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The Links between Brain Insulin Resistance and Alzheimer's Disease

Negar Khezri, Golnaz Yaghoubnezhadzanganeh, Amirreza Attarzadeh

***Abstract*—**Type 2 Diabetes (T2DM) and Alzheimer's disease (AD) are two main health problems influencing millions of people in the world. Neuron loss and synaptic impairment that interfere with cognition and memory cause for the behavioral indications of AD. While it is now accepted that insulin has central neuromodulatory purpose, it was contemplated for many years that brain is insusceptible to insulin, involving its function in memory and learning, which are impaired in AD. The common characteristics of both AD and T2D are impaired insulin signaling, oxidative stress, the excitation of inflammatory pathways and unqualified glucose metabolism. This review summarizes how the recognition of these mechanisms may lead to the development of alternative therapeutic approaches. Here we summarize how the recognition of these mechanisms may lead to the development of alternative therapeutic approaches.

***Keywords*—**Alzheimer's disease, diabetes, insulin resistance, neurodegenerative.

I. Introduction

AD only recently stopped being narrowly understood as a kind of neurodegenerative dementia associated with irregularly elevated levels of neurofibrillary tangles and amyloid b (Ab) plaques in the forebrain. The contemporary definition of AD is broader and includes the pathophysiological processes responsible for the gradual onset of dementia [1], [2]. Because only a small group of cases are the result of inherited genetic causes [3], the etiology and pathogenesis of intermittent, late-onset AD are still not fully understood. Some studies have drawn the conclusion that AD is a kind of diabetes specific to the brain [4], [5]. AD and T2DM are both age-related disorders of a largely coincidental nature [4]. On the basis of the over two decade-old Rotterdam study providing epidemiological evidence of a link between dementia and diabetes [6], even more evidence has been provided in support of a link between the two conditions. The risk of dementia is twice as high for patients with T2DM [7], [8]. A further association between diabetes and major depressive disorders has also been suggested to highlight the link between cognitive dysfunction and AD [9]. Elevated glycaemia increases the risk of dementia for non-diabetic individuals by 18% and has been linked to a reduced hippocampal volume and cognitive decline [10], [11]. The occurrence of AD has also been shown to have a positive correlation with hyperinsulinemia and hyperglycemia [12], [13].

T2DM is a complicated metabolic disorder accompanied by high levels of glucose in the blood, the increased production of hepatic glucose, and the failure of pancreatic β-cells and insulin receptor to produce insulin [14]. T2DM is characterized by the resistance of peripheral organs to insulin, specifically muscle, the liver, and adipose tissues [15]. The two primary forms of diabetes, differentiated by etiology, are Type 1 diabetes, which involves the complete absence of insulin due to the autoimmune destruction of pancreatic b-cells, and T2DM, which is characterized by the combination of insulin resistance and decreased insulin secretion. Insulin performs both neurotropic and neuroprotective roles, as well as regulates synaptic plasticity in neurons [16], [17], making it an important means of modulating cognition (reviewed in [18]). Significant epidemiological evidence has also established a link between cognitive impairments and both types of diabetes [19]. Of note is the impairment of the pathway for signaling insulin in AD brains discovered by some studies [20], (reviewed in [21]) using a diversity of *in vivo* and *in vitro* experimental AD models, including non-transgenic and transgenic animal models [22]-[24]. Overall, these conclusions highlight insulin resistance as a common molecular mechanism linking AD and diabetes.

AD is one of the more common neurodegenerative disorders and involves neuronal and progressive memory loss, and the buildup of two poorly-soluble abnormal structures in the brain: amyloid plaques generated from Ab peptides, produced by the c-secretase complex and the b-site amyloid b precursor protein (APP) cleavage enzyme 1 (BACE1) from the sequential cleavage of the APP [25], and neurofibrillary tangles generated from the neuron-enriched, microtubule-associated protein, tau. The behavioral deficits attributed to AD are due to the synaptic dysfunction and death of memory and cognition-mediating neurons. The reduced function and viability of neurons are mediated by the biological and biochemical relationships between tau and Ab, particularly the soluble forms that serve as the foundation of plaque and tangles [26]. Some researchers have taken the view that the reduction in brain insulin signaling found in AD is proof that it is a form of T2D known as type 3 diabetes (T3D), especially when it is accompanied by evidence of altered CSF insulin [20], [27]. This conclusion is misrepresentative and the resistance to brain insulin found in AD cases is not T3D, although it has been posited that [28] neuronal insulin resistance syndrome is feature of AD.

