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REVIEW ARTICLE

Amylin Pharmacology in Alzheimer's Disease Pathogenesis and Treatment

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Abstract: The metabolic peptide hormone amylin, in concert with other metabolic peptides like insulin and leptin, has an important role in metabolic homeostasis and has been intimately linked to Alzheimer's disease (AD). Interestingly, this pancreatic amyloid peptide is known to self-aggregate much like amyloid-beta and has been reported to be a source of pathogenesis in both Type II diabetes mellitus (T2DM) and Alzheimer's disease. The traditional "gain of toxic function" properties assigned to amyloid proteins are, however, contrasted by several reports highlighting neuroprotective effects of amylin and a recombinant analog, pramlintide, in the context of these two diseases. This suggests that pharmacological therapies aimed at modulating the amylin receptor may be therapeutically beneficial for AD development, as they already are for T2DMM. However, the nature of amylin receptor signaling is highly complex and not well studied in the context of CNS function. Therefore, to begin to address this pharmacological paradox in amylin research, the goal of this review is to summarize the current research on amylin signaling and CNS functions and critically address the paradoxical nature of this hormone's signaling in the context of AD pathogenesis.

Keywords: Alzheimer's disease, amylin, therapy, diabetes, metabolism, amyloid, neuroprotection.

1. INTRODUCTION

Alzheimer's disease (AD) is a form of dementia characterized by progressive memory loss and changes in cognitive and neuropsychiatric behaviors that lead to the inability to perform everyday tasks and death [1, 2]. There are two classifications of AD, familial and sporadic. Familial AD, representing only <1% of all cases, is inherited through mutations in 3 genes which include: presenilin (PSEN-1 and -2) or amyloid precursor protein (APP) genes. These cause the overexpression and cleavage of APP, producing excess amyloid beta (Aβ) peptide accumulation. Sporadic AD, also known as late onset AD, is a multifactorial form of neurodegeneration where the cause is currently unknown.

The main cellular hallmarks of AD include neurodegeneration of hippocampal neurons that progressively spread to other regions and two main pathological entities, extracellular Aβ plaques and intracellular tangles made of hyperphosphorylated tau protein [3-7]. The progressive accumulation of these hallmarks is thought to lead to the progressive cognitive and neuropsychiatric decline observed in these patients [5]. However, despite both tau and Aβ pathology being hallmarks of AD, it is not yet fully clear whether in late-onset AD, pathology is the driver of cellular dysregulation or rather a result of dyshomeostasis of more fundamental cellular processes. The latter suggests a more complex AD development, likely associated with multiple independent insults to which we are exposed throughout our lifetime [8-10].

1.1. The Exposome in Late Onset AD

Although aging is the number one risk factor for the development of sporadic AD [11], AD is not a normal consequence of aging [1, 12]. A growing list of genes, the most prominent of which being APOE [13], are also being implicated in late onset AD. However, several environmental exposures throughout one's lifespan can independently, or in combination with aging, drive AD development. These range from traumatic brain injury [14-18], viruses [19, 20] or toxins [21-24] to socioeconomic aspects such as low education levels [25], or lifestyle choices such as a sedentary lifestyle [26, 27]. In fact, clinical outcomes associated with lack of exercise and poor diet, namely high blood pressure, cardiovascular disease and particularly Type II Diabetes Mellitus (T2DM), have all been linked to AD development [28-36].

The exact mechanisms that underlie the relationship between AD and T2DM remain unknown, however, both diseases share multiple commonalities as detailed previously [37]. T2DM is characterized by the presence of hyperglycemia, hyperinsulinemia, and insulin resistance [38], both systemically and centrally. In fact, a consequence of systemic hyperglycemia and hyperinsulinemia is the reduction of insulin receptors within the blood-brain barrier (BBB), which in turn lead to decreased insulin and glucose signaling within the brain [39-42].

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Importantly, clinical reports show that diabetic patients have reduced thickness of brain regions, or atrophy, in regions affected in AD, such as the hippocampus [43-45]. Thus, not surprisingly, 70% of T2DM patients report cognitive impairment [46, 47]. Like AD, T2DM is also associated with exacerbated reactive oxygen species (ROS) production linked with increased mitochondrial and ER stress [48-50], and activation of inflammatory cascades [51-54] within the brain. Also, of note, is the fact that T2DM and AD, albeit different amyloid proteins (amylin in T2DM and Aβ in AD) share amyloidogenesis and amyloid processing, clearing and aggregation changes as potential common pathogenic mechanisms, one in the pancreas and the other within the brain.

The assessment of metabolic hormone levels throughout normal aging and during disease states and their impact on neuronal processes may offer new biomarkers and novel directions to target therapeutics for AD. In this regard, the common pathogenic mechanism between the two pathologies and the potential relationship between the two amyloids (amylin and Aβ) in the initiation of both diseases has been the focus of increasing research in the last decade as will be discussed throughout this review. Interestingly, data supports both a pathogenic and therapeutic role of amylin for AD pathogenesis [55, 56]. This paradox highlights an incomplete understanding of mechanisms underlying this relationship. This is further exacerbated by the complex physiology of amyloids and receptor signaling system through which amyloids - like amylin - signal [57-59]. The latter is a potential source for further understanding the pathophysiology of both diseases as well as a fruitful pathway for novel pharmacology development. Thus, here we summarize the current research in the area of amylin and CNS function and AD, provide an up-to-date review of its receptor signaling mechanisms, and critically discuss the pharmacological paradox associated with amylin pharmacological therapy in the context of AD pathogenesis.

Although peripheral mechanisms have been suggