Prospective of managing impaired brain insulin signalling in late onset Alzheimers disease with excisting diabetic drugs

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Abstract

Late onset Alzheimer's disease (AD) is the most common cause of dementia among elderly. The exact cause of the disease is until now unknown and there is no complete cure for the disease. Growing evidence suggest that AD is a metabolic disorder associated with impairment in brain insulin signalling. These findings enriched the scope for the repurposing of diabetic drugs in AD management. Even though many of these drugs are moving in a positive direction in the ongoing clinical studies, the extent of the success has seen to influence by several properties of these drugs since they were originally designed to manage the peripheral insulin resistance. In depth understandings of these properties is hence highly significant to optimise the use of diabetic drugs in the clinical management of AD; which is the primary aim of the present review article.

Keywords Alzheimer's disease · Diabetic mellitus · Drug repurposing · Intranasal insulin

Introduction

Alzheimer's disease (AD), the most common cause of dementia among elderly is an age-related progressive neurodegenerative disorder characterized by the loss of memory, cognition and language handling inabilities [1]. AD brain is characterized by the presence of deregulation of cholinergic [2] and glutaminergic neurotransmitter systems [3] that correlate with memory loss [4] and cognitive impairment [5] in AD patients; accumulation of two neurotoxic proteins called extra neuronal “amyloid beta ($A\beta$) plaques” and intra neuronal “neurofibrillary tangles” (NFT) [6]; oxidative stress; mitochondrial dysfunction and neuro-inflammation. Progression of above pathological features with time ultimately lead to neurodegeneration, synaptic dysfunction, loss of connectivity between neurons finally the complete loss of memory [1].

Worldwide almost 46 million people are living with AD and other type dementias [1]. Scientists around the world are still struggling to identify the exact mechanism of the disease in order to treat and manage the disease efficiently [7]. Until now two classes of drugs are approved by US FDA (United States food and drug administration) for the management of AD; those include the three anticholine esterase (Donepezil, rivastigmine, and galantamine) and one NMDA receptor antagonist (memantine). Treatment with these drugs are limited as they solely gives symptomatic relief; but do not prevent or stop the disease progression [8]. Even though certain disease-modifying therapies targeting the $A\beta$ or tau production, oxidative stress and neuro-inflammation had also been investigated in AD, most of these trials ended up with disappointing results [9]. It is expected that the number of AD patients would rise to one among every 85 individuals by the year 2050, if this situation continues [10].

Identification of the involvement of brain insulin signalling impairment in AD open up the new area of research in AD management (DM) [11–13]. This endogenous impairment has seen to occur in the brain even in absence of type 2 DM [14, 15]. How the brain insulin signalling impairments can lead to AD is being discussed in the following section briefly. These findings enriches the scope for the repurposing of diabetic drugs in AD management [16] as it will take around 14 years and a cost of about US Dollar 2.6 billion to bring a new molecule to the market approval. However the repurposed

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drug that has already passed many of the initial studies bypass much of the early time and cost [17].

Even though diabetic drugs such as insulin, Glucagon-like peptide-1 (GLP-1) analogues etc. are moving in positive direction in the ongoing clinical studies, the extent of success of diabetic drugs in the AD has seen to be limited by several factors. The primary reason is that these drugs are originally designed to manage the peripheral insulin resistance but not for the brain insulin resistance. Hence the diabetic drugs themselves have certain limitations for their repurposing. For that the same treatment approaches that manage the type 2DM may not work well in AD. Probably this could be the reason why the diabetic drugs are unable to prevent the development of AD in many of the diabetic patients despite of the undergoing diabetic treatment. Therefore better understanding of those properties of the diabetic drugs that might limit their therapeutic success in AD is highly significant for the clinical management of AD with existing diabetic drugs; which is the primary objective of the present review article.

Brain insulin signaling; a therapeutic target in AD

In addition to controlling the cellular uptake of glucose and energy metabolism, insulin is having many more functions in brain tissue as well as in the peripheral tissues also [18]. In the brain, the significance of insulin signaling impairment in AD lies in the fact that insulin controls most of the functions disrupted in AD such as cerebral blood flow, accumulation of A β and tau, apoptosis, oxidative stress, neuro-inflammation, impairment in memory and cognition [19].

The downstream signaling of IR activates phosphatidylinositol 3-kinases (PI3K/Akt) pathway. This pathway plays critical roles in metabolism, growth, proliferation, and survival of neurons [20]. Activated PI3K/Akt down-regulates the expression of glycogen synthase kinase 3 (GSK-3) enzymes; the major enzyme involved in the hyper-phosphorylation of tau protein in AD [21]. Aggregation of hyper-phosphorylated tau finally results in the formation of neurofibrillary tangles (NFT); one of the primary biomarkers of AD. Insulin signaling also promotes neuronal survival via modulating the activation of several pro-apoptotic agents (Bad, FoxO transcription factors, GSK-3) and NF κ B protein complex that controls the neuro-inflammation [22].

Insulin signaling regulates the A β plaque formation in such a way that impaired insulin signaling can alter the expression as well as processing of amyloid precursor protein (APP). APP is a membrane glycoprotein, sequential cleavage of which releases the A β fragments. In normal cases the cleavage is mediated by α secretase enzyme followed by γ secretase. The end product of this pathway are soluble A β fragments. Internally, the impaired brain

insulin signaling activates the β secretase enzyme; cleavage of APP by β secretase followed by γ secretase produces insoluble A β fragments [23, 24] in the brain. Brain insulin resistance also has been seen to inversely affect the clearance of A β from the brain [25]. Another link between insulin action and A β plaque formation is the “insulin-degrading enzyme (IDE)”. Besides degrading insulin, the IDE also degrades glucagon, atrial natriuretic peptide, and A β peptide and regulates proteasomal degradation [26]. Since IDE degrades both insulin and A β ; hyperinsulinemia; a condition associated with insulin resistance could elevate the A β level by competitively inhibiting the IDE-mediated A β degradation [27]. Internally, insoluble A β oligomers inhibit insulin signaling by desensitizing and limiting the surface expression of insulin receptors. Competing with insulin, A β reduces the affinity of insulin to its own receptor [28].

Another important function of insulin in the brain is the formation of memory and cognition. Insulin receptors are present densely in the areas of the brain involved in memory consolidation and recollection of events such as the hippocampus and medial temporal cortex [29]. The mechanisms through which insulin modulates memory include enhancement of brain glucose metabolism, influence on components of long-term potentiation cascade and by improving neurogenesis [30]. Insulin also modulates the level of certain neurotransmitters that control memory and cognition especially acetylcholine and norepinephrine [31, 32]. A pictorial representation of the roles played by insulin in the brain is illustrated in Fig. 1.

Mechanism of impaired brain insulin signaling in AD

Even though the components of both the insulin deficiency and insulin resistance were observed in the AD brain [13], the exact reason of why and how it happens is unknown. Earlier reports say that the prolonged peripheral insulin resistance reduces the capacity of the insulin transporters at the BBB [33]. Therefore it can be assumed in type 2DM people that the initial insulin deficiency starts the pathophysiological changes in the brain. A β plaques, oxidative stress and neuro-inflammation developed slowly lead to the desensitization of the insulin receptors of the brain and thereby insulin resistance [28, 34, 35]. Also, insulin signaling deficiency can exacerbate mitochondrial dysfunction, free radical accumulation and inflammation as discussed in the previous section. However, it has been observed that all the type 2DM patients are not developing AD since there is an involvement of multiple factor interaction in the development of AD in diabetic patients. It has been reported that unmanaged peripheral insulin resistance, genetic risk factors especially the presence of APOE4 positive allele, other

Fig. 1 Insulin signaling in normal brain and diseased brain in AD

co-existing vascular risk factors, degree of oxidative stress and inflammation increases the risk of development of AD in type 2DM patients [36]; yet type 2DM alone is appeared to have strong association with vascular dementia than the AD [37].

Development of brain insulin signaling in the absence of peripheral insulin resistance is still more complicated. The major risk factor for the development of AD is the advancing age as the brain insulin signaling decline with age [38]. Also, advancing age is associated with increased production of free radicals and neuro-inflammation, another risk factors for the development of insulin resistance in elderly [39–42]. The process of normal brain aging is also associated with reduction in the cortical insulin level as well as the impairment of insulin receptor binding capacity [43] as permeability of insulin across the BBB is declining with normal aging [44]. Further studies by Kullmann S et al. has shown that it was the reduction in the expression of insulin transporters at the BBB that diminishes the permeability of insulin to the brain in the elderly [45].

Changes observed with glucose transporters of the brain represent another mechanism in AD. Reduction in the protein levels of GLUT1 and GLUT3 transporters, the major glucose transporters of the brain have reported in the brain of AD patients long back [46]. The decline has seen to be more prominent in the areas of cerebral cortex, with significant loss of GLUT3 [47–49]. Whereas, the level of GLUT2 has increased markedly and no significant changes in GLUT4 level was observed [50]. Insulin insensitive-GLUT1 and partially insulin dependent-GLUT3 [51] are the predominant GLUT protein responsible for glucose transport in brain [52]. Defective glucose transport provoked by the down regulation of GLUT1 and GLUT3

transporters have led to reduced glucose metabolism; that directly induce abnormal tau phosphorylation and downregulation of O-GlcNAcylation via the inhibition of hexosamine biosynthesis pathway [50, 53, 54]. Also investigation in animal model had shown cerebral microvascular degeneration and impairments in Aβ homeostasis with GLUT1 deficiency [55]. GLUT2 involved in the neurotransmitter release, glucose sensing and release of glucose by the glial cells [56, 57]. While the insulin dependent- GLUT4, rapidly provide additional glucose to neurons under conditions of high energy demand. GLUT4 transporters have seen to work in the brain in a similar way as it work in the peripheral tissues; that is insulin signalling modulated activation of PI3k/Akt pathway induces translocation of GLUT4 from intracellular compartments to plasma membrane to bind with glucose [58]. Eventhough there was no reported change in the number of GLUT4 transporters in AD patients, animal studies have shown defects in translocation of brain GLUT4 transporters in insulin resistance [59, 60].

Prospective of managing impaired brain insulin signaling with diabetic drugs

All these evidences suggests that the restoration of the falling insulin signaling probably be a promising approach in AD management. The three different approaches to boost the insulin signaling include [1] treatment with insulin, [2] insulin sensitizer therapy and [3] therapy with insulin secretogauges. Details of these approaches investigated for the AD management is being discussed in the following section.

Insulin

Same as that of the peripheral insulin resistance, brain insulin resistance can also be describe as the situation where the known quantity of insulin is failed to give a pharmacological response in an individual as much as it does in a normal population [61]. Even though, insulin can bind with its receptor in insulin resistance, the signal is not properly transduced through the PI3K/AkT pathway. The inability of body tissues to respond to normal physiological level of insulin demands an exogenous insulin therapy or insulin sensitizer for carrying out the normal physiological functioning. It was found that AD patients required higher doses of insulin to improve the clearance of A β from the brain on comparison with normal volunteers [62]. In addition, an early clinical trial with insulin in AD patients has shown that hyperinsulinemia without hyperglycemia enhance the memory of adults with AD [63].

However, administration of insulin via systemic route (subcutaneous or infusion) was not a viable method in AD more especially with those who are not diabetic because of the associated side effects such as hypoglycemia [64] and changes in plasma ionic balances [65, 66]. Also peripheral insulin therapy can furthermore induce or exacerbate peripheral insulin resistance [67]. Additionally, the concomitant insulin therapy reduces the capacity of the insulin transports at BBB [33]. For that reasons, the intranasal (IN) insulin has been introduced. Since the IN route is the direct route to the brain, this route minimizes the peripheral exposure of administered drug. Intranasally administered insulin was found to reach the CSF of human beings within 10 min of administration, and the peak level was attained after 30 min⁶⁸. Moreover this particular route of administration has not seen to alter peripheral glucose or plasma insulin levels and was devoid of all the adverse effects associated with peripheral insulin therapy [68].

The detailed description of the clinical trials done with IN insulin in patients with AD or amnesic mild cognitive impairment is given in Table 1. Results from these trials indicate that the IN insulin therapy is a promising approach in AD management. Even though small; but consistent improvement in cognition, memory and AD biomarkers were observed with the treatment. As these trials were conducted in patients with only AD but no diabetes; the results also confirm the safety of IN insulin in nondiabetic-AD patients. Currently IN insulin is in Phase II clinical trial for AD management [69].

However it should note that the observed benefit was small and the duration of treatment was very short in these trials as compared with the duration of disease [70]. Therefore the long term adverse effects of the intranasal insulin is not yet been investigated. Similar to the peripheral insulin therapy exacerbate the peripheral insulin resistance, there may be chances for exacerbation of brain insulin resistance with prolonged IN insulin therapy. This situation enriches the scope for the

second approach that is insulin sensitizer in the management of AD.

Insulin sensitizers

Peroxisome proliferator-activated receptor gamma (PPAR γ) agonists

This class of drugs are also called as thiazolidinediones and their primary mechanism of action is improving the sensitivity of insulin receptors (IRs) [71]. They unlikely causes hypoglycemia on peripheral administration. The advantage of these drugs over insulin is that they have direct action on multiple targets involved in AD independent of insulin signaling. PPAR γ agonists regulates the transcription of β secretase enzyme via the activation of the PPAR γ response element present in the promoter region of the enzyme. Activation of this particular region by the agonists suppress the transcription of β secretase [72]. In addition, they were found to improve the ubiquitination and subsequent degradation of APP [73] and enhance the clearance of A β from the brain [74]. They upgrade the mitochondrial functions and the energy production [75] via the activation of peroxisome proliferator-activated receptor gamma coactivator1 (PGC1) family of proteins [76]. Also, they are directly involved in the regulation of the neuro-inflammation and antioxidant defense mechanisms [77–79]. This class of drugs inhibit [80] the abnormally increased the level of Cyclin-dependent kinase 5 (Cdk5) in AD brain [81]. Even though the Cdk5 are required for the normal functioning, its hyper activation accelerate the NFT formation [82] and neurodegeneration.

The most investigated drugs in this class are the rosiglitazone and pioglitazone. These drugs were appeared to be very much promising in the early preclinical trials. They were found to improve various biomarkers of AD such as plaque formation, NFT, oxidative stress and neuro-inflammation in addition to improving the insulin signaling [77, 83–88]. Unexpectedly, the later clinical trials with these drugs have given only a limited success. The details of these clinical investigation were summarized in Table 2.

The literature survey is pointing towards the involvement of three factors such as “bioavailability of the drug at the target site (that is the brain), stage of drug intervention and the type of dosage form” in limiting the clinical success of PPAR γ agonists. Reports says that these drugs permeate BBB poorly [77, 89, 90] and are the substrate for efflux transporters present at BBB [78, 91] that efflux out the drug entering the brain. Hence the usual diabetic doses via peripheral route is insufficient to deliver a therapeutic concentration in the brain that might lead to therapeutic failure ultimately. On agreement with these observation Morgenweck J, et al. in 2010 had used direct intra cerebroventricular (icv) injection of rosiglitazone to activate PPAR γ receptors of the CNS. They have observed

Table 1 Clinical investigations with IN insulin in AD

Title of investigation	Dose	Duration of treatment	Patient population	Major findings
Effects of intranasal insulin on cognition in memory-impaired older adults: Modulation by APOE genotype ⁷⁰	20 or 40 IU	Single day	Patients with probable AD or amnesic mild cognitive impairment (MIC) or normal controls	IN insulin treatment was seen to improve verbal memory in memory-impaired APOE4 negative adults. The benefit was stronger with memory-impaired APOE4 negative volunteers compared to memory-impaired APOE4 positive subjects and normal control
Intranasal insulin improves cognition and modulates amyloid in early AD ⁷¹	20IU BID	21 days	adults with AD or MCI with amnesic features	It has seen that the memory and cognition were improved in IN insulin treated group. Also there was a decline in the level of insoluble A β 42 in the treatment group. The ratio of soluble A β 40 to insoluble A β 42 was also increased on comparison with placebo.
Intranasal Insulin Administration Dose-Dependently Modulates Verbal Memory and Plasma Amyloid- β in Memory-Impaired Older Adults ⁶⁸	10, 20, 40, or 60 IU	Single day	AD or amnesic MIC or normal adults	It has seen that the IN insulin treatment improved the verbal memory and the peak effect was observed with 20 IU concentration in APOE4 negative volunteers. While a decline in the performance was reported with APOE4 positive individuals and no observable change with normal control.
Intranasal Insulin Therapy for Alzheimer Disease and Amnesic Mild Cognitive Impairment ⁷²	20 or 40 IU	4 months	Mild to moderate AD or with amnesic MIC	Treatment with 20 IU of Insulin improved delayed memory. While both doses preserved caregiver-rated functional ability and general cognition. The improvement in cognition was found to have a direct related with changes in CSF-A β 42 level and tau protein to A β 42ratio.

significant anti-inflammatory and anti-hyperalgesia effects by the activation of CNS- PPAR γ receptors with icv injection of PPAR γ agonist; however no noticeable pharmacological effects have seen with peripheral administration of the drug [92]. Matias et al. in 2017 has used icv injection of rosiglitazone to understand the effect of the drug on food intake regulation in chicks model [93]. Similarly, Zhishuo et al. in 2006 have used the icv injection of 15d-prostaglandin J₂, another PPAR γ agonist to investigate the protective effect of PPAR γ in neurons in cerebral ischemia [94].

Since the diabetic doses via peripheral route is insufficient to manage the AD, all the preclinical trials have used comparatively higher doses [84–88, 95] However, higher doses of these drugs via peripheral route cannot be recommended in human volunteers because of the risk of cardiac toxicity associated with rosiglitazone [96] and the increased risk of bladder cancer associated with pioglitazone [97] in addition to their common side effect that is peripheral edema.

Another crucial factor that determines the bioavailability of a drug is the type of pharmaceutical dosage form. Extended release formulations are usually not suitable for drugs those are the substrate of efflux transporters. The efflux transporters has less impact on higher concentrations of the substrate as the transport activity get saturated on high concentrations [98, 99]. On other hand the extended release formulation releases

the incorporated drug slowly over an extended period of time; the concentration of drug reaching the BBB at every time will be lower to saturate the efflux transporter. Therefore significant amount of the drug that crossed the BBB may get efflux out of the brain. This could be the reason for failure of extended release formulations of pioglitazone and rosiglitazone in their clinical trials for AD. But in place of an extended release formulation, a brain targeted drug delivery formulation might be much more effective in the repurposing of PPAR γ agonists for the AD. In contrast to conventional dosage forms, a targeted drug delivery system offers better bioavailability from a lower dose. The current trend in brain targeting is the intranasal route of administration and nano formulations. Being a direct route to the central nervous system (CNS) the intranasal route of administration bypasses the BBB and offers a direct delivery of the administered drug to the brain. Different types of nanoformulations administered by various route has also seen to be very much effective in targeting the brain. Moreover they have the capacity to escape the efflux transporters at the BBB [100].

