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Amylin: what might be its role in Alzheimer's disease and how could this affect therapy?

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Amylin, an amyloidogenic hormone synthesized and co-secreted with insulin by pancreatic β-cells, has binding sites in the brain possibly regulating satiety and gastric emptying. It is elevated in obesity and pre-diabetic insulin resistance (hyper-amylinemia) leading to amylin amyloid deposition in the pancreas. Moreover, amylin deposition in pancreatic islets is an important source of oxidative and inflammatory stress leading to atrophy of pancreatic islets and development of type 2 diabetes (T2D). One possible mechanism of amylin accumulation in peripheral organs is through deposition of circulating amylin oligomers, which were found in both blood vessels and parenchyma of kidneys, heart and – as we have recently shown – brain. Hence, amylin amyloid infiltration in the brain may be an important contributor to cerebrovascular injury and neurodegeneration observed in demented humans. Treatment of hyperamylinemia or the consequent formation of circulating amylin oligomers, therefore, could be a feasible therapeutic target to protect the aging brain or slow neurodegenerative processes.

Numerous epidemiological studies show significant associations between presumed T2D and risk for Alzheimer's disease (AD) [1]. This increased risk extends to both obesity, the major risk factor for insulin resistance, and T2D [2]. Pathological studies indicate that dementia risk associated with T2D is independent of Alzheimer's pathology and suggest that the increased dementia risk is likely due to vascular brain injury [3,4]. An independent study also showed increased AD pathology in T2D [5]. Brain imaging studies, however,

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demonstrate that the risk associated with dementia and T2D is independent of vascular disease [6]. At least one study found significant hippocampal atrophy suggesting that the association between diabetes and AD may involve shared pathophysiological processes [7]. Recent reviews point to possible pathological pathways whereby hyperinsulinemia may lead to increased AD pathology through altered cerebral clearance of amyloid β protein and hyperphosphorylation of τ [1,8]. As hypothesized by de la Monte, peripheral hyperinsulinemia is associated with impairments in cerebral glucose utilization through brain insulin and IGF resistance [8]. Impaired insulin and IGF signaling lead to increased amyloid precursor protein expression, increased amyloid β production and hyperphosphorylation of microtubule τ protein, which are the two hallmark pathologic features of AD. Similarly, increased insulin levels in the brain may saturate the brain insulin degrading enzyme system or reduce LRP-1 levels which are also mechanisms for amyloid β clearance [9,10]. Accumulation of amyloid β is hypothesized to be further enhanced by the presence of advanced glycation end-products that further impair amyloid β clearance from the brain. Intriguingly, there is no evidence that amyloid plaque is increased in the brain of diabetic patients [4,11]. Moreover, induced hyperinsulinemia in AD patients demonstrated memory improvement [12], suggesting that not the elevated insulin levels *per se*, but conditions secondary to hyperinsulinemia may play a significant role in the AD pathology in diabetics. One possible mechanism may involve elevated secretion of amylin (hyperamylinemia). Hyperamylinemia coincides with hyperinsulinemia [13] and induces amylin amyloid deposition and proteotoxicity not only in the pancreas (a hallmark of T2D) but also in other organs, including kidneys [14] and, as we have recently shown, in heart and brain [15,16].

Amylin, a 37-amino acid peptide, is synthesized and co-secreted with insulin by pancreatic β-cells [13]. Within the pancreas, amylin restrains insulin and glucagon secretion [13]. It also has binding sites in the brain, possibly regulating satiety and gastric emptying [13]. Human amylin hormone may lose its function by oligomerization. Amylin oligomization and deposition is common in patients with obesity and pre-diabetic insulin resistance who have an increased secretion of this hormone [13]. Over 95% of humans with T2D stain positive for amylin amyloid deposition in pancreatic islets, where it is believed to be cytotoxic [13]. Oligomerized amylin and amylin amyloid are also detected in vasculature and tissue parenchyma of failing hearts and kidneys from obese and T2D patients suggesting the possibility of a systemic effect [15]. In the brain, we identified amylin deposits in the blood vessels and parenchyma of AD patients [16]. Moreover, we found that amylin formed the core protein deposit of some amyloid plaques or co-localized with amyloid β as part of a combined plaque. Importantly, these findings occurred in AD patients who did not suffer with T2D. These preliminary findings suggest that amylin oligomerization may be a second form of amyloid involved in AD pathophysiology. In this article we hypothesize potential mechanisms whereby amylin may interact with the AD process to increase the likelihood of expressed dementia. These hypotheses also suggest potential new avenues for AD treatment that will be discussed.

