

Type-2 diabetes, pancreatic amylin and neuronal metabolic remodeling

**in Alzheimer's Disease**

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**Keywords:** Alzheimer's disease, amylin, diabetes, metabolism, vascular cognitive impairment and dementia (VCID)

**List of Abbreviations:**

AD – Alzheimer's disease, AKO – amylin knockout, a murine model, APP - amyloid precursor protein, A $\beta$  - amyloid beta; beta-amyloid, BBB – blood-brain barrier, CAA – cerebral amyloid angiopathy, CNS – central nervous system, CSF – cerebrospinal fluid, CU – cognitively unimpaired, fAD – familial Alzheimer's disease, GLP-1 – glucagon-like peptide 1, GWAS – genome-wide association study, HIP – human amylin in pancreas, a murine model, IAPP – islet amyloid polypeptide; amylin, IHC – immunohistochemistry, MCI – mild cognitive impairment, PET – positron emission tomography, PD – Parkinson's disease, PKU – phenylketonuria, PPP – pentose phosphate pathway, PS1 – presenilin 1, sAD – sporadic Alzheimer's disease, TWD – Typical Western Diet

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Received: 21/06/2022; Revised: 26/09/2022; Accepted: 13/01/2023

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1002/mnfr.202200405](https://doi.org/10.1002/mnfr.202200405).

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## Abstract

Type-2 diabetes raises the risk for Alzheimer's disease (AD)-type dementia and the conversion from mild cognitive impairment to dementia, yet mechanisms connecting type-2 diabetes to AD remain largely unknown. Amylin, a pancreatic  $\beta$ -cell hormone co-secreted with insulin, participates in the central regulation of satiation, but also forms pancreatic amyloid in persons with type-2 diabetes and synergistically interacts with brain amyloid  $\beta$  (A $\beta$ ) pathology, in both sporadic and familial Alzheimer's disease (AD). Growing evidence from studies of tumor growth, together with early observations in skeletal muscle, indicate amylin as a potential trigger of cellular metabolic reprogramming. Because the blood, cerebrospinal fluid, and brain parenchyma in humans with AD have increased concentrations of amylin, amylin-mediated pathological processes in the brain may involve neuronal metabolic remodeling. We summarize recent progress in understanding the link between prediabetic hypersecretion of amylin and risk of neuronal metabolic remodeling and AD and suggest nutritional and medical effects of food constituents that might prevent and/or ameliorate amylin-mediated neuronal metabolic remodeling.

Alzheimer's disease (AD) and related dementias present significant public health challenges and economic burdens that underscore the need for development of safe and effective interventions. The one approved drug for prevention of AD, aducanumab, is directed at reducing brain A $\beta$  lesions in a "one-size-fits-all" approach. There is mounting evidence that diabetic states (insulin resistance/prediabetes, and type-2 diabetes) raise the risk for dementia and conversion from mild cognitive impairment (MCI) to dementia.<sup>[1-7]</sup> Associations between glycemic control and cognitive status, however, are inconsistent.<sup>[8-12]</sup> Thus, there is a need for mechanism-based therapeutic strategies directly targeting diabetes-related risk for AD.

**Amyloid-forming amylin is associated with cerebral A $\beta$  pathology.**

Amylin (or islet amyloid polypeptide; IAPP) is co-expressed and co-secreted with insulin by pancreatic  $\beta$ -cells in response to food intake and regulates satiation through binding to receptors on circumventricular organs.<sup>[13-15]</sup> It also crosses the blood-brain barrier (BBB) and, in common with A $\beta$ , is broken down by the insulin degrading enzyme.<sup>[16,17]</sup> Similarities and differences between human amylin and A $\beta$  are described in **Table 1**. In humans and rodents, plasma amylin levels rapidly increase several-fold after meals.<sup>[15]</sup> Amylin from humans, but not rodents, forms amyloid, a pathological hallmark of the pancreatic islet in persons with type-2 diabetes.<sup>[14]</sup> Islet amylin deposition triggers the inflammasome through phagosomal destabilization, leading to interleukin-1  $\beta$  (IL-1 $\beta$ ) overexpression and apoptosis of pancreatic  $\beta$ -cells.<sup>[18,19]</sup>

