The Link between Type 2 Diabetes and Neurodegeneration: Roles for Amyloid-β, Amylin, and Tau Proteins

Prashant Bharadwaia,b,1, Nadeeja Wijesekarac, Milindu Liyanapathiranaa, Philip Newsholmea, Lars Ittnert, Paul Fraserc and Giuseppe Verdilea,b,c,*

aSchool of Biomedical Sciences, Faculty of Health Sciences, Curtin Health Innovation Research Institute, Curtin University, WA, Australia
bCentre of Excellence for Alzheimer’s Disease Research and Care, School of Medical Sciences, Edith Cowan University, WA, Australia
cTanz Centre for Research in Neurodegenerative Diseases, Krembil Discovery Tower, and Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada
dSchool of Medical Sciences, University of NSW, Kensington, NSW, Australia
eSchool of Psychiatry and Clinical Neurosciences, University of Western Australia, Crawley, Australia

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Abstract. A wealth of evidence indicates a strong link between type 2 diabetes (T2D) and neurodegenerative diseases such as Alzheimer’s disease (AD). Although the precise mechanism remains unclear, T2D can exacerbate neurodegenerative processes. Brain atrophy, reduced cerebral glucose metabolism, and central nervous system insulin resistance are features of both AD and T2D. The T2D phenotype (glucose dyshomeostasis, insulin resistance, impaired insulin signaling) also promotes AD pathology, namely accumulation of amyloid-β (Aβ) and hyperphosphorylated tau and can induce other aspects of neuronal degeneration including inflammatory and oxidative processes. Aβ and hyperphosphorylated tau may also have roles in pancreatic β-cell dysfunction and in reducing insulin sensitivity and glucose uptake by peripheral tissues such as liver, skeletal muscle, and adipose tissue. This suggests a role for these AD-related proteins in promoting T2D. The accumulation of the islet amyloid polypeptide (IAPP, or amylin) within islet β-cells is a major pathological feature of the pancreas in patients with chronic T2D. Co-secreted with insulin, amylin accumulates over time and contributes to β-cell toxicity, ultimately leading to reduced insulin secretion and onset of overt (insulin dependent) diabetes. Recent evidence also suggests that this protein accumulates in the brain of AD patients and may interact with Aβ to exacerbate the neurodegenerative process. In this review, we highlight evidence indicating T2D in promoting Aβ and tau mediated neurodegeneration and the potential contributions of Aβ and tau in promoting a diabetic phenotype that could further exacerbate neurodegeneration. We also discuss underlying mechanisms by which amylin can contribute to the neurodegenerative processes.

Keywords: Alzheimer’s disease, amylin, amyloid-β protein, insulin, tau, type 2 diabetes

INTRODUCTION

Epidemiological, cognitive, and neuropathological evidence links type 2 diabetes (T2D) with promoting neurodegenerative diseases such as Alzheimer’s disease (AD). Further support is provided by in vivo
animal studies. Experimental AD mouse models exhibit a diabetic phenotype [1–3] while memory dysfunction is accelerated in rodent models of insulin resistance and T2D [4–7]. In addition, transgenic mouse models combining AD and T2D phenotypes also show more severe impairment in metabolic control and cognitive dysfunction as compared to control animals [7–9]. These studies provide direct evidence to strengthen the link between T2D and AD. The biological basis and the molecular mechanism(s) that underlie this risk are still not completely understood but can involve impaired insulin signaling, inflammatory or oxidative stresses that promote metabolic, vascular, and neuronal dysfunction. The amyloidogenic proteins that accumulate to form the pathological hallmarks of T2D and AD have important roles in the pathogenesis of these chronic diseases.