Apart from the apparent metabolic implications, relatively

N. K. and G. Y. are with the Pharmacy Department, Eastern Mediterranean University, Famagusta, North Cyprus (e-mail: negarkhezri1371@gmail.com, ynzgolnaz@yahoo.com).

A. A. is with Economics Department, Eastern Mediterranean University, Famagusta, North Cyprus (e-mail: amirreza_attarzadeh@yahoo.com).

little was known about the relationships between specific AD phenotypes and reduced brain insulin signaling. Oddly, no proof of ectopic neuronal cell cycle re-entry (CCR) creating new neurons by dividing cells exists. Instead, CCR appears to be followed by neuron death accounting for as much as 90% of all AD-related neuron loss [29]. The resistance of the brain to insulin could indicate a lesion that significantly precluded the emergence of AD, or could alternatively occur after synaptic function and neuronal life-span have already been compromised by signaling processes. While the position of T2D as a risk factor for AD [30] presents insulin resistance in the brain as a causative factor, virtually nothing is known regarding the underlying causative mechanisms. The proceeding sections offer a review of contemporary research establishing a link between deficiencies in brain insulin signaling and the neurotoxic impact of Abs in AD. The apparent similarity between the pathways responsible for insulin dysfunction in AD and insulin resistance in diabetes provides the basis for a discussion of the molecular justification for the use of antidiabetic agents in AD treatment.

II. Insulin Signaling

Insulin is a b-cell hormone produced by the pancreas to counteract elevated glucose levels from feeding. Insulin signaling physiologically begins when insulin is recognized and then bound to a transmembrane tyrosine kinase receptor, the insulin receptor (IR). The IRs, once activated, then phosphorylate a preserved group of adaptor proteins known as insulin receptor substrates 1 through 4 (IRS-1 through IRS-4) [31]. These IRSs then differentiate insulin stimulation into various unique pathways, the most important of which is the phosphoinositide 3-kinase (PI3K)/murine thymoma viral oncogene homolog (Akt)/mammalian target of rapamycin (mTOR) pathway, thereby permitting cells to be metabolically and transcriptionally reprogrammed [32]. The better-studied IRS-1 and IRS-2 substrates can be dissociated from the IR by undergoing inhibitory serine phosphorylation (pSer), which can also decrease tyrosine phosphorylation (pTyr) [32] consequently inhibiting downstream insulin signaling. Downstream insulin signaling can also be regulated by dephosphorylating tyrosine residues in IR and IRS-1 using the protein tyrosine phosphatase 1B (PTP1B) [33]. The central nervous system (CNS) is covered in enzyme insulin, IR and its substrates [34]. Brain insulin regulates body weight and food intake [35], as well as synaptic plasticity and neurotransmitter release, [36], thereby making it important for learning and memory [37]. Havrankova first highlighted the presence of IR in the brain, which has since been confirmed by others [38]. Insulin binds to the abundant but selectively-distributed insulin receptors (InsRs) in the brain. Studies involving rodents have found that the nerve terminals of crucial brain regions like the cerebellum, olfactory bulb, cerebral cortex, hypothalamus, and hippocampus contain the highest IR concentrations [18], [39], [40]. Insulin signaling is of particular importance for cognitive function in the hypothalamus and the limbic system, and is unaffected by changes in peripheral glucose [30]. While insulin is present in the CNS, virtually none of it is locally produced. Insulin in the CNS is gotten from circulation and is able to cross the BBB due to a blood-to-brain saturable transport system [41]. The regulation of this transport system is performed by triglycerides, nitric oxide, hibernation, inflammatory events, glucose, obesity and the diabetic state independent of glucose [42]. Pancreatic b-cells synthesize most of the insulin that gets to the brain [43], while the brain synthesizes a small portion. The synthesis of preproinsulin 1 and 2 mRNA and insulin occurs in neuronal cells but not in glial cells [44]. The importance of insulin for the CNS goes beyond the metabolism of glucose. It has also been described as neuroprotective [45] and important for neuronal growth and survival [46], [47]. One recent study found an increased number of peripheral IR biomarkers in the hippocampus of AD patients without diabetes [28]. The impact of these studies is that the pathology of AD pathology is now understood to include defective brain insulin signaling [48].