The stage of drug intervention is also an important criteria. The drug intervention starting at an advanced stage of disease progression may not be much effective as the early stage drug intervention do. Because the degree of neuronal damage present at an advanced stage of disease progression may

Table 2 Clinical trials with PPAR γ agonists in AD

Title	Patient population	Dose	Key results
Preserved cognition in patients with early Alzheimer disease and amnesic mild cognitive impairment during treatment with rosiglitazone: a preliminary study ⁹⁴ .	MCI or mild AD	4 mg per day or placebo for six months	Rosiglitazone treated group exhibited better delayed recall at Months 4 and 6 and selective attention at Month 6. But there was observable change in the plasma A β levels.
A multi-center randomized proof-of-concept clinical trial applying [¹⁸ F]FDG-PET for evaluation of metabolic therapy with rosiglitazone XR in mild to moderate Alzheimer's disease ⁹⁵ .	Mild to moderate AD	8mg extended--release (RSG XR) for 12 months	The drug treatment was associated with an early improvement in glucose metabolism. There was no sign of slowing of disease progression over one year of treatment.
Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease ⁹⁶ .	Mild-to-moderate AD	2mg, 4mg, and 8mg for 24 weeks	The APOE4 negative patients has shown cognitive improvement with 8mg of the drug while there no change was reported with APOE4 positive patients. In fact, a decline in cognition was noted in the ApoE4 positive group receiving the lowest dose.
Rosiglitazone does not improve cognition or global function when used as adjunctive therapy to AChE inhibitors in mild-to-moderate Alzheimer's disease: two phase 3 studies ⁹⁷ .	mild-to-moderate probable AD	2 mg or 8 mg RSG XR release for 48 weeks	No significant change in the cognition or global function was reported between the for 2 mg or 8 mg RSG XR as adjunctive therapy to ongoing acetylcholine esterase therapy. There was no observable interaction between treatment and APOE4 status.
A randomized pilot clinical trial of the safety of pioglitazone in treatment of patients with Alzheimer disease ⁹⁸ .	mild to the moderate AD	45 mg or placebo	The primary aim of this study was to investigate the frequency of reported adverse effects (AE) in these patients. Other than that of the most common AE of PIO i.e peripheral oedema, no other serious problems were observed. Even then there was no evidence for a clinical benefit.
Pioglitazone improved cognition in a pilot study on patients with Alzheimer's disease and mild cognitive impairment with diabetes mellitus ⁹⁹ .	Patients with both mild AD and type 2 DM	15 or 30 mg or placebo	Treated group was benefited from the improvement in cognition, cerebral blood flow and insulin sensitivity. The magnitude of these effects were seen to proportionate with dose. Still there was no significant change in the plasma A β 40/A β 42ratio
<i>Trial discontinued</i> ⁷³	Healthy older volunteers but at high risk of AD	0.8 mg sustained release	Study was discontinued because of inadequate treatment effects

overwhelm the treatment effect [101]. Therefore only the further studies designed in such a way to overcome the drawbacks of PPAR γ agonists can exactly define their repurposing potential in AD management.

Metformin

Unlike the PPAR γ agonists, Metformin is a BBB permeable insulin sensitizer [102] act via the AMP-activated protein kinase (AMPK). Activation of AMPK phosphorylate and activate the insulin receptors and their by the downstream signaling mediated by insulin [103]. Physiological stresses like energy depletion in cells, oxidative stress etc. also triggers the activation of AMPK [103]. AMPK signaling in the brain cells was found to have major roles in regulating energy metabolism, insulin sensitivity, lipid homeostasis, neuro-

inflammation and also the A β and tau pathology [103–105]. A number of studies reported a down regulation of AMPK in AD brain and the amplification of the down regulated AMPK has seen to ameliorate AD pathology notably [106–108]. Preliminary study in cell line model of AD has shown significant improvement in insulin resistance and AD like changes with metformin treatment [109]. Systemic administration of metformin in a murine model of leptin-resistant obese mice ameliorated the total tau and phospho-tau in the hippocampus [110].

Later, five major clinical trials had investigated the efficacy of metformin in delaying the progression of AD. The initial four trials studied how efficiently metformin lower the risk of development of dementia/AD in patients with diabetes while the fifth trial investigated the efficiency of the drug as a treatment option in AD patients having no diabetes. The

initial trial conducted has reported an elevated risk of dementia among the type 2DM patients; but the incidence of dementia got reduced in the users of metformin and sulphonylureas [111]. Another but retrospective study has investigated the risk of development of AD or dementia in diabetic patients undergoing treatment with different classes of diabetic drugs. According to the investigators, the long term use of metformin increases the risk of AD while other classes of drugs have no effect on development of AD in these patients [112]. In contrast to this report, another prospective study conducted has reported significantly lower the risk of cognitive impairment with the use of metformin for more than 6 years [113]. While the forth study conducted has used a population having no diabetes and no dementia initially. They followed this population till the development of type 2 DM (median follow-up 2.4 years). These patients were followed by the investigators for further 3.1 years to investigate the risk of development of dementia with particular class of diabetic drugs. On agreement with the initial trial, the risk of development of dementia has seen to be lower with metformin and sulphonylureas [114]. The latest study with metformin investigated its efficacy in AD patients having no diabetes. Metformin treatment at a dose of 2000 mg/d (1000 mg twice daily) was found to improve learning, memory and attention. Also by this study it has seen that the drug is safe and well tolerated even in non-diabetic patients at a higher dose [115].