The AD brain is characterized by extensive neuronal loss leading to brain atrophy and the presence of the neuropathological hallmarks, amyloid plaques and neurofibrillary tangles. The major component of amyloid plaques, the amyloid-β protein (Aβ), plays a key role in AD pathogenesis that results in synaptic loss and cognitive dysfunction (reviewed in [10]) and is thought to accumulate early in the disease process [11]. The major component of neurofibrillary tangles, hyperphosphorylated tau, also has an important contribution to AD pathogenesis, as it is required (together with Aβ) to drive neurodegeneration [12, 13]. Cerebral insulin signaling, neurovascular dysfunction, and cerebral glucose metabolism have roles in these events and can trigger Aβ accumulation, tau phosphorylation, and neuroinflammatory processes that contribute to overall neurodegeneration.

The early stages of T2D are characterized by a failure of cells to respond to insulin and activate signaling in insulin sensitive tissue (insulin resistance), resulting in reductions in uptake and utilization of glucose thereby raising blood glucose levels. To compensate, an increased burden is placed on pancreatic β-cells to produce and secrete insulin to control elevating glucose levels. Over time, persistent insulin resistance and continued exposure of β-cells to excess glucose and lipids promotes β-cell dysfunction failure and ultimately death, leading to reduced insulin secretion and overt diabetes. A key feature of T2D pancreatic pathology is the accumulation of the amyloidogenic protein, islet amyloid polypeptide (IAPP) (also referred to as amylin) [14–16]. Amylin is a 37-amino acid peptide hormone generated by proteolysis of an inactive 67 amino acid long pro-peptide. The hormone is co-secreted with insulin in response to food intake [17]. It functions to reduce gastric acid secretion, limits the rate of gastric emptying and glucagon secretion, and regulates body weight [18–20] but also has a direct functional role in the central nervous system (CNS) to modulate food intake and body weight [21–23]. Accumulation of amylin aggregates (fibrils) is a feature in >90% of patients with chronic T2D and is a contributor to β-cell toxicity [14, 15, 24]. Due to primary sequence differences within the fibrillogenic domains, unlike human amylin, rodent amylin does not aggregate to form amyloid and does not exhibit cellular toxicity [25]. Evidence is mounting for an additional role for amylin in the neurodegenerative process of AD [16, 26, 27]. In this article, we outline roles of the amyloidogenic proteins Aβ, amylin, and the tau protein in the neurodegenerative process that occurs in T2D and AD brain. We also discuss evidence that implicates Aβ and tau in promoting peripheral insulin resistance/T2D that could potentiate a vicious cycle that exacerbates neurodegeneration.

**T2D PROMOTES Aβ- AND TAU-MEDIATED NEURODEGENERATION**

Although imaging and biomarker studies in humans are beginning to provide insight into how T2D/insulin resistance may influence the progression of neurodegeneration, our understanding of underlying mechanisms linking T2D and AD have come from in vitro and in vivo studies. Numerous studies in various AD transgenic animal models have shown that diet-induced (high-fat diet/sucrose/fructose) insulin resistance or chemically induced (i.e., administration of the β-cell toxin streptozotocin) impairments in insulin signaling, promote AD pathology (Aβ accumulation, tau hyperphosphorylation), synaptic degeneration, and neuronal dysfunction [5, 28–31]. The potential underlying mechanisms have been reviewed extensively [32–34] and involve neuroinflammatory and oxidative stress mechanisms that promote synaptic and neuronal dysfunction. Impaired cerebral insulin signaling can play a key role in this process.

The brain is an insulin sensitive organ, where insulin signaling can regulate peripheral energy homeostasis (reviewed in [35]). However, the presence of insulin receptors (IR) in high density in other brain regions, particularly the hippocampus, suggests that signaling also modulates/facilitates memory and learning (recently reviewed in [36]). Impairments in
hippocampal signaling can lead to events that promote neurodegeneration. Reduced insulin levels and binding to IR and increased serine phosphorylation of the IR substrate 1 (IRS-1), are all events that result in impaired insulin signaling and have been reported in the AD brain [37–42]. Further, insulin levels have been reported to be reduced in the cerebrospinal fluid of AD [43] and in mild cognitive impairment patients [44] and associated with high saturated fat and high glycemic diets known to promote T2D. Together, these studies support that impaired brain insulin signaling is not only featured in the AD brain but could be an early event in the disease process.