Given that human amylin is amyloidogenic, increased concentrations of amyloid-forming amylin in the blood may promote accumulation of amylin amyloid in extra-pancreatic cells and tissues.<sup>[14]</sup> In our initial study, we examined post-mortem temporal lobe tissue from 42 human donors for histological evidence of cerebral amylin deposits.<sup>[20]</sup> One control group consisted of 13 non-diabetic, cognitively normal individuals with low Braak and Braak scores. The second control group consisted of temporal lobe tissue from 14 non-diabetic AD patients. We hypothesized that brain tissues from this group would serve as AD pathological controls for comparison to those with diabetes and dementia. The results show: 1, amylin is present in the brains of both diabetic and non-diabetic persons with AD; 2, amylin appears to originate from an influx of circulating amyloid-forming amylin

species, as evidenced by the presence of amylin staining in blood vessels and perivascular spaces, and the absence of amylin mRNA in AD brains; 3, accumulation of oligomerized amylin in the brain coincides with tissue morphological alteration, consisting of areas of increased interstitial space, vacuolation, and spongiform change not present in the brains of non-diabetic controls; 4, parenchymal and plasma amylin species appear to be primarily in the form of tetramers, which appear to be selectively increased in AD brain as compared to blood; 5, amylin amyloid is also present in the parenchyma of AD brains at a nearly fourfold increase compared to controls; and 6, amylin-A $\beta$  co-staining was found in 10-15% of all plaques, consisting of amylin at both the core and surroundings.<sup>[20]</sup> These results were subsequently confirmed in separate cohorts by different research teams, including individuals with mixed amylin-AD pathology in the absence of a clinical diagnosis of diabetes.<sup>[21-25]</sup>

Therefore, even if pancreatic amylin secretion is normal in AD, amylin may be harmful to the brain by interacting with A $\beta$ -associated pathology. Because individuals with early-onset familial forms of AD develop AD pathology, next, we examined evidence of amylin-A $\beta$  cross-seeding in the brains of persons with familial AD (fAD), which could support the hypothesis of a role of circulating amyloid-forming amylin in AD pathogenesis.<sup>[26,27]</sup> We, therefore, analyzed the brains of individuals inheriting mutations in the amyloid precursor protein (*APP*) or presenilin 1 (*PS1*) for immunochemical evidence of amylin interaction with areas of AD-related histopathology (A $\beta$  and *tau* deposits).<sup>[27]</sup> Amylin immunoreactivity was detected in neuronal soma and neuritic plaques in the brains of persons with fAD (n=31). In some amylin-A $\beta$  neuritic plaques, immunostaining showed the presence of amylin in small proteinaceous fragments. Tissue containing amylin-positive neurons revealed no overlap between the immunoreactivity signals for amylin and p-*tau* suggesting distinct amylin and *tau* pathologies. Identity of the amylin peptide in human AD brains was confirmed by liquid chromatography tandem mass spectrometry.<sup>[28]</sup> Immunohistochemistry (IHC) analyses of serial sections for amylin and amylin-A $\beta$  cross-seeding, and Congo red staining suggest that amylin is a component of cerebral amyloid angiopathy (CAA) pathology.<sup>[20,27]</sup> This was further supported by

confocal microscopy analysis of brain sections triple-stained for amylin, A $\beta$ , and  $\alpha$ -smooth muscle cell actin.<sup>[27]</sup> Analyses of the association of common and rare amylin gene variants with the risk of developing AD revealed that amylin-fAD interaction is not linked to a genetic predisposition.<sup>[27]</sup>