A. Insulin Resistance

Peripheral metabolic disorders like T2D are characterized by decreased cellular responsiveness and insulin signaling caused by pro-inflammatory signaling and extended metabolic stress [49]. Known as insulin resistance, these pathological states exert a negative influence on cell capacity to sustain energy homeostasis. Remarkably, similar abnormalities are present in AD brains, including neuroinflammation and metabolic stress [22], [28], [50], [51]. The combined focus of the research was on whether neural changes in an AD brain are related to T2DM. Microvascular injury in the brain caused by T2DM can generate and/or accentuate the neuropath logical symptoms of AD even if it is not directly linked to the AD neural substrate [52]. It is therefore conceivable that a similar mechanism can be used to explain peripheral insulin resistance in T2D and the diminished insulin signaling in AD brains. In fact, recent studies have established a link between diabetic peripheral insulin resistance and AbO-triggered neuropathogenic mechanisms [21], [22]. Hoyer et al. first suggested the idea of brain insulin resistance in AD about two decades ago [53] when they hypothesized that the reduction in brain glucose metabolism is due to the desensitization of neuronal IRs. While some [28], [54], but not all [55], studies found IR sensitivity to be reduced in the hippocampus and/or neocortex of AD brains, no conclusions have been drawn about the link to decreased brain glucose metabolism since insulin is known to have no independent effect on forebrain neuronal glucose absorption [18], [28] and they tested their hypotheses using intracerebroventricular (ICV) streptozotocin (STZ) in rodents [56]. STZ is a nitrosamide methyl nitroso urea associated with the C2 position of D glucose. N-nitrosoureido is released once it has been metabolized and damages DNA by generating reactive oxygen types like nitric oxide, hydrogen peroxide, and superoxide [57]. The peripheral administration of STZ is a proven source of diabetes mellitus accompanied by moderate hepatic steatosis and neurodegeneration [58]. Insulin-producing cells like beta cells absorb the STZ in pancreatic islets [59] thereby damage the β-

cell. In fact, long-term cognitive behavioral deficits were observed in rats after the ICV injection of STZ, which decreases insulin by terminating pancreatic β-cells [60] as were neurodegenerative symptoms akin to those in AD without the added effect on insulin and peripheral glucose levels [54]. Insulin treatment could be used to prevent these deficits. Deficits in brain insulin signaling are partially responsible for the cognitive impairment in AD and diabetes [61]. These conclusions present IR as a common trigger in the development of both AD and T2DM. As such, sporadic AD (SAD) manifests itself as a form of T3D responsible for even more functional and structural brain changes. The available data render the application of this model to humans questionable as STZ is not widely available to humans. Conversely, the hypothesis posits STZ as a compound related to nitrosamine and Western societies have experienced an increase in exposure to environmental and food-related nitrosamines over recent decades [18]. The causal link between sub-mutagenic nitrosamine doses in food, e.g. N-nitrosodiethylamine (NDEA) and IR-related disorders has been experimentally proven [39]. Some studies have also shown that similar to STZ, even limited low-dose exposure to NDEA can cause visceral obesity, cognitive impairment, non-alcoholic steatohepatitis, T2DM, and AD-type neurodegeneration with peripheral and brain IR [61].