The formation and accumulation of Aβ aggregates have key roles in downregulating insulin signaling. Aβ is generated by the processing of its parent protein, the amyloid-β protein precursor (AβPP) first by β-AβPP cleaving enzyme-1 (BACE1), then by the γ-secretase enzyme. This process, generates multiple Aβ peptides of varying length, including the most common soluble monomeric peptides of 40 amino acids (Aβ40) and the more insoluble peptide of 42 amino acids (Aβ42) (reviewed in [45]). In AD, Aβ42 monomers aggregate into progressively larger oligomeric species. Although, studies in transgenic AD mouse models reveal that accumulation of Aβ oligomers induces synaptic dysfunction and mild cognitive impairment (reviewed in [46]), it may require Aβ-driven instigation of downstream events, including tau hyperphosphorylation and accumulation to cause overt neuronal loss or brain atrophy as seen in the AD brain. Impaired signaling as seen in T2D is a possible link between Aβ synaptic toxicity progressing to tau accumulation and overt neuronal degeneration.

In animal studies, inducing insulin resistance is known to promote Aβ accumulation. Under these conditions, upregulating BACE and γ-secretase processing of AβPP to favor Aβ42 production [4, 47, 48], or reduced activity of Aβ degrading enzyme, such as insulin degrading enzyme [49], have been suggested as contributors to the accumulation of Aβ oligomers, which can in turn impair neuronal IR signaling. Aβ has been shown to inhibit autophosphorylation of IR [50] and reduce IR levels or activity at the surface of neuronal dendrites [51–53]. This process appears to be an early event, occurring prior to dendritic or synaptic deterioration and can be completely prevented by administering insulin [51, 52]. Aβ accumulation can lead to release of pro-inflammatory cytokines such as tumor necrosis factor-α, activating kinases that phosphorylate IRS-1 [42, 52], preventing binding to IR and thereby blocking downstream signaling pathway, including the PI3K/Akt/MAPK pathway. The PI3K/Akt/MAPK pathway regulates a number of downstream signaling pathways important for synaptic plasticity and neuronal function (i.e., through Wnt/β-catenin pathway or mTOR signaling) [54, 55]. This pathway also regulates activity of glycogen synthase kinase-3 (GSK3) [56, 57], a major tau phosphorylating kinase, and modulates tau expression [56, 57]. Disrupting PI3K signaling may therefore result in synaptic and neuronal dysfunction and lead to tau hyperphosphorylation and accumulation, thereby promoting neurodegeneration.

Although impaired cerebral insulin signaling has a key role in promoting neurodegeneration, other mechanisms have been proposed. These include impaired neuronal glucose transport resulting in reduced ATP production; Aβ mediated mitochondrial dysfunction and oxidative stress, which can promote further disruptions in insulin signaling and Aβ production [31, 58, 59]; and aberrant activation of N-methyl D-aspartate receptors (i.e., Aβ/glutamate excitotoxicity) can promote influx of Ca^{2+}, resulting in neuronal oxidative stress, phosphorylation of IRS-1, and down regulation of insulin signaling [51, 52]. Recent evidence also suggests a role for amylin accumulation in the neurodegenerative process.

A ROLE FOR AMYLIN IN THE NEURODEGENERATIVE PROCESS

Co-localization of amylin and Aβ in brain

Recent findings from clinical and animal studies implicate the pancreatic amyloid, amylin in mediating neuronal loss in AD, suggesting its role as a potential link between AD and T2D pathogenesis [16, 26, 27]. In the study by Fawver and colleagues [27], amylin was identified in human cerebrospinal fluid, brains of diabetic patients with vascular dementia or AD, and nondiabetic patients with AD. In addition, co-localized mixed amylin and Aβ deposits were also observed in post-mortem human brains [27]. Similar findings were observed by Jackson and colleagues [26], where amylin deposits were identified in the temporal lobe gray matter in diabetic patients. Mixed amylin and Aβ deposits were also observed. Interestingly, extensive amylin deposition was found in blood vessels and brain parenchyma associated with altered microvasculature and tissue structure in patients with late onset AD without clinically apparent diabetes [26]. These findings above demonstrate
the co-existence of Aβ and amylin in the CNS, suggesting the potential ability of amylin to infiltrate the brain and promote amyloid deposition in the brain.