Even though most of the clinical trials with the metformin was success, the most important thing need immediate attention is the vitamin B12 level in these patients as metformin treatment can disrupt the absorption of vitamin B12 in several ways [116, 117]. The deficiency is severe with increasing age, metformin dose, and duration of use [118]. Since Vitamin B12 is an important factor required for normal neuronal functions, its deficiency itself can result neuronal damages and dementia [118]. Agreeing to this reports, another study conducted in patients with diabetes has shown elevated risk of dementia among the metformin users and the association was found to weaken after adjusting the serum vitamin B12 levels [119]. Hence it is highly important to diagnose and maintain the serum Vitamin B12 level during metformin therapy to avoid complications.

Another vital factor need further confirmation is the exact role of AMPK in AD. Even though its role in regulating normal functioning of the brain is proven, consistent activation of AMPK happening in cellular stress condition is neurotoxic [107, 120]. There were also reports supporting the abnormally increased activation of AMPK in AD and even reports for the amelioration of AD characteristics on treatment with AMPK inhibitors [121–123]. Interestingly Chen Y et al. in 2009 has reported an enhanced biogenesis of A β by up-regulation of β secretase in the cell line models with metformin at a concentration that activate AMPK. However a combined use of insulin with metformin enhanced the insulin's effect in reducing

A β plaques [124]. This study was further supported by Picone P in 2015 and Min Son S et al. in 2016. Picone P et al has reported increased expression of APP with metformin treatment which, in turn, promotes aggregation of A β . Also the drug has shown to induce oxidative stress, mitochondrial dysfunction and activation of NF κ B in in vitro, ex vivo and in vivo models [125]. Min Son S et al. reported metformin treatment promote the activation of both β secretase and γ secretase enzymes in AD models [126].

Even though metformin was appeared to be a promising molecule in majority of the clinical trials; there are few clinical and preclinical investigations showing negative results too. The degree of activation of AMPK might have played the major role here. Is there any changes in the degree of AMPK activation with disease progression or with coexisting diabetes need to make clear as the trials with metformin had conducted at varying stage of disease progression and coexisting sdiabetes?

Insulin secretogauges

Sulfonylureas

The mechanism of action of sulfonylureas in the diabetes is stimulation of the insulin secretion from the pancreas by closing ATP-sensitive K⁺ channels (KATP) in the β -cell plasma membrane [127]. KATP channels of the brain were found to have specific role in regulation of cognition and normal functioning of the brain independent of insulin signalling. Icv modulation of KATP channels by channel openers have shown to impair the memory of healthy rodents; while this effect was impede upon treatment with channel blockers [128–130]. Salgado-Puga K et al. has observed beneficial effect of specific KATP channel blocker-Tolbutamide on memory and synaptic plasticity even in subclinical dose [131]. Contradictorily, Liu D et al. in 2010 has reported amelioration of A β and tau pathology along with memory enhancement upon treatment with KATP channel activator-diazoxide [132]. Eventhough initial study with glipizide has shown to improve the learning of verbal materials in type 2DM patients and cognition in patients with both AD and type 2 DM [133], later it is been confirmed that in general long-term use of sulphonylureas does not alter the risk of development of AD [112].

According to the Literature, majority of the insulin in the brain comes from the periphery [134], hence the peripheral insulin secretion induced by usual diabetic doses of sulphonylureas are sufficient to manage the brain insulin impairment is an uninvestigated side. Also, there are lot of evidences for the local release of some small quantity of insulin from the cortical and hippocampal neurons in the brain [135–138]. Interestingly, the molecular mechanisms involved in the local release of insulin in the brain is also found to be KATP channel dependent [139]. Whether the sulphonylureas have any effect on

the local insulin release at the investigated doses is unclear yet. Another factor that might influence the repurposing potential of these drugs is the altered expression of KATP channels of brain in AD. Although KATP channels present in neurons are found to preserve in AD state in the previous investigations [140], according to the latest reports, expression of KATP channels are aberrant in AD [141]. Therefore further studies are required to resolve the troubles and uncertainty in the repurposing of sulphonylureas for AD management.

Glucagon-like peptide-1 (GLP-1) analogs

More recently glucagon-like peptide-1 (GLP-1) becomes another important target. It is an insulinotropic peptide secreted by small intestinal L cells following food intake [142]. GLP-1 stimulates the insulin secretion, inhibit glycogen secretion, decrease food intake and delay the gastric emptying peripherally. GLP-1 receptors are widely distributed in the brain [143, 144]. It passes the BBB and binding of GLP-1 with its receptors in the brain activate the pathways that coverage with insulin signaling pathway. Thus facilitate insulin signaling by modulating the PI3K/Akt and mitogen activated protein kinase (MIPK) pathways [116]. Activation of MIPK pathway induce the construction of genes involved in the cellular growth, repair and differentiation [145, 146]. GLP-1 also activates the adenyl cyclase that interns increases the intracellular cAMP that open the Ca²⁺ channels in the neurons and thus the release of neurotransmitters involved in cognition and memory [147]. Also the Ca²⁺ response to glutamate and membrane depolarization regulates the neuronal plasticity and cell survival [148]. Since the GLP-1 is having a very short half-life, novel GLP-1 analogues were introduced and are freely permeable across the BBB. The preclinical investigations with the two GLP-1 analogous such as liraglutide and extendin-4 in the AD model was found to improve various biomarkers of the AD. Overall improvement in insulin signaling, plaque formation, NFT formation, neuro-inflammation, oxidative stress, neurodegeneration and synaptic plasticity [148–153] have observed with the treatment. Later, a pilot clinical study was conducted to evaluate the efficacy of Liraglutide in nondiabetic AD patients over a period of 6-months. The treatment improved the declining brain glucose metabolism. But there was no significant change in the cognitive function as compared to the placebo group; probably because the duration of therapy was short to bring a change in cognition [154]. Presently, the drugs liraglutide and exenatide are under phase 2 clinical trial for the AD.

Leptin – A centrally acting agent

Leptin is an adipokine produced in adipose tissue, activates central nervous system (CNS) networks to regulate food consumption and energy expenditure. As summarized by

MarwarhaG et al. in addition to the metabolic functions, leptin also have major roles in the neuronal functioning including memory task [155]. In the preclinical models, Leptin treatment was found to reduce the A β plaque formation, BACE1 activity [156] and tau hyperphosphorylation [157]. While the neurogenesis [148], and spatial learning and memory were improved by leptin therapy [149]. Moreover, elevated levels of leptin in human beings is found to reduce the chances of development of the AD [150].

The major challenge for the repurposing of leptin may occur in the AD patients with obesity. Obesity is another recognized risk factor for the AD independently of insulin resistance or other vascular risk factors [158]. Obesity can lead to a leptin resistance state [159] that interns reduces the transport of leptin across the BBB [160]. Since the prevalence of obesity is increasing even among elderly; it will be challenging in obese patients to obtain a therapeutic concentration of leptin in the brain via conventional route. The applicability of various pharmaceutical techniques to achieve a targeted delivery of therapeutic agents to the brain hopefully can overcome the situation. Research in this area has been already started at the preclinical level where Fernandez-Martos CM et al. delivered leptin intranasally to the mouse model of AD in combination with intraperitoneal injection of pioglitazone [88]. Even though there are evidences supporting the use of leptin for the AD management [161–163], the clinical researches with this particular agent is very much limited. Hence it is required to conduct further studies especially with AD patients to confirm the practicability of leptin as a therapeutic agent in the AD management.

Discussion

It is almost 20 years that the involvement of impaired insulin signaling in the development of the AD has been identified. Till on date a great number of investigations have done in this area and almost all the diabetic drugs were investigated in several times for their repurposing potential in AD. The hypothesis of impaired brain insulin signaling in the AD is widely accepted, even then the success of many of the diabetic drugs in AD was found to be limited. Few of these drugs are still under clinical trial while the trials with few others have discontinued. Although most of the diabetic drugs are capable of managing the central insulin signaling impairments, it has observed that the same diabetic treatment approach may not work as well in AD. This is because the two diseases are entirely different in their pathogenesis and origin even though the primary cause of the two is appeared to be the same. Moreover these drugs are originally designed to manage the peripheral insulin signaling, hence they have their own limitations for their repurposing.

First of all, it cannot guarantee that a dose optimum for managing the diabetes is also optimum for the AD management as the brain is a BBB protected organ and bioavailability of the drug at the target site is dependent on its rate of permeability across the BBB. Few of the diabetic drugs permeate the BBB poorly (eg PPAR γ agonists) while the rate of permeability of insulin and leptin is seen to alter with coexisting peripheral insulin resistance and obesity respectively. Moreover permeability of the insulin across the BBB is reported to declining with aging. Even though the IN insulin has used the usual diabetic doses, the concentration of insulin reaching the brain from the intranasal route will be much higher than that from the peripheral route since this is the direct route to the CNS bypassing the BBB. The results published until now supports the use of IN insulin therapy in the AD management. But the long term side effects like exacerbation of brain insulin resistance with insulin therapy is not yet been investigated. Sometimes a combination of insulin with insulin sensitizer may much more advantageous since both the components of insulin resistance and insulin deficiency is present in AD brain. With an insulin sensitizer, a lower dose or physiological concentration of insulin is adequate to execute the normal physiological functioning of the insulin resistant patients [164–166]. Also, such a combination probably limits the exacerbation of insulin resistance associated with prolonged insulin therapy. Even though these combinations were investigated in the diabetes, no such studies are studied in AD.