The discovery that Ab Oligomers (AbOs) provoked the rapid and wide-ranging redistribution of IRs into the somatic cytoplasm from the surfaces of cultured neuron dendrites through the entry of calcium into the dendrites via NMDA receptors provided one of the earliest insights into neuronal insulin insensitivity [62]. It is unlikely that this process is dependent on the synthesis and degradation of proteins as it occurs < 30 mins after exposing the neurons to AbOs; it is more likely a reflection of the increase in the IR endocytosis to exocytosis ratio. While it is not yet known which mechanism is responsible for the altered IR trafficking, the functional repercussion is that the IRs are secluded from the extracellular space and cannot be accessed by the ligands to which they need to bind to begin insulin signaling. In addition to this IR sequestration, AbOs also decrease neuronal insulin signaling by inducing the secretion of aberrant tumor necrosis factor-a (TNFa) in cultures containing neurons, which are then bound to neuronal TNFa receptors and cause the stress kinase c-Jun Nterminal kinase (JNK) to activate [63]. The activated JNK causes IRS-1 serine phosphorylation (IRS-1pSer), thereby blocks insulin signaling and leads to peripheral insulin resistance [49]. Similarly, it was recently discovered that AbOs initiate the irregular activation of the TNF-a/JNK pathway and IRS-1 inhibition in principal hippocampal neurons [22], as well as in the hippocampi of cynomolgus monkeys subjected to ICV infusions of AbOs. The inhibition of IRS-1 was also proven in the brain of an AD model using a transgenic mouse [22]. Demonstrating the increased IRS-1pSer [22], [28] and activated JNK in AD brains postmortem was the most important step in ensuring these findings were clinically relevant. Microglia are a source of the TNFa behind this process. While AbOs are known to regularly target neurons, they also affect microglia. TNFa was discovered to be secreted when primary microglia were exposed to AbOs, and in turn motivate the activation of JNK in primary neurons [64]. Since microglia are common components of primary neuron cultures, it is probable that some of the deficiencies in neuronal insulin signaling that are resulting from the exposure of primary neurons to AbOs, was triggered by TNFa derived from the microglia. Primary neuron cultures are also significantly populated with astrocytes, which are another potential source of TNFa in cultures treated with AbO [65].

III. IR Reduction in AD

In an effort to determine if exposing neurons to AbOs *in vivo* influences insulin signaling in any other ways, western blotting and quantitative RTPCR were used in measuring protein and IR mRNA in human brain tissue samples [20]. To test brain insulin resistance in AD, tests were run and due to diabetic conditions, cases with a history of diabetes were excluded [28], [66]. IRS-1 was the first molecule in this signaling pathway showing severe dysfunction, which, accordingly, seems to be a central factor in brain insulin resistance. The subsequent *ex vivo* stimulation studies [67] have shown that brain insulin resistance can develop early in AD, even in the absence of diabetes. In contrast, basal (i.e., not insulin stimulated) levels of activated or suppressed forms of those molecules below the IR were all increased in the same AD cases [28]. Unlike insulin resistance, IGF-1 resistance was severe, even at the level of the hormone receptor. The significance of this phenomenon remains to be determined.

A. Inflammation

Inflammation is an important characteristic of diabetes and AD is of vital importance for the pathogeneses of both disorders [49], [68] and has been posited as an auto inflammatory disease [69]. Similar inflammatory processes are believed to take place in the brain, as well as surrounding tissue [40], [70]. Patients with T2D have been reported as having higher circulating levels of chemokines, cytokines, and acute-phase proteins [71], [72], as well as a reduced IL-1 receptor antagonist, higher level of b-cell IL-1b, and local inflammation in the pancreatic islet, evidenced by the increased number of islet-associated macrophages [73]. AD has similarly been associated with a wide selection of inflammatory and immune pathways with post-mortem brains displaying significantly unregulated levels of pro-inflammatory chemokines, cytokines, and complement proteins. Impartial microarray research has also highlighted the increased expression of inflammation-related genes [74], [75]. Furthermore, a number of studies have genetically confirmed inflammation to be a powerful driver of AD pathology in mouse models based on a review by [76]. A methodical review of epidemiological studies provides evidence of an association between a reduced risk of AD and the consumption of non-steroidal anti-inflammatory drugs (NSAIDs) [77].

