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# Visions & Reflections (Minireview)

# Common features between diabetes mellitus and Alzheimer's disease

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**Abstract.** Epidemiological studies establish a link between Type 2 diabetes (T2DM) and Alzheimer's disease (AD), both leading causes of morbidity and mortality in the elderly. These diseases also share clinical and biochemical features suggesting common pathogenic mechanisms. Specifically, both are amyloidoses as they are characterized by fibrillar protein aggregates – amylin in T2DM pancreatic islets, and β-amyloid (Aβ) and neurofibrillary tangles (NFTs) in AD brain. Amylin aggregation is associated with pancreatic β-cell loss, and Aβ and NFT formation with neuronal cell loss. We discuss the possibility that amylin and Aβ exert their toxicity by similar mechanisms, with components of the pathocascades shared, and that therapies based on amyloidogenic properties are beneficial for both T2DM and AD.

**Keywords.** β-Amyloid, Alzheimer's disease, amylin, tau, Type 2 diabetes mellitus.

## Introduction

Type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD) are chronic, age-related diseases that have attained epidemic proportions. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 [1]. Some risk factors implicated in the development of T2DM are genetic predisposition, obesity, diet, physical inactivity and age [2]. In comparison, there are 24 million dementia patients worldwide, and numbers continue to increase exponentially [3]. AD is the most frequent form of all dementing disorders, and in rare familial cases it is caused by autosomal dominant mutations [4]. In contrast, sporadic cases are caused by environmental conditions like oxidative stress, with age being a major risk factor [5]. For both T2DM and AD, despite some insight into causative and susceptibility genes, their molecular pathophysiology is not yet fully understood. Interestingly, a number of well-designed epidemiological studies have established a link between the two diseases [6–8]. More importantly, they share clinical and biochemical features suggesting common pathogenic mechanisms [9–11].

## AD and T2DM are conformational diseases

AD is characterized by a progressive loss of memory and other cognitive functions, resulting in dementia. In the AD brain, the Aβ peptide and the microtubule-associated protein tau undergo a change in tertiary structure followed by self-association and deposition. Aβ is derived from the amyloid precursor protein, APP, and is the major constituent of β-amyloid plaques; hyperphosphorylated tau is the major constituent of neurofibrillary tangles (NFTs) [9, 12]. In

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familial cases of AD, mutations have been identified in the APP gene itself, and in genes encoding APP proteases. In frontotemporal dementia (FTD), the second-most prevalent form of dementia, mutations have been identified in tau [13]. This information has been used to develop transgenic animal models with Aβ plaque and NFT formation, along with memory impairment [14]. Significant neuronal cell loss, another hallmark of the AD and FTD brain, has been achieved upon massive overexpression of FTD mutant tau [15].

Diabetes mellitus (DM) is subdivided into Type 1 (T1DM) and Type 2 (T2DM), with the latter accounting for 90% of all cases. T2DM is characterized by insulin resistance of target tissue, leading to elevated blood glucose levels. Disease progression correlates with amylin deposition, which, similar to Aβ and tau, undergoes a change in tertiary structure and is finally deposited in insulin-producing pancreatic islet β-cells [10]. Amylin is also known as islet amyloid polypeptide (IAPP). In humans, it is synthesized as an inactive 67-residue propeptide that is colocalized with insulin in β-cell granules. The mature 37-amino acid peptide is produced by proteolysis. *In vitro* and *in vivo* studies have revealed that its formation causes β-cell death [10, 16]. Interestingly, differing from non-amyloidogenic rat amylin, human amylin and Aβ (that are both amyloidogenic) cause a dose-, time- and cell type-specific neurotoxicity, supporting the notion of a similar toxic mechanism [17].

Like AD, T2DM has been modeled in mice: in the ob/ob (leptin knockout) and db/db (leptin receptor knockout) strains, both of which are insulin resistant [18, 19], and in mice overexpressing human IAPP in pancreatic islet cells [20–23]. Breeding of IAPP transgenic mice to homozygosity caused islet amylin aggregation, β-cell death and DM [22]. An alternative strategy to induce T2DM is by injecting streptozotocin that causes β-cell destruction [24]. β-cell destruction can be further caused by allogeneic expression of MHC antigens [25].

In conclusion, both T2DM and AD are characterized by insoluble protein aggregates with a fibrillar conformation – amylin in T2DM pancreatic islets, and Aβ amyloid and NFTs in AD brain. Amylin aggregation is associated with pancreatic β-cell loss, whereas Aβ and NFT formation is associated with neuronal cell loss. β-cell loss leads to diabetes, nerve cell loss to dementia. Therefore, T2DM and AD are both conformational diseases.

## Need for effective therapies targeting DM and AD

The mainstay of non-pharmacological DM treatment is diet and physical activity. Although T2DM patients do not critically depend on insulin, about one third of them need insulin to reduce high blood glucose levels [26, 27]. The current treatment of AD is symptomatic and only moderately slows the cognitive decline; treatments include acetylcholine esterase inhibitors and the NMDA glutamate receptor antagonist Memantine, to counteract excitotoxicity [28]. Recent clinical trials include vaccination strategies, metal chelation, anti-inflammatory drugs, anti-oxidants, and kinase inhibitors, among others [14].