Studies in animal models provide further evidence to support the role of amylin in mediating amyloid deposition and neuronal loss in the brain. In one study, rats overexpressing amylin in the pancreas showed development of neurological deficits associated with increased amylin accumulation in the brain [60]. Compared to wild-type rats, large amylin deposits (>50 μm diameter) and increased levels of oligomerized amylin were observed in the brains of transgenic rats over-expressing amylin. A more recent study also showed that intravenous injections with preformed fibrils of amylin and Aβ into human amylin transgenic mice triggered amyloid formation in the pancreas and brain [16], demonstrating that protein aggregates can induce amyloid deposition through homologous and heterologous seeding (discussed further below). Overall, these studies suggest that amylin accumulation in brain may contribute to cognitive deficits, and that Aβ and amylin proteins can interact and act synergistically to promote amyloid deposition.

**Amylin-Aβ aggregation and cross-seeding**

Amyloid proteins, including amylin and Aβ, have an increased propensity to aggregate and form structures, such as oligomers and fibrils, and accumulate in cells and tissues with aging. Accumulation of protein aggregates is often associated with disease, in particular neurodegenerative and age-related pathologies. Pre-aggregated proteins can act as templates for further polymerization with seeding as the likely basis by which the aggregated protein acts as an infectious agent to propagate amyloid deposition [61, 62]. This seeding process could be homologous or heterologous and is a characteristic feature of amyloid formation. Homologous seeding has been widely documented for several amyloid proteins, including Aβ and amylin. In contrast, heterologous seeding or “cross-seeding,” when aggregates of one amyloid protein can promote the aggregation of a different protein, is relatively unexplored. Such cross-seeding processes may provide a mechanistic explanation for: i) the simultaneous presence of multiple amyloid proteins in tissues [63, 64]; ii) the epidemiological observation that one amyloid disease may be a risk factor for development of another; iii) and the exacerbation of clinical features when various aggregate proteins accumulate simultaneously.

Several lines of evidence support a mechanistic link between the pancreatic and neuronal amyloids: amylin and Aβ. Amylin shares many biophysical and physiological properties with Aβ. Despite having little similarities in their primary sequence, the two proteins are similar in size and fold into similar secondary protein structures [65]. It has been demonstrated that amylin directly interacts with Aβ, functioning as seeds for its aggregation [66]. It has also been suggested that amylin may modulate the conformation and aggregation of Aβ, forming stable hetero-complexes [27, 67–69]. Whether hetero-complexes result in altered structures leading to greater toxicity in tissues remains to be determined.

**Potential mechanisms of amylin-Aβ induced toxicity in neurons and pancreatic β-cells**

With aging, there is concomitant increase in accumulation of amyloid proteins along with a decrease in proteolytic mechanisms mediated by the autophagy-lysosome and proteasome pathways. The long-term health of the cell is inherently linked to protein quality control and terminally differentiated cells, such as neurons, are particularly vulnerable to the detrimental effects of aggregated proteins. Over the past two decades, extensive work on understanding the mechan-ism of amyloid protein toxicity has been undertaken. Amyloid aggregates have been found to be associated with disruption of several cellular functions, including mitochondrial activity [70–73], oxidative stress [70, 74], receptor mediated functions [75–79], disruption of Ca^2+ homeostasis [80, 81], membrane depolarization and disorder [82, 83], and microglial activation [84].

Plaques containing fibrillar amyloid deposits associated with dying cells and inflammatory processes are hallmark pathological features in AD and T2D. Although amyloid plaques are associated with cell death, they are poorly correlated with the clinical manifestations of the disease. Growing evidence suggests that smaller intermediate structures, known as oligomers are the main cytotoxic agents that correlate with disease progression [85]. Supporting evidence from a range of studies including Huntington’s disease, Parkinson’s disease, prion diseases, and many other amyloidoses point to soluble protein oligomers as an indicator of cell loss rather than the insoluble fibrillar deposits [86, 87]. It is also indicated that oligomeric and fibrillar assemblies maybe formed via distinct mechanisms, possibly mediated by
external factors (binding ligands including other proteins, metals, lipids, etc.) (reviewed in [88]).