To test whether circulating amylin is involved in early AD pathological processes, we analyzed the amylin-A $\beta_{42}$  relationship in CSF from humans with AD pathologic changes and a diagnosis of mild cognitive impairment (MCI) or dementia, and in CSF from cognitively unimpaired (CU) individuals.<sup>[27]</sup> Increases in CSF amylin and decreases in CSF A $\beta_{42}$  levels appeared in the setting of cognitive impairment in the MCI stage of AD. These results are relevant to published analyses of plasma data from two large cohorts (the Alzheimer's Disease Neuroimaging Initiative, and the Texas Alzheimer's Research and Care Consortium), which identified circulating pancreatic peptides as mediators of age-specific effects on dementia severity.<sup>[27,29]</sup> In addition to clinical data suggesting a correlation between levels of circulating amyloid-forming amylin and age-related cognitive decline, a genome-wide association study (GWAS) using age-specific [18F]-AV45 positive electron tomography (PET) amyloid signals as an endophenotype found single-nucleotide polymorphisms in the amylin gene to be predictive of CNS amyloidosis.<sup>[30]</sup> It is important to note that AV45 PET labels pancreatic amylin deposits, which suggests that the AV45 amyloid PET signals may have an amylin component that is a confounder, *i.e.*, a signal that is not due to A $\beta$ , and that quantifying the amylin component could refine diagnosis and prognosis of amylin amyloid pathology in the setting of AD dementia.<sup>[31]</sup> A summary of key findings in human studies in relation to amylin is provided in **Table 2**.

### **Cerebral amylin deposition induces neurological deficits.**

To identify specific amylin-induced pathology in the central nervous system, we used rats with pancreatic overexpression of human amylin.<sup>[27,28,32,33]</sup> Employing rodent models "humanized" for amylin is critical for testing amylin pathology, because amylin from rodents is not amyloidogenic and does not accumulate in cells and tissues.<sup>[34]</sup> Rats overexpressing human amylin (~2 fold) in the pancreas (HIP rats) develop cerebrovascular amylin deposition associated with brain

microhemorrhages, white matter rarefaction and behavior deficits, including altered motor function and recognition memory.<sup>[33]</sup>

To directly address the potential for modulation of circulating amylin levels as a means to alter AD-related pathology/symptoms, we manipulated the pancreatic secretion of amylin through gene suppression and overexpression in APP/PS1 rats and infused human amylin intravenously in APP/PS1 rats.<sup>[27]</sup> In APP/PS1 rats, genetic suppression of amylin secretion protected against the development of neurological deficits, whereas hypersecretion of human amylin accelerated A $\beta$ -like pathology through (at least in part) circulating aggregated amylin.<sup>[33]</sup> At the molecular level, circulating aggregated amylin correlated with disrupted CSF-brain A $\beta$  exchange and amylin-A $\beta$  cross-seeding in the brain.<sup>[33]</sup> Intravenous infusion of aggregated human amylin in young APP/PS1 rats (~9-month of age) (i.e., before APP/PS1 rats normally develop cerebral A $\beta$  plaques) led to the formation of mixed amylin-A $\beta$  deposits in the brain, suggesting the hypothesis that aggregated crossing from blood to brain could seed amylin-A $\beta$  plaques in vivo.<sup>[33]</sup>

### **Hypersecretion of amyloid-forming triggers neuronal metabolic reprogramming.**

Given the systemic impact of amylin dysregulation in HIP rats, we conducted non-targeted metabolomics analyses on brain, heart, liver, and plasma samples from 12-month-old HIP rats vs. age-matched rats with obesity-induced type-2 diabetes, without amylin dyshomeostasis.<sup>[35]</sup> HIP rat brains uniquely had significant *decreases* in five amino acids (lysine, alanine, tyrosine, phenylalanine, and serine), with phenylalanine decreased across all four tissues investigated, including plasma.<sup>[35]</sup> Although the deficiency in phenylalanine was found across tissues including plasma and could be monitored, tyrosine was only reduced in the brain. The 50% reduction in phenylalanine and tyrosine in HIP brains is important, given their role in supporting brain metabolism as a precursor for catecholamines (*e.g.*, dopamine, norepinephrine, epinephrine), which may contribute to the increased morbidity and mortality in diabetics at a multi-system level beyond the effects on glucose metabolism. Others have suggested the decrease in phenylalanine (in

HIP rats) could serve as a useful biomarker for functional dysregulation as a result of hyperamylinemia.<sup>[36]</sup>

Alterations in the pentose phosphate pathway (PPP) and precursors of catecholamines in HIP rat brains are reduced compared to wildtype littermates. Reduced pentose phosphate fluxes result in selective dopaminergic cell death leading to motor deficits, which are characteristics of HIP rats, but are not common in type-2 diabetes. There is emerging evidence demonstrating that down-regulation of PPP enzymes and failure to increase the antioxidant reserve influences pathogenesis in both sporadic Parkinson's disease (PD) and AD.<sup>[37,38]</sup>

### **Could nutritional interventions reduce deleterious effects of amylin dysregulation?**

Recently, there is increasing evidence that nutrition exhibits effects on AD risk and AD severity in both directions.<sup>[39-44]</sup> Large-scale epidemiological studies indicate that certain nutrients, such as dietary vitamins (as opposed to supplemental), polyphenols, fish, fruits, vegetables, and especially antioxidants are protective against AD risk.<sup>[39]</sup> Similar epidemiological studies suggest that whole-fat dairy, trans-fatty acids, and saturated fatty acids worsen AD risk, while evidence on the impact of carbohydrates is conflicting.<sup>[39]</sup> These findings suggest that interventions targeting nutrition may protect against the onset of AD but do not suggest the rate of AD progression can be modified once initiated.

Since no nutrient is consumed alone, it is crucial to understand the effects of diet on the risk for AD. Studies in AD mouse models established that long-term intake of the cholesterol-enriched Typical Western Diet (TWD) is associated with increased deposition of  $\beta$ -amyloid plaques in the brain.<sup>[39,40]</sup> Conversely, a study of over 1,000 elderly Japanese individuals identified the dietary pattern consisting of high intake of soybeans, vegetables, algae, and milk/dairy products with a low intake of rice as protective against dementia risk.<sup>[39,41]</sup> Other studies report that a diet positively correlated with intake of fruits, vegetables, whole grains, nuts, tea, and fish (amongst others) and negatively correlated with intake of meats, refined grains, and poultry is associated with improved cognitive

function, cognitive performance, and decreased risk of AD.<sup>[39-44]</sup> Despite an inability to determine causality, there appears to be strong evidence from epidemiological studies supporting the hypothesis that dietary patterns and nutrition may play a role in the development of AD and other cognitive impairments.

When considering the effect of diet and nutrition on AD risk and pathology, it may also be important to consider the effect on amylin and its cellular metabolic pathways. Other groups report that heterozygous transgenic human IAPP (amylin)-expressing mice (hIAPP mice) fed with a high-fat diet for 12 months show dramatically increased neural degeneration, increased amylin accumulation in hippocampal tissue, and increased hippocampal aging.<sup>[36,37]</sup> These mice also demonstrated reduced efficiency in glucose utilization and impaired learning; brain parenchymal glucose utilization may be indicative of preclinical AD pathology.<sup>[36,45,46]</sup>

Phenylketonuria (PKU) is a genetic disorder wherein phenylalanine hydroxylase (an enzyme that typically converts phenylalanine to tyrosine) deficiency leads to heightened phenylketone body production and increased phenylalanine levels in the blood and brain.<sup>[47]</sup> PKU is the most common inborn error of metabolism in many human populations. This increased phenylalanine concentration is in stark contrast to deficient phenylalanine levels seen in HIP rats, as noted above.<sup>[35]</sup> Dietary management, focusing on the restriction of high-protein foods (such as meat, cheese, nuts, wheat, fish, and eggs), is an accepted treatment for individuals with PKU and certain other disorders of amino acid metabolism such as Maple Syrup Urine Disease.<sup>[47,48]</sup> Therefore, conversely, it may be beneficial for individuals with noted hyperamylinemia, or those at risk for AD, to increase intake of high-protein foods because these foods increase levels of phenylalanine, potentially reducing the effects of amylin-induced deficiency of phenylalanine and tyrosine.<sup>[35,49]</sup> Rodent studies demonstrated that tyrosine concentrations could be increased by high-protein diets and be sustained for several days, suggesting the effect is not diminished after a small number of meals.<sup>[50]</sup>