B. mTOR Deregulation in AD

In mammals, the target of rapamycin (mTOR) is a serine/ threonine kinase. The functional forms of mTOR are integrated into one of two multi-protein, membrane-associated complexes: mTOR, mLST8 and raptor assemble in mTORC1 and mTOR, mLST8 and rictor in mTORC2 (reviewed in [78]). These two complexes are collectively responsible for how cells react to extracellular cues, such as growth factors, insulin, and nutrients like glucose and amino acids [79]. mTORC1 is primarily involved in controlling cell growth, while the major function of mTORC2 is survival and proliferation [80]. mTORC1 mainly functions by activating S6K and ATF4 and inhibition of 4EBP [81], while mTORC2 operates by activating SGK, PKC and Akt [82]. By testing cultured mouse neurons and transgenic mice, it was discovered that CCR requires the activation of both mTORC1 and mTORC2 by AbOs to proceed, and that mTORC1 activation is required for tau phosphorylation at S262 [83]. The AbO-facilitated activation of mTORC1 was discovered to be unconventional. While mTORC1 is typically activated at the lysosomal surface by other stimulants, thereby resulting in autophagy suppression [79], mTORC1 activation by AbOs occurs at the plasma membrane. Interestingly, this mislocalized mTORC1 activation is dependent on both the presence of tau and its mTORC1-dependent phosphorylation at S262 [83]. AbOs consequently instigate a toxic feedback loop between mTORC1 and tau, in which the former must induce tau phosphorylation at S262 to enable the latter gather at the plasma membrane, rather than the lysosomes. Tau phosphorylation at this site is likely catalyzed by S6K, rather than by mTORC1 directly; S6K is phosphor-activated by mTORC1 and phosphorylates tau at S262 [84]. Finally, it is possible to inhibit CCR by stimulating lysosomal mTORC1 using one of numerous experimental manipulations – like adding insulin to the culture medium [85] – while AbOs simultaneously activate mTORC1 at the plasma membrane. Collectively, research into AbO-induced neuronal CCR [83], [85] and AbO-induced insulin resistance [22], [74] suggests the toxic potential of AbOs to cause CCR and eventually neuron death is due to their ability to hinder neuronal responses to insulin. In fact, CCR can already be detected a few hours following the exposure of neuron to AbOs, suggesting that this occurrence is especially important in the pathogenesis of AD and could happen to individual neurons for many years during the disease's presymptomatic stages. Furthermore, the occurrence of neuronal CCR is independent of the incorporation of tau and Ab into tangles and plaques respectively, despite being initiated by Ab and proceeding using a tau-dependent mechanism.

C. Cerebroenergetic Failure

An unusual characteristic of AD is a significant reduction in the energy metabolism of brain areas that are affected [86]. Insulin's primary role in the CNS is the stimulation of glucose uptake into tissues using glucose transporters (GLUTs 1–8), [87]. The synthesis of numerous neurotransmitters responsible for cognitive function and synaptic plasticity, such as glutamate, GABA, dopamine, acetylcholine, amongst others, requires the use of glucose. In contrast to the noral ageing process where the cerebral energy pool decreases only slightly, sporadic AD impairs both the production and utilization of energy [88]. Seemingly hypothetical, describing AD as "diabetes mellitus of the brain" is nonetheless interesting in light of the growing body of evidence of similarities in the biochemical irregularities observed in glucose hypo-metabolism AD and T2DM [89]. Furthermore, the IR-induced hyperglycemia observed in T2DM is also attributed to glucose hypo-metabolism and energy failure [90]. These findings point to a shared link in the pathogenic molecular mechanisms of AD and T2DM.