Although the toxicity of amylin has not been extensively studied as Aβ, it has been shown to have similar neurotoxic properties [89]. Similar to Aβ, amylin induces toxicity dose-dependently in neuronal cells [89]. Unlike amylin and Aβ42, rat amylin does not display neurotoxic properties [65]. Both amylin and Aβ treatment deregulate mitochondrial proteins, reduce mitochondrial complex IV activity and respiration, and increase the generation of reactive oxygen species [90]. Although the neurotoxicity of oligomer and fibrillar preparations of Aβ and amylin were not comparatively assessed in the above studies, the findings overall show that both the peptides are toxic to neuronal cells and possibly share common mechanisms of toxicity such as targeting mitochondrial functions.

A ROLE FOR Aβ AND TAU IN PERIPHERAL INSULIN RESISTANCE/T2D

Although it is established that Aβ and tau have key roles in AD pathogenesis, mounting evidence suggest that these proteins also have functions in the periphery and in particular may promote peripheral insulin resistance or β-cell dysfunction.

Aβ in peripheral tissues may drive glucose dysregulation

AβPP, from which Aβ is proteolytically-derived, is expressed in a number of peripheral tissues including heart, lung, testis, pancreas, liver, and skeletal muscle (Fig. 1); however, its functional properties in the periphery have not been extensively investigated. Interestingly, Aβ binds to a variety of receptors in the periphery, suggestive of potential functional impact beyond the central nervous system [91]. It has been hypothesized that Aβ may induce insulin resistance and glucose dysregulation since it is expressed in pancreas, liver, and skeletal muscle [92, 93]. Both insulin and glucose have also been shown to drive Aβ accumulation [94–97].

Studies have suggested that Aβ may reduce insulin sensitivity, glucose tolerance, and hepatic insulin signaling in mice via upregulation of the JAK/STAT/ SOCS pathway [1, 98]. In contrast, introduction of anti-Aβ antibodies in an AD mouse model led to the inhibition of this signaling and improved insulin sensitivity and blood glucose regulation. Aβ may therefore drive changes in glucose homeostasis via induction of inflammatory cytokines. Furthermore, a recent study showed that acute intrahypothalamic infusion of Aβ25–35 leads to an increase in glucose production and hyperglycemia in rats [99]. Another study has demonstrated that intracerebroventricular infusion of Aβ oligomers induce peripheral glucose intolerance and activation of pro-inflammatory signaling in the hypothalamus [100]. These recent data suggest that the hypothalamus may play a primary role in Aβ-induced glucose dysregulation. Aβ deposition has in fact been detected in the hypothalamus in postmortem brains, raising the possibility of impaired neuronal function in a key brain region associated with obesity and T2D [101]. Most intriguingly, reduced activity of BACE1, which is required for production of Aβ, led to improved peripheral insulin sensitivity in mice [102]. These studies indicate that Aβ must indeed have an important role in regulating the ability of peripheral tissues to respond to insulin. In keeping with this idea, it has been suggested that Aβ can competitively bind to IR [103].

In addition to a loss of insulin sensitivity in peripheral tissues such as skeletal muscle, liver, and adipose tissue, T2D is characterized by impaired insulin secretion by pancreatic β-cells. A number of factors, including amyloid aggregation may contribute to the loss of β-cell mass and function. While amylin is the primary contributor to amyloidogenesis, expression of AβPP has been detected in pancreatic beta