Previous groups have already suggested modified dietary patterns as anti-inflammatory therapies in the context of A $\beta$  deposition in AD, recommending a diet rich in fruits and vegetables, n-3 fatty acids from fish, and polyphenols.<sup>[51]</sup> The overarching goal of dietary interventions suggested elsewhere is delayed AD progression through the activation or inactivation of circulating biomarkers, though clinical trials are needed.<sup>[51]</sup>

Therefore, through carefully supervised dietary intervention, there is reason to believe that amylin-induced metabolic disturbances, such as those of phenylalanine and tyrosine, could be ameliorated and that this relief could improve patient outcomes or delay disease progression. **Table 2** includes short summaries of the described human studies on nutrition and AD progression.

#### **Amylin-focused therapeutics may be on the horizon.**

Growing evidence from studies of tumor growth in a p53-deficient tumor model, together with early observations in skeletal muscle, indicate amylin functions through calcitonin receptor RAMP3 to alter cellular glucose metabolism.<sup>[52-57]</sup> The beneficial metabolic effects of amylin led to an approved amylin analog drug, pramlintide; however, a recent clinical trial showed that pramlintide induces migraine-like attacks in patients.<sup>[58-60]</sup> More recently, the amylin analogue cagrilintide has reportedly led to sustained weight loss with co-administration of GLP-1 (glucagon-like peptide-1) agonist semaglutide increasing these effects.<sup>[61-64]</sup> However, cagrilintide is closely related to pramlintide structurally, and the initial nausea and vomiting caused by pramlintide may not be reduced by the longer-acting cagrilintide.<sup>[65]</sup> Modified peptide structures, such as amyloid core mimics, are being developed and pursued for their ability to decrease amyloid self-assembly.<sup>[66]</sup> Other pharmacological interventions focused on amylin include amylin agonists, oligomerized amylin-targeting vaccines, and several distinct classes of amyloid-inhibitors such as natural products, small molecules, organometallic molecules, and nanoparticles.<sup>[67-69]</sup> While several amylin-focused therapeutics are in research and development phases, there is still a need for non-pharmacological interventions that may ameliorate amylin's induced disturbances in the interim.

Intraperitoneal injections of amylin or pramlintide reduced behavioral impairment and brain amyloid pathology in murine AD models.<sup>[70,71]</sup> In contrast, other research teams reported robust amylin-A $\beta$  cross-seeding and accelerated A $\beta$  pathology in APP/PS1 rats/mice following the injection of human amylin intravenously or intracerebroventricularly.<sup>[27,72,73]</sup> Furthermore, if amylin lowers A $\beta$  pathology, we should then expect that the genetically suppressed amylin gene in APP/PS1 rats will exacerbate AD pathology and behavior deficits, whereas overexpressing amylin will slow disease progression. However, our published results demonstrate the opposite and are consistent with data showing that pancreatic expression of amyloid-forming human amylin in murine AD mice exacerbate cerebral amyloid burden through cumulative diabetogenic effects of the co-expressed human amylin and A $\beta$ .<sup>[27,72,73]</sup>

In summary, amylin is a pancreatic hormone co-expressed and co-released with insulin by pancreatic  $\beta$ -cells and participates in glucose homeostasis (Fig. 1; left pathway).<sup>[13-15,52-57]</sup> Prediabetic hypersecretion of amylin and the amyloidogenicity of human amylin are contributing factors to pancreatic amyloid formation.<sup>[14]</sup> Chronically increased concentrations of pancreatic amyloid-forming amylin in the blood promote accumulation of aggregated amylin in extra-pancreatic tissues, including the brain.<sup>[20-25,27]</sup> Increased brain amylin concentration is associated with AD through direct amylin-A $\beta$  plaque formation (Fig. 1; right pathway).<sup>[20,22,23,27]</sup> Additionally, in murine models, published data suggest that brain amylin accumulation (or amylin loss-of-function) significantly decreases phenylalanine (a catecholamine precursor) in both the circulation and the brain, indicating neuronal metabolic reprogramming (Fig. 1; lower-right pathway).<sup>[35]</sup> Given the common secretory pathway of insulin and amylin, insulinogenic diets may promote amylin amyloid contribution to AD pathology.<sup>[13]</sup> Dietary intervention could alter the metabolic dysregulations induced by amylin and the relationship with AD pathology. Evidence indicates that dietary pattern may modulate AD progression and severity; accordingly, dietary interventions may also ameliorate amylin-induced

