOD and decreased MDA levels in the brain. Similarly, another study observed improvement in memory in STZ-induced diabetic rats, following vildagliptin treatment [187]. There was also decreased apoptosis of hippocampal neurons in the treated rats. The authors suggested the activation of Akt as a potential mechanism of the neuroprotective action of the drug.

Alogliptin

We have reported the dual beneficial actions of alogliptin in pancreatic β cells and in the brain by a common CREB-dependent mechanism in two different studies [90, 188]. The plasma levels of GLP-1 were elevated in alogliptin-treated Zucker diabetic rats, which

resulted in improved survival of β cells [188]. Alogliptin activated CREB in insulin positive β cells of islets and increased the levels of CREB-regulated proteins including anti-apoptotic bcl-2, the caspase inhibitor, BIRC3, and IRS-2, an adapter protein required for insulin signaling. We also reported that alogliptin administration in Zucker diabetic rats for 10 weeks led to increases in the levels of CREB-dependent neuroprotective proteins in the brain [90]. Elevated levels of neuroinflammatory markers in the diabetic brain were also decreased, suggesting the potential therapeutic benefits of DPP-4 inhibitors in treating AD.

Linagliptin

A cardiovascular outcome trial with linagliptin did not find any change in cognitive decline [189]. Kosaraju et al. (2017) reported significant beneficial effects of linagliptin in 3xTg-AD mouse model [190]. In this study, 9-month-old 3xTg-AD mice were administered linagliptin orally for 8 weeks. The treated mice showed significant improvement in the Morris Water Maze and Y-maze. Furthermore, linagliptin attenuated β-amyloid accumulation, tau phosphorylation and neuroinflammation in the AD mice. Another study observed improvement in cerebrovascular dysfunction in GK rats, independent of glycemic control [191]. Linagliptin was also shown to ameliorate HFD-induced cognitive decline and increase cerebral blood flow in a tauopathy mouse model [192]. In this study, linagliptin reversed the cognitive impairment and brain atrophy induced by bilateral common carotid artery occlusion-mediated cerebral ischemia in db/db mice [193]. This DPP-4 inhibitor also increased the levels of tight junction protein claudin-5 and prevented neuronal loss in the hippocampus and cortex of these mice.

Conclusions

Recent studies have recognized that the CNS is negatively affected under conditions of insulin resistance. Clinical and preclinical studies have reported cognitive dysfunction during conditions of insulin resistance, including metabolic syndrome, obesity and diabetes. Hyperglycemia in diabetes can generate advanced glycation end products which can pass through the BBB and cause neuronal dysfunction. In addition, there are circulating factors including cytokines and fatty acids, generated by the peripheral tissues, in the diabetic state that can have indirect effects on the CNS. These observations raise an important question on whether treating cognitive dysfunction needs to be directed specifically to the brain cell types or can be accomplished at the systemic level. Recent studies are suggesting that insulin resistance can be targeted therapeutically to prevent cognitive decline. Antidiabetic drugs have been shown to improve cognitive functions by clinical and preclinical studies. Their actions may be directly on the CNS or indirectly through glycemic control. However, there are also reports showing negative effects on cognition with these drugs. Even among those studies, some beneficial actions at the molecular level in the brain are being reported. It is possible that timing of the intervention with these drugs was not early enough to reverse cognitive decline or the effects were not sufficient enough to tilt the scale. Among the antidiabetic drugs, GLP-1-based drugs have demonstrated consistent beneficial actions in the brain. They have the potential to delay cognitive decline in conditions of insulin resistance. Furthermore, these drugs, well tested for use in diabetic patients, can be also repurposed for the treatment of patients with dementia including Alzheimer’s disease.