PPAR γ agonists (rosiglitazone and pioglitazone) and metformin are the most investigated insulin sensitizers in the AD. Even though the PPAR γ agonists were appeared to have direct action on multiple targets involved in the AD, their properties of poor BBB permeability and being a substrate for the efflux transporter limited their success. Therefore it is required to administer higher doses via the peripheral route to achieve a significant concentration in the brain; which cannot be recommended due to the serious peripheral side effects. This situation enrich the scope of a brain targeted drug delivery system for the repurposing of PPAR γ agonists for AD management. The risk of dementia in the diabetic patients was found to be lower with the BBB permeable insulin sensitizer metformin. Metformin was also found to manage the symptoms of AD patients who were nondiabetic. As the metformin treatment can result vitamin B12 deficiency, regular monitoring and maintenance of vitamin B12 level in the treatment population is necessary. Another factor appeared to alter the response of metformin in AD patients was found to be the AMPK. The exact role of the AMPK (primary target of metformin) in AD is unclear. There are evidences for both the down regulation as well as the up regulation of AMPK in AD. There might be a possibility for the change in AMPK activation with the progression of the disease; however further studies in this direction are necessary to confirm this observation and thereby to optimize the stage of drug intervention with metformin.

Another way to boost brain insulin signaling is the insulin secretogauges such as sulfonylureas and GLP-1 analogues. Unfortunately, sulphonylureas have given only a limited success in AD clinical trials. The specific reasons that has limiting their success in AD is unclear yet. In contrast to sulfonylureas, GLP-1 analogues having direct action on certain targets involved in AD, have reported with notable improvement of the disease state. Moreover the risk of development of hypoglycemia with GLP-1 and its analogues were very much lower on comparison with sulfonylureas. Currently these the two GLP-1 analogues such as liraglutide and exenatide are under phase 2 clinical trial for the AD. Leptin, a centrally acting agent was also reported to have beneficial effects in AD pathology. Since the coexisting obesity can inversely influence the bioavailability of leptin, application of novel techniques are sometimes required to ensure a therapeutic concentration of the drug in brain in these patients.

Conclusion

Growing evidences suggests that AD, the most common cause of dementia among elderly is a metabolic disorder associated with impaired insulin signaling in the brain and hence is also termed as type 3DM. Even though the primary cause of type 2DM and the AD is appeared to be the insulin signaling abnormality, both the disease are entirely different. So the therapeutic success of the diabetic drugs in AD is observed to be depend on certain properties of these drugs such as their primary targets, specific role of these targets in AD, the BBB permeability of these drugs and stage of drug intervention. Hence the same formulation approaches or doses work well in type 2DM may not work in AD for drugs such as peripheral insulin, PPAR γ agonists and leptin (in obese patients). The possible change in the degree of activation of primary targets of drugs like metformin and sulphonylureas made the stage of drug intervention of the drug highly important. Hence, at first, it is necessary to understand the properties of the drugs as well as its targets in AD very well in order to optimize the use of these drugs in the clinical management of AD.

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Compliance with ethical standards

Conflict of interest The authors report no conflict of interest.

Abbreviations AD, Alzheimer's disease; $A\beta$, Amyloid beta; *ApoE4*, Apolipoprotein E4; *APP*, Amyloidprecursor protein; *BBB*, Blood brain barrier; *cdk-5*, Cycline dependent kinase 5; *CNS*, Central nervous system; *CSF*, Cerebro spinal fluid; *CS*, Chitosan; *GLP-1*, Glucagon-like peptide-1; *GSK-3*, Glycogen synthase kinase 3; *IDE*, Insulin degrading enzyme; *IGF*, Insulin like growth factor; *IR*, Insulin receptors; *IN*, Intranasal; *MAPK*, Mitogen-activated protein kinases; *MCI*, Mild cognitive impairment; *NFT*, Neurofibrillary tangles; *NIA*, National institute on aging; *NMDA*, N-methyl-D-aspartate; *PEG*, Polyethylene glycol; *PET*, Positron emission tomography; *PI3K*, Phosphatidylinositol 3-kinases; *PLGA*, Poly lactic-co-glycolic acid; *PPAR γ* , Peroxisome proliferator-activated receptor gamma; *ROS*, Reactive oxygen species; *TNF α* , Tumor necrosis factor alpha

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