metabolic dysregulation.<sup>[39-44,51]</sup> Future studies should explore whether diets similar to those protective against AD or used to treat PKU may ameliorate amylin-induced metabolic dysregulation (Fig. 1; bottom arrow).

**Acknowledgements/Funding.**

Funding in part by National Institutes of Health AG057290, AG053999 and NS116058

JRB would like to acknowledge the following funding resources: 5R01DK117491, 1U24DK129557, 2P30AG028716, and 1P30DK124723, and US Department of Agriculture 2020-28640-31521.

**Conflict of Interest Statement.**

The authors declare no conflict of interest exists.

Accepted Article

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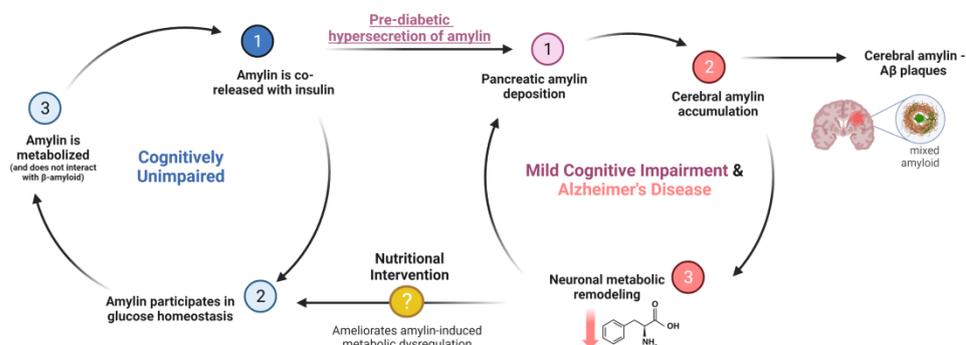


Fig. 1

### Figure Legend

**Figure 1. Proposed role of pancreatic amyloid-forming amylin in neuronal metabolic remodeling and Alzheimer's dementia.** The pancreatic hormone amylin is co-released with insulin and participates in glucose homeostasis (left pathway). Prediabetic hypersecretion of amylin and amyloidogenicity of human amylin contribute to pancreatic amyloid formation, and also promote amylin accumulation in the brain leading to amylin-A $\beta$  plaque formation (upper-right). Amylin

dysregulation is associated with altered synthesis of amino acids such as phenylalanine (a catecholamine precursor) in various tissues, including the brain, which suggests a potential effect of amylin dysregulation in inducing neuronal metabolic reprogramming (lower-center). Nutritional interventions might ameliorate amylin-mediated dysregulation of amino acid synthesis (bottom arrow).

**Table 1. Summary table comparing amylin to  $\beta$ -amyloid.**

**Table 2. Table summarizing key human study findings in the field of amylin research.**

	Human Amylin	Beta-Amyloid
<b>Peptide Length</b>	37 <sup>[74]</sup>	$\beta$ - and $\gamma$ -secretases secrete 37-49 residue peptides. Cleavage fragments 40 and 42 are thought to be the primary toxic forms. <sup>[75]</sup>
<b>Primary Sequence</b>	KCNTATCATQRLANFLVHSSNDFGAILSSSTNV GSNTY <sup>[74]</sup>	DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMV GGVVIA <sup>[75]</sup>
<b>Abbreviation</b>	IAPP <sup>[74]</sup>	A $\beta$ <sup>[75]</sup>
<b>Source</b>	Secretion from pancreatic $\beta$ -cells <sup>[13]</sup>	Proteolytic cleavage of amyloid precursor protein (APP) <sup>[75]</sup>
<b>Normophysiological binding site</b>	CGRP receptors on circumventricular organs <sup>[76]</sup>	Ganglioside GM1 in lipid rafts; plasma membrane; extracellular space <sup>[75]</sup>
<b>Amyloidogenicity</b>	Yes <sup>[14]</sup>	Yes <sup>[17]</sup>