D. Oxidative Stress

The emergence of mitochondrial dysfunction and oxidative stress is partly caused by cerebroenergetic failure [91]. Oxidative stress is the result of an imbalance between the antioxidant capacity of the cell and the amount of free radicals generated by metabolic activity, thereby causing lipids, nucleotide, proteins, and their damaged biological activities to be attacked and eventual cell death. The disproportionate production of free radicals can be caused by hyperglycemia [92]. Mitochondrial dysfunction enhances the generation of ROS, decreases the production of ATP, and impairs the functioning of the electron transport chain. A substantial body of experimental and clinical evidence exists showing enhanced oxidative stress in both T1D and T2D [93] as a part of the diabetic neuropathy [92], [94]. AD brains also display a heightened expression of the pro-oxidant enzymes responsible for catalyzing the introduction of reactive nitrogen (RNS) and oxygen species (ROS) like nitric oxide synthase (NOS) and NADPH oxidase (NOX). The observations that the formation of Ab plaque precedes oxidative damage [95] and the upsurge in RNS corresponds to the beginning of Ab deposition observed in a transgenic AD mouse model [96] led researchers to hypothesize that enhanced Ab production can be triggered by oxidative stress. This contention is backed by sufficient experiential evidence illustrating how the expression of b-secretase and c-secretase is regulated by oxidative stress, which also promotes Ab production and the amyloidogenic processing of APP [97], [98]. It is noteworthy that recent studies have reported the possibility of Ab interaction with mitochondrial proteins, disrupting the electron transport chain, promoting mitochondria dysfunction, and the generation of ROS, thereby supporting a vicious cycle [99]. Furthermore, oxidative stress can increase tau hyperphosphorylation and ensuing tangle formation by transforming and disturbing peptidyl-prolyl cis–trans isomerise Pin1 [100]. Redox proteomics analysis has been used to identify other oxidatively-modified proteins in the AD brain hypothetically relevant to the pathogenesis of AD [101].

E. Tau Tangle Formation

The role of the unusual tau phosphorylation in the pathophysiology of AD was identified in the 1980s [102]. The folding of tau protein with tubulin is generally used to enhance

vehicular transport and microtubule formation. When hyper phosphorylated, tau becomes insoluble and becomes less compatible with microtubules, resulting in the formation of neurofibrillary tangles (NFTs) [103]. NFTs are a hyper phosphorylated and cumulative form of tau protein, the accumulation and pathology of which correlate most significantly with dementia in AD [104]. In fact, different animal AD, obesity, and T2DM models with a reduction in insulin signaling have been found to have higher levels of insoluble hyper phosphorylated tau and the deposition of NFTs [105], [106] As a result, a reduction in insulin signaling appears to encourage NFT formation, give on to the loss of synaptic connections, interrupt neuronal cytoskeletal networks and axonal transport, and incremental neurodegeneration. Collectively, these conclusions insinuate that the onset of AD and its severity are heightened by IR, particularly in cases with a tendency towards tau pathology [40].

IV. Anti-Diabetic Drugs in AD

Most proposed approaches to AD treatment till date have resulted in disappointing failures in clinical trials [107]. Experimental evidence is increasingly establishing the different links between the pathogenic mechanisms of AD and T2DM/metabolic diseases, and the vital role of insulin in the growth and development of neurons rationalizes the use of anti-diabetic agents in modern AD therapies. Similarly, a number of potentially successful insulin-based AD treatment strategies have also been developed [21]. Insulin signaling diminishes overtime as part of the ageing process [108]. Since age is an important AD risk factor, this suggests that patients with AD might benefit from the restoration of insulin signaling.

Because the systemic administration of insulin has a problematic impact on the periphery, intranasal insulin delivery provides a seemingly harmless and efficient alternative method of increasing concentrations of CSF insulin without affecting the levels of systemic insulin and glucose. Particularly interesting is the discovery that the intranasal administration of insulin, a preferred method of CNS delivery [109], enhances memory function, such as in the delayed word recall test for young adults with a normal cognitive capacity [110], improves verbal memory in subjects with mild cognitive impairment (MCI) and AD [111], enhances declarative memory and selective attention performance in patients with early-onset AD, and also implying an increase in Aβ clearance and reduced amyloid pathology. Some studies, however, have suggested that only patients with ApoE-ε4-negative genotypes can be effectively treated using intranasal insulin [112].