Amylin amyloid, a contributor to the cerebral pathology in AD

In the brain, amylin and amyloid β may share similar pathophysiology. This hypothesis is suggested by the fact that both amylin and amyloid β form toxic oligomers and amyloid fibrils [17]. Similar to amyloid β oligomers, the amylin oligomers are membrane-permeable, altering cellular structures [13]. Hence, they can compromise the blood–brain barrier (BBB) and can diffuse into brain. Amylin oligomers may also engage RAGE and promote inflammation, thus exacerbating BBB damage and further toxic brain amylin accumulation. Cerebrovascular inflammation is considered a disruptor of normal synaptic function at the starting point of AD pathological progression. Hence, hyperamylinemia may be a risk factor for cerebral inflammation. Moreover, diffusion of amylin oligomers in the brain through damaged BBB may promote a direct interaction with neurons. The interaction of amylin oligomers with cultured neurons is known to rise $[Ca^{2+}]_i$, which is similar to the neuronal effect induced by Aβ oligomers in AD [17]. We have recently shown that the attachment of amylin oligomers to cardiac myocytes increases the amplitude of Ca^{2+} transients leading to the activation of Ca-mediated pathological hypertrophy pathways in the heart [15]. Hence, cerebral accumulation of amylin may directly contribute to the development of AD pathology through multiple pathological pathways involving inflammation, oxidative stress and neuronal $[Ca^{2+}]_i$ dysregulation. Additional studies are needed to mechanistically investigate: how amylin is involved in cerebrovascular alteration and amyloid deposition in brain parenchyma and what are the specific amylin-mediated deleterious effects in the brain. If our hypothesis of toxic amylin deposition in the brain is proven then, hyperamylinemia may be an early pathological mechanism linking diabetes with AD.

Circulating amylin oligomer, a possible predictor of brain injury & dementia

Amylin oligomerization occurs preponderantly within the secretory vesicles of pancreatic β cells, where this hormone is generally found at high concentrations [13]. Amylin oligomers are then released in the blood along with insulin. Indeed, oligomerized amylin is present in the plasma of AD patients [16]. Hence, circulating amylin oligomers are a possible mechanism of amylin accumulation in the brain. Because the amylin oligomers are also cytotoxic, an elevated blood level of such molecular species may be a predictor of brain injury. It is worth noting that amylin aggregates are known to participate in stimulating lipolysis, elevating plasma free fatty acid level, activating the renin-angiotensin-aldosterone system, stimulating RAGE expression and promoting the inflammatory process [13]. Recently, we demonstrated that accumulation of oligomerized amylin in the heart accelerates diabetic heart failure [15]. Since neurons and cardiac myocytes have similar Ca^{2+} regulatory properties, amylin is likely to have similar toxic effects on neurons as well. Future studies are needed to decipher the specific amylin oligomer-mediated pathological effects in the brain, which may improve prognosis and diagnosis of cerebrovascular complications and neurodegeneration observed in humans with dementia.

Hyperamylinemia, a novel therapeutic target to improve the treatment of AD

Greater understanding of the mechanisms underlying the amylin oligomer-induced deleterious effects in the brain will potentially lead to new treatments. For example,

accumulation of toxic amylin oligomers in the brain suggests that treatments that increase insulin (and thus, amylin) secretion from the diseased pancreas should be avoided. Preventing overstimulation of susceptible pancreatic β cells may protect the cerebrovascular system by lowering the possibility of toxic oligomerized amylin being secreted in the blood. In addition, hyperamylinemia and consequent release of oligomerized amylin in the blood is potentially a new therapeutic target in the treatment of diabetic brain injury and AD. Blocking amylin oligomerization and/ or increasing the elimination of oligomerized amylin though kidneys may reduce the amylin oligomer toxic effect in the brain. This aspect of treatment may be especially important as amylin is manufactured only in the pancreas and therefore peripheral clearance will likely have a significant effect on amylin influx into brain. Another potential venue for interventions is to limit the attachment of oligomerized amylin to endothelium and amylin oligomer-mediated BBB damage. *Ex vivo* and *in vivo* data show that surfactants with membrane sealing properties, such as poloxamers, can restore membrane integrity and reduce cell death [18]. Treatments with poloxamers increased the survival of neuronal cells after incubation with amyloid β oligomers [19], suggesting possible therapeutic effects *in vivo*. Amyloid deposition in pancreatic islets has been reduced by intravenous oligomer inhibitor injection in a rodent T2D model transgenic for human amylin [20]. Other oligomer inhibitors successfully blocked amyloid formation in pancreatic islets, but were not able to lower apoptosis in β cells when the amylin oligomers formed intracellularly [20]. Although a direct extension of these findings to the human disease is rather limited, as noted previously, the fact that the oligomerized amylin is detected in the blood offers new venues for interventions. Reversing amylin-mediated brain injury by curbing cerebral amylin oligomer accumulation, amylin oligomer attachment to endothelium and BBB damage may be therapeutic strategies to delay/prevent the development of AD in T2D setting.

In summary, identifying mediators of hyperamylinemia and mechanisms of amylin-mediated brain injury has a translational potential of immediate relevance for individuals with pre-diabetes and T2D, who can benefit of improved prognosis and new treatments.

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