<b>Typical Amyloid Deposition Site</b>	Pancreatic beta cells, brain parenchyma, microvasculature <sup>[14,20-25,27]</sup>	Hippocampus, neocortex, cerebrovasculature <sup>[75]</sup>
<b>Downstream effects</b>	Apoptosis of $\beta$ -cells; IL-1 $\beta$ overexpression; extra-pancreatic accumulation; cross-seeding with A $\beta$ in amyloid plaques <sup>[18,19]</sup>	Senile plaques in the neocortex; hippocampal and prefrontal cortex neuronal loss; dementia <sup>[36]</sup>
<b>Degradation pathway</b>	Insulin degrading enzyme <sup>[17]</sup>	Insulin degrading enzyme <sup>[17]</sup>
<b>Associated disease states</b>	T2DM, MCI, AD, CAA, <sup>[14,26,27]</sup>	AD, CAA, PD, Huntington's disease <sup>[75]</sup>

Table 1. Summary table comparing amylin to  $\beta$ -amyloid.

Table 2. Table summarizing key human study findings in the field of amylin research.



**Reference(s)**

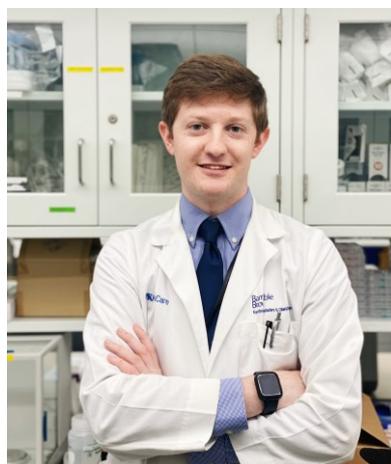
**Amylin-related pathophysiology**

**Key Finding**

1-7	Diabetic state	Prediabetes and T2DM raise the risk for dementia and MCI/AD conversion.
8-12	Glucose control	Associations between glycemic control and cognitive status are inconsistent.
14	Amyloidogenicity	Human, but not rodent, amylin is amyloidogenic, forms amyloid deposits, and is a pathological hallmark of pancreatic islets in T2DM.
15	Postprandial signaling	Amylin increases several-fold following meals.
18,19	Islet amyloid deposition	High glucose concentrations induce IL-1 $\beta$ which leads to downstream apoptosis.
20, 21-25	T2DM, AD	Amylin is present in the brains of individuals with and without T2DM who have Alzheimer's disease. Amylin-A $\beta$ co-staining was found in 10-15% of all plaques.

27, 29	fAD, MCI	Amylin was detected in neuronal soma and neuritic plaques of fAD patients. Increased amylin and decreased A $\beta$ 42 in CSF were noted in MCI patients.
30	CNS amyloidosis	Singly-nucleotide polymorphisms in the amylin gene predicted CNS amyloidosis, indicating AV45 PET signals are not entirely specific for A $\beta$ .
39-44	AD risk	Nutrition may increase or reduce AD risk and AD severity.
39, 42-44	AD risk	Diets consisting of fruit, vegetables, whole grains, nuts, tea, and fish are positively correlated with decreased AD risk. Diets consisting of meats, refined grains, and poultry are negatively associated with cognitive function.
58-60, 65	Cagrilintide, pramlintide	Initiation of amylin-analogue therapy is often accompanied by nausea and vomiting. Pramlintide may induce migraine-like attacks in patients.