Fig. 1. AβPP is expressed in a majority of peripheral mouse tissues. 10–20 µg of total homogenates were resolved by SDS-PAGE and immunoblotted with monoclonal C1/6.1 AβPP antibody against the first 20 amino acids of the C-terminal cytoplasmic domain of AβPP provided by Dr. Paul Matthews, New York University School of Medicine. Similar to that observed in brain the peripheral tissues expressed a ~100 kDa protein representing AβPP: TgAβPP mice overexpressing human AβPP with Swedish and Indiana mutations under the control of hamster prion gene promoter; WT, wild type.
cells [104]. It has been suggested that cross-seeding of Aβ and amylin could occur in vivo, leading to heterogeneous aggregates of Aβ-amylin [105]. This is supported by the observation of Aβ deposition in pancreas of T2D patients [93]. A study using an AD mouse model showed no change in amylin but significant Aβ immunoreactivity in 90% of the islets, increased cell death, and reduced insulin staining in Aβ-positive areas [3]. Thus, in addition to its effects on insulin sensitivity, Aβ may also reduce glucose-dependent insulin secretion and contribute to the onset of diabetes.

**Tau expression in peripheral tissues may be important for maintaining glucose homeostasis**

Although tau is thought of as primarily a neuron-specific protein, relatively high expression of both mRNA and protein has been shown in rat skeletal muscle, heart, lung, testis, and kidneys [106]. Different splice variants were shown to be expressed in different tissues, such that a ~50 kDa species is present in the cerebral cortex while a larger ~110 kDa form of tau is found in skeletal muscle based on immunoblot analyses. In addition, we have recently observed expression of spliced isoforms of tau in human and mouse pancreatic islets (Fig. 2). Elevated tau expression and increased hyperphosphorylation similar to AD are also found in pancreas tissue of T2D patients compared to controls [93]. Exposing RIN-5F pancreatic β-cell line to sera from T2D patients also resulted in a marginal increase in tau expression [107]. Therefore, the presence of tau in islets may have significant functional consequences possibly related to insulin secretion and related metabolic pathways.

In support of a functional role for tau in islets, a study using RIN-5F cells has shown that tau overexpression leads to an inhibition in insulin secretion [108]. These investigations also demonstrated that inhibition of the PI3 kinase pathway leads to a reduction in insulin secretion, suggesting that hyperphosphorylation of tau may lead to reduced binding to microtubules and destabilization of microtubules, resulting in disruption of insulin granule trafficking. Previous investigations have reported that insulin granules are transported along microtubules and disruption of microtubules can inhibit glucose-stimulated insulin secretion [109–112]. However, a recent study describes a phenomenon where destabilized microtubules could in fact lead to excessive docking of insulin granules, leading to over-secretion of insulin upon stimulation [113]. Nonetheless, these observations suggest that the changes in both tau expression and phosphorylation could potentially affect insulin secretion.

Glucose uptake by skeletal muscle and adipose tissue is highly regulated, most notably by insulin and is facilitated by the GLUT4 glucose transporter [114]. Studies have suggested GLUT4 vesicles move along microtubules and microtubule-depolymerizing agents inhibit GLUT4 translocation and glucose uptake [115, 116]. An intact microtubule system may be important for the insulin-induced actin remodeling prior to the transporter translocation [117]. Microtubules undergo rapid reorganization into new clusters of networks, vacating space for subsequent actin remodeling. Future studies may delineate the molecular mechanisms of insulin-induced microtubule reorganization. GSK3 has been shown to phosphorylate tau, and activity of GSK3 is downregulated in response to insulin via the activation of the PI3 kinase signaling pathway [118]. Therefore, insulin stimulation likely reduces tau phosphorylation and promotes tau binding to microtubules. However, it has been shown that heterologous overexpression of tau protein, despite being localized to microtubules in 3T3-L1 adipocytes, delays the initial appearance of GLUT4 at the cell membrane following insulin stimulation [119].

The presence of both Aβ and tau in peripheral tissues and pancreatic β-cells presents a possible link in the association between AD and T2D. Aβ-induced insulin resistance, combined with the loss of pancreatic β-cell mass and function, may lead to poor insulin
signaling, oxidative stress, and neuroinflammation within the brain. This would result in further Aβ accumulation, phosphorylation of tau, and increased cognitive dysfunction. Future studies are required, not only to understand the impact of these two very important proteins on both glucose uptake and insulin secretion and the mechanisms involved, but also to identify their role in T2D pathogenesis.

CONCLUSION

Roles for Aβ and tau in AD are well established; similarly, the functions of amylin in the periphery and the impact on β-cell function and progression of T2D have been described. The presence of Aβ and tau in pancreas and insulin-sensitive tissues and their roles in inducing peripheral insulin resistance or disruptions in insulin secretion are a potential mechanistic link for these AD-related proteins in promoting T2D. Similarly, the accumulation of amylin in the brain, its ability to induce neurotoxicity, and form “cross-seeding” aggregates with Aβ provides a role for this pancreatic amyloidogenic protein in neurodegeneration. The underlying pathways remain to be determined and maybe similar to those that have already been explored for insulin resistance, β-cell dysfunction, as well as synaptic and neuronal dysfunction. However, it does provide for an intriguing scenario where Aβ, and tau mediated disruptions in peripheral insulin signaling/glucose metabolism promote further neurodegenerative processes, perhaps via inducing cerebral insulin resistance, disruption in cerebral glucose metabolism, or cerebrovascular disruptions (Fig. 3). Accumulation of amylin (and Aβ) in the pancreas over time could be a contributor to β-cell toxicity and subsequent reduced insulin secretion and hyperglycemia impacting on cerebral insulin

Fig. 3. Mechanisms underlying the link between AD and T2D. AD and T2D are chronic degenerative conditions that share common pathological mechanisms, especially cell loss and abnormal deposition of amyloid proteins Aβ, tau, and amylin. Co-existence of Aβ, tau, and amylin proteins in brain and pancreas demonstrate their ability to cross-seed and promote amyloid accumulation and cell dysfunction in neuronal and pancreatic β-cells. Aβ, tau, and amylin can synergistically interact to promote amyloid deposition, oxidative stress, mitochondrial dysfunction, inflammation, insulin resistance and cell death eventually culminating to dysregulation of glucose metabolism and neurodegeneration in AD and T2D.
signaling and glucose metabolism, further contributing to neurodegeneration (Fig. 3). Accumulation of amylin aggregates in the brain, together with Aβ aggregates, could also contribute to synaptic and neuronal degeneration (Fig. 3). A potential source of this buildup of amylin in the brain is the periphery. Amylin can cross the blood-brain barrier and receptors are distributed throughout the brain, a mechanism by which amylin (and Aβ which also binds amylin receptors [120]) could mediate neurotoxicity [23, 26, 121, 122]. This sets up an interesting scenario where hyperamulinemia, as a result of insulin resistance, may promote increased deposition of amylin in the brain. Understanding these pathways would also be important for therapeutic or preventative interventions.

Numerous studies have shown potential benefits of anti-diabetic medications in slowing down or preventing neurodegeneration. Insulin sensitizers, drugs that stimulate insulin production and improve insulin signaling and insulin itself have shown benefits in animal models of AD and some are in human clinical trials targeting AD and mild cognitive impairment patients (recently reviewed in [34]). More recently, analogues of amylin, for example pramlintide have been used as adjunctive therapy with insulin for diabetes [123], are also being evaluated for their ability to prevent neurodegeneration [120, 124, 125]. Benefits of exploring T2D therapeutics for AD are clear, but could AD-targeted therapies also be of benefit for T2D? In AD mouse models, reducing activity of enzymes (e.g., BACE1) that generate Aβ [102] or Aβ-immunotherapies [1, 98] have been shown to improve insulin sensitivity and blood glucose regulation. This prompts the intriguing notion that amyloid-based therapies such as Aβ immunization could be a potential strategy for reversing both cognitive dysfunction and glucose dysregulation. However, large individual fluctuations in plasma Aβ have long been a challenge in AD therapeutics [126], and the benefits (and potential effects in the periphery) require further exploration in both animal and human studies. Although a similar notion could be extended to the potential of therapeutics targeting tau in T2D, this would need to be evaluated in animal studies.

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