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Abbreviations

3xTg	triple transgenic
AD	Alzheimer's disease
Ang	Angiotensin
ApoE4	apolipoprotein E4
APP	β-amyloid precursor protein
ARB	Ang II type 1 receptor blocker
BBB	blood brain barrier
BDNF	brain-derived neurotrophic factor
BECs	brain endothelial cells
CBF	cerebral blood flow
CFT	category fluency test
CNS	central nervous system
CSF	cerebrospinal fluid
dMCAO	distal middle cerebral occlusion
DPP-4	dipeptidyl peptidase-4
DS	Down syndrome
GIP	gastric inhibitory polypeptide
GK	Goto-Kakizaki
GLP-1	glucagon-like peptide-1
HbA1c	hemoglobin A1c
H/I	hypoxic/ischemic
HFD	high-fat diet
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance

IGF	insulin-like growth factor
IN	intranasal
IR	insulin receptor
IRS-1	insulin receptor substrate-1
LTP	long-term potentiation
MCAO	middle cerebral artery occlusion
MCI	mild cognitive impairment
MDA	malondialdehyde
MetS	metabolic syndrome
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MWMT	Morris water maze test
P-gp	P-glycoprotein
RAS	renin-angiotensin system
ROS	reactive oxygen species
SAMP8	senescence-accelerated mouse prone 8
SGLT2	sodium-glucose co-transporter 2
STZ	streptozotocin
T2DM	type 2 diabetes mellitus
TBI	traumatic brain injury
TCA	tricarboxylic acid
VaD	vascular dementia
ZDF	Zucker diabetic fatty

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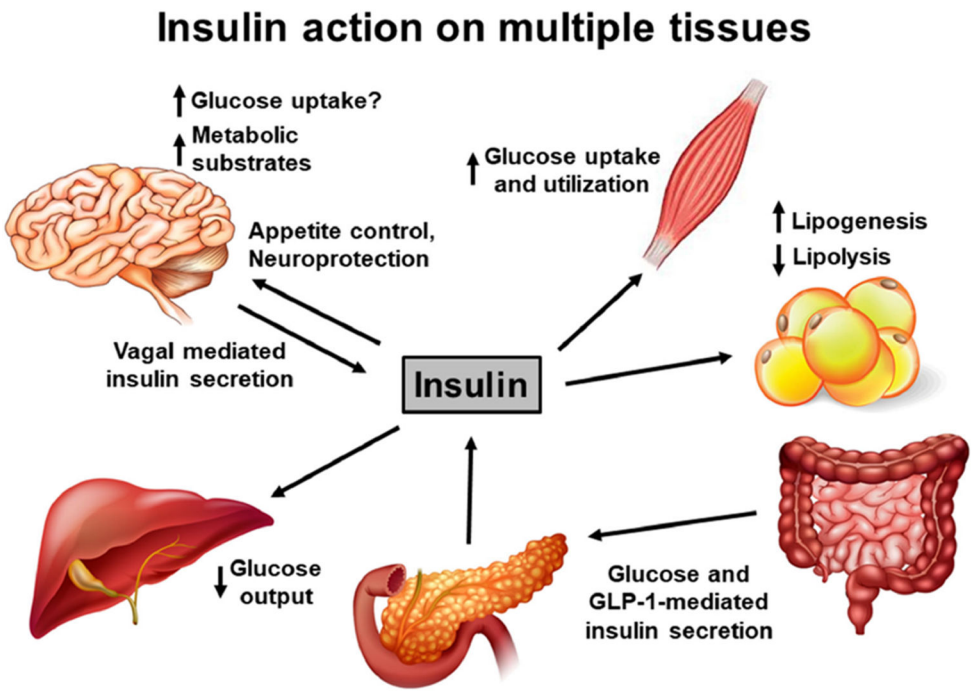

Fig. 1.

Insulin action on multiple tissues. Insulin is primarily produced by the β cells of the pancreatic islets and secreted in response to glucose. In addition, food consumption promotes intestinal secretion of GLP-1, which acts on the β cells to enhance insulin release. Insulin release may also be modulated by the vagus nerve. Insulin acts on multiple tissues to regulate glucose metabolism. It stimulates glucose uptake and utilization in the muscle, while suppressing hepatic glucose release. Insulin promotes lipogenesis and suppresses lipolysis in the adipose tissue. While the effect of insulin action in the brain on appetite control is known, it may not play a significant role in glucose uptake. Insulin action on neuroprotection and cognitive function are being recognized recently