When the number of surface IRs is reduced in the later stages of AD, insulin can be used to stimulate alternative receptors (e.g., insulin-like growth factor 1 (IGF-1) receptors) and continue to improve the deficiencies caused by AD. Regardless, the evidence provided by these studies suggests that intranasal insulin could still be used in the treatment of patients with early AD and MCI. Alternative strategies could also be employed, such as using insulin sensitizers like peroxisome proliferator-activated receptors [(PPARs) PPAR-γ] and glucagonlike peptide-1 (GLP-1) agonists, both known to have therapeutic benefits similar to intranasal insulin. PPARs are a group of nuclear receptors responsible for regulating how the genes used in lipid and glucose metabolism are transcribed. Clinical tests of pioglitazone and rosiglitazone – PPAR-γ agonists in T2DM, MCI, or AD patients have generated mixed results. While this shortcoming hindered any further development, this position needs to be reevaluated [113]. Incretins, glucose-dependent insulinotropic peptide (GIP) and GLP-1, are a family of GI hormones capable of affecting how the entire body utilizes glucose [114]. GLP-1R agonists were recently posited as an additional/alternative therapeutic approach to insulin-based AD therapies. GLP-1 analogs or mimetics are a top choice amongst drugs marketed for development as AD therapeutic agents [115]. Glucagon-like peptide 1 receptor (GLP-1R) agonists have been identified as activating pathways commonly used for insulin signaling and facilitate the plasticity of hippocampal synapses, cognition, and cell survival [116], [117]. GLP-1 analogs such as Exendin-4 and liraglutide which are authorized for T2D treatment are stable in blood and represent well brain permeation [118], [119]. The impairment of insulin signaling in hippocampal neurons due to AbO was recently discovered to be blocked by Exendin-4 [22]. It also facilitated the restoration of diminished brain insulin signaling in a transgenic mouse AD model, thereby mitigating the accumulation of Ab and improving cognition [22]. More significantly, liraglutide appears to offset memory deficiencies in mice induced by Ab [120], minimize neuropathology, and improve cognition in AD transgenic mice [121]. The full range of cellular mechanisms used by the activation of GLP-1R to facilitate neuroprotection and enhance cognition has yet to be accounted for. Consequently, the activation of GLP-1R could provide a new approach to resensitizing diminished insulin signalizing in the brain and to halt or even prevent neurodegeneration in AD entirely. Experimental studies have concluded that GLP-1Rs agonist enhances cognitive function and mitigates the formation of Aβ and tau tangles in various AD animal models [122].

V. Conclusion

In conclusion, the establishment of a molecular link between AD and diabetes will have important ramifications for understanding the underlying mechanisms responsible for neuronal dysfunction in AD. This review has highlighted the importance of impaired insulin signaling, inflammation, oxidative stress and mitochondria dysfunction. The recently discovered pathophysiological and clinical similarities between diabetes and AD highlight the potential cognitive benefits of antidiabetic agents. This proposition is supported by evidence showing that AbOs (increasingly recognized as important synaptotoxins in AD) use proinflammator mechanisms to interrupt normal insulin signaling in the brain in a manner similar to the experience of peripheral tissue in diabetes. Insulin signaling in the brain can be stimulated to counteract the resultant cellular stress and synapse

dysfunction, using either insulin or an antidiabetic drug like a GLP-1R agonist. The inability of various T2D treatments to reduce the risk of AD or enhance cognition in AD dementia indicates that merely reducing the level of peripheral insulin resistance is an ineffective strategy. This is especially true for treatments involving the peripheral administration of insulin, sulfonylureas, metformin, and thiazolidinediones like rosiglitazone and pioglitazone [123], [124].

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