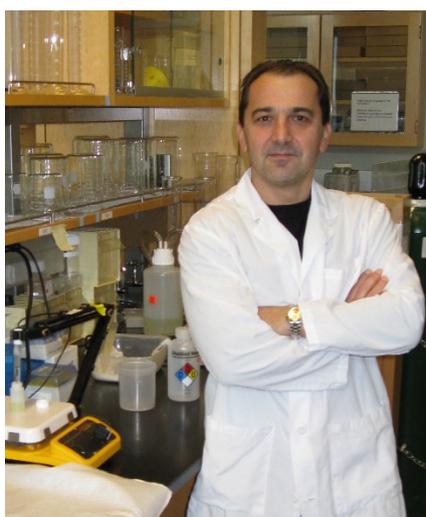
### Biographies



**Noah Leibold** is a graduate student in Dr. Florin Despa's laboratory at the University of Kentucky College of Medicine in the Department of Pharmacology & Nutritional Sciences. Through his affiliation with the Despa Lab, he is also a member of the Research Center for Healthy Metabolism at the University of Kentucky. Noah received his undergraduate degree in 2020 from the University of Dayton where he studied biology and psychology. Now, Noah studies the role of amyloid-forming amylin in microvascular dysfunction and human disease.



**James R. Bain, Ph.D.**, is a Professor of Endocrinology at Duke. He was one of the founders of the Metabolomics Lab in Duke's Sarah W. Stedman Nutrition and Metabolism Center. The lab, now in its twentieth year, is an integral part of the Duke Molecular Physiology Institute. Though their team collaborates widely in biomedicine, they have always maintained a strong focus on diabetes, obesity, and cardiovascular disease. In the present work, James is delighted to build upon his collaboration with his colleagues at the University of Kentucky in seeking a better understanding of the role of amylin in Alzheimer's disease.



**Florin Despa, Ph.D.**, is Professor in the Department of Pharmacology and Nutritional Sciences at the University of Kentucky. His laboratory in collaboration with the University of Kentucky's Alzheimer Disease (AD) Research Center and UCL Queen Square Institute of Neurology identified amyloid-forming amylin secreted from the pancreas as a contributing factor to brain microvascular and AD pathologies, in both sporadic and early-onset, familial AD. Despa laboratory integrates biochemical investigations of human tissues with clinical data, physiological analyses and in vivo phenotyping of genetically engineered rodent models to delineate nodal regulatory points of amylin biology that could be modulated to prevent AD.

The amylin hormone is secreted from the pancreas and is involved in glucose regulation. Excess amylin is secreted in persons with diabetes and can induce metabolic changes in the brain. Excess amylin can also form amyloid plaques and cause cells to die. Here, we hypothesize that nutritional interventions could reduce deleterious effects of dysregulated amylin.

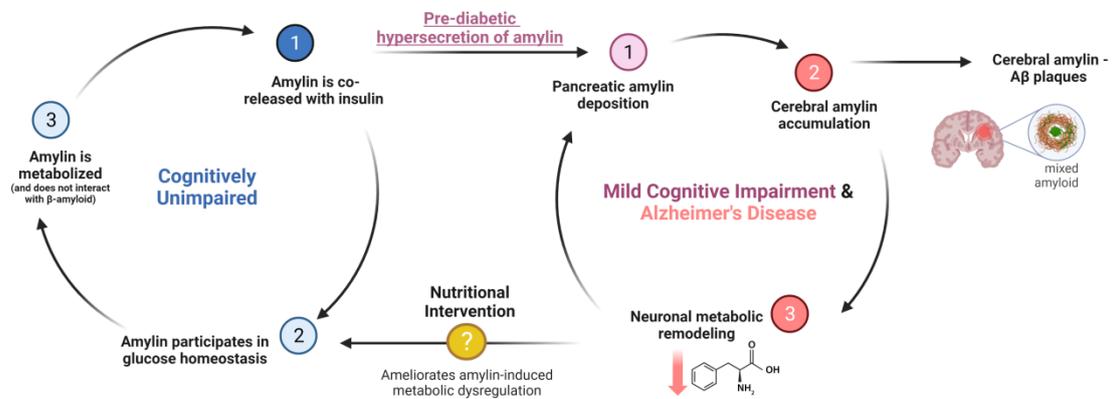


Fig. 1