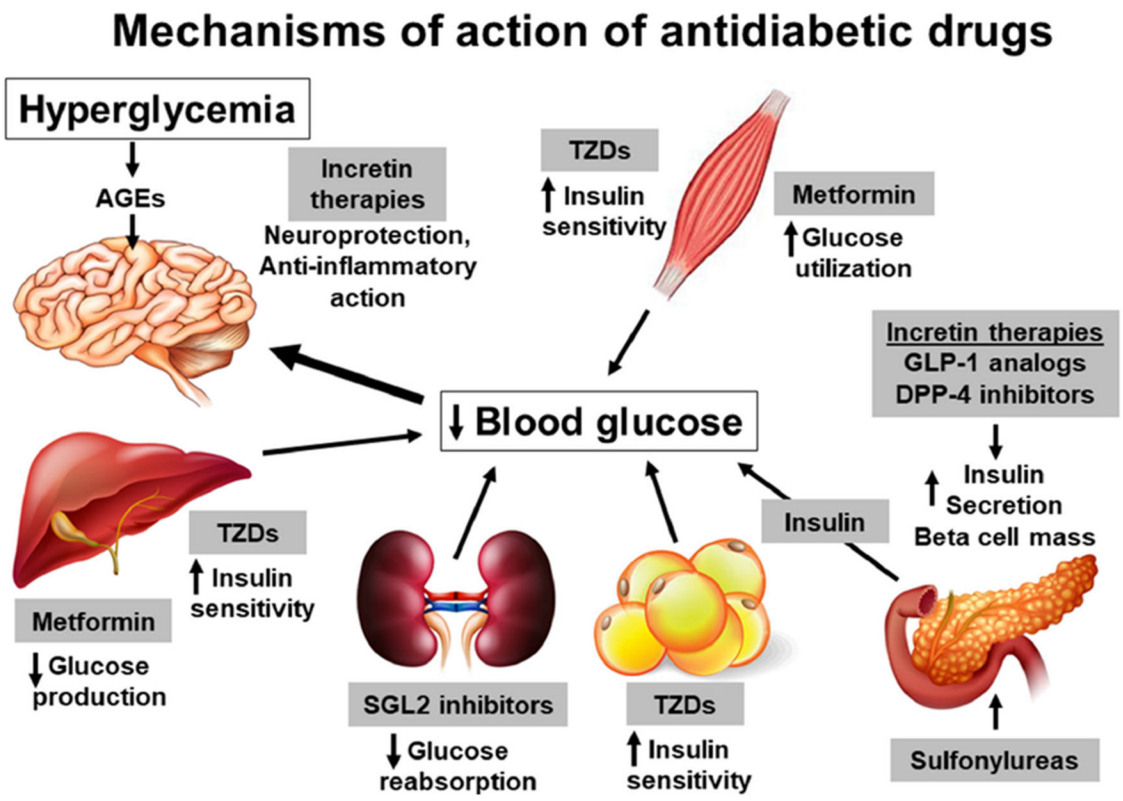

Fig. 2.

Mechanisms of action of antidiabetic drugs. The lifespan of type 2 diabetic patients is increasing steadily because of the availability of a wide range of antidiabetic drugs. These drugs decrease blood glucose levels by multiple mechanisms. Metformin, a widely used hypoglycemic drug, acts by increasing glucose utilization in the peripheral tissues and by reducing hepatic glucose output. Sulfonylureas stimulate insulin secretion from pancreatic β cells. The use of this class of drug is associated with hypoglycemic episodes. Thiazolidinediones (TZDs) improve the sensitivity of adipose tissue, skeletal muscles, and the liver towards insulin. Incretin therapies, such as DPP-4-resistant GLP-1 analogs and DPP-4 inhibitors that enhance endogenous GLP-1 levels, promote pancreatic release of insulin. In addition, they are reported to have insulin-independent actions in other tissues, including the brain. Recently introduced SGLT2 inhibitors increase glucose excretion in the urine by preventing glucose reabsorption in the renal tubules. Overall, these antidiabetic drugs have been shown to have beneficial actions in the brain either directly or indirectly through glycemic control