## Commonalities of T2DM and AD

**Similar mechanisms of degradation and clearance of Aβ and amylin.** Aβ and amylin levels are determined by (i) production through precursor processing, and (ii) degradation and clearance. Interestingly, the missense mutations in familial cases of AD all either increase Aβ production or enhance Aβ fibril formation [29]. Neprilysin (NEP) and insulin-degrading enzyme (IDE) degrade Aβ *in vivo*. Amylin and insulin are additional substrates of IDE [30]. Enhanced IDE activity correlates with decreased Aβ levels in brains of IDE/APP double transgenic mice [31], and IDE shows decreased degrading activity of Aβ in AD compared to control brains [31]. *In vivo*, IDE substrates can compete with each other, with an imbalance of the substrates possibly influencing the pathogenesis of AD or T2DM [30]. Moreover, mutations in IDE cause human T2DM-like symptoms [32]. Hence, modulating these clearing enzymes in their activity may be beneficial in the treatment of both AD and T2DM.

**Toxicity of Aβ and amylin.** A diverse range of fibrillar peptides that include Aβ and human amylin can cause increased levels of APP, a putative Aβ receptor [33], in both primary neuronal and astrocyte cultures [34]. Furthermore, there is increasing evidence that amylin, similar to Aβ, can induce apoptotic cell death [35]. Finally, distinct integrin signaling pathways mediate both Aβ- and amylin-induced neurotoxicity, and both can be inhibited with integrin antibodies and cytochalasin D [11]. This presents components of the integrin signaling pathway as putative targets in drug screenings for AD and T2DM. A second interesting signaling pathway involves the kinase GSK3 that is downstream of insulin. When inhibited by insulin, glycogen and protein synthesis is induced [36]. In diabetic and obese mice levels of GSK were found to be elevated

[37]. Together this encouraged the development of GSK3 inhibitors to treat T2DM [36]. GSK3 has also been suggested as a link between Aβ and tau [38], as GSK3 phosphorylates tau and regulates APP cleavage and Aβ production; hence, GSK3 inhibitors including lithium are considered for the treatment of AD [39].

**Amylin and Aβ aggregates impair cellular functions by similar mechanisms.** Amylin and Aβ aggregation cause increased oxidative stress and mitochondrial dysfunction, and *vice versa.* We recently demonstrated a mitochondrial dysfunction in our P301L tau mutant mice, associated with higher levels of reactive oxygen species (ROS) and an up-regulation of antioxidant enzymes [40]. P301L tau mitochondria display an increased vulnerability towards fibrillar Aβ peptide [40]. Mitochondrial dysfunction also characterizes APP transgenic mice with an Aβ pathology [41]. The amyloidogenic similarities between human Aβ and amylin make it likely that a mitochondrial dysfunction may be found in IAPP transgenic mice.

Cells dealing with the excessive production of ROS and oxidative stress require a cascade of intracellular events known as the "unfolded protein response". Oxidative stress and increased insulin production contribute to protein misfolding and the induction of the unfolded protein response in β-cell [42]. Transgenic expression of human IAPP in islets induces endothelial reticulum stress-mediated β-cell apoptosis, a characteristic of humans with T2DM but not T1DM [43]. Our proteomic and biochemical data of Aβ-injected P301L tau mice, a model combining the NFT and Aβ pathology of AD [44], also suggest an impaired unfolded protein response [45]. Together, this supports the notion of an impaired unfolded protein response in both AD and T2DM.

The relative contribution of fibrillar and oligomer forms of Aβ and amylin, respectively, in the pathogenesis of AD and DM is highly controversial [46, 47]. While in AD brain, Aβ forms both stable oligomers and fibrils [48], an oligomeric Aβ dodecamer has been identified as a major toxic species [49]. We found that oligomeric Aβ species can cause a mitochondrial dysfunction, similar to fibrillar Aβ [50]. For T2DM, there is accumulating evidence that oligomeric amylin participates in β-cell apoptosis [51]. Again, this notion is supported by transgenic mouse work [52], while the relative contribution of fibrillar *versus* oligomeric species is far from clear.

Thus, the production of Aβ and amylin, the exertion of biological activity (both physiological and pathological), as well as their clearance are so similar that a therapy targeting any of these steps is likely to benefit both diseases.

## Comparative proteomics reveals similar proteomic profile

T2DM and AD also share a remarkably similar proteomic profile. This is impressively illustrated by a proteomic analysis of pancreatic islets that identified several novel proteins that are associated with AD pathogenesis [53]. Interestingly, in a proteomic study using Aβ-injected P301L tau transgenic brains, we showed that a significant subset of these 'islet' proteins are deregulated upon Aβ injection, such as GRP78, valosin-containing protein, calreticulin, the HSP family or peroxiredoxin [45]. Similarly, in the formic acid fraction of Aβ-treated P301L tau-transfected cells, we identified insulin-like growth factor binding protein 2 precursor (IGFBP-2) as an up-regulated protein, again demonstrating a similar proteomic profile of DM and AD (unpublished data). This implies that similar proteins and pathways are activated by amylin and Aβ, respectively, in either pancreatic islets (T2DM) or brain (AD).

## Common treatment strategies?

What does this imply in practical terms and what can be envisaged for the near future? It seems logical to pursue comparative transcriptomic and proteomic analyses of AD brain and T2DM pancreata and to extend these studies, in a comparative manner, to transgenic mouse tissue. This will not only identify deregulated genes and proteins, but is likely to decipher shared pathomechanisms. It may even be possible, using this comparative approach, to identify the putative Aβ and amylin receptor(s) by which these peptides may exert toxicity. So far their identity has remained elusive, despite the fact that many candidates have been proposed in the past [54]. The information gained by a comparative approach will undoubtedly assist in the development of treatment strategies for such debilitating diseases as AD and T2DM that so far have defied proper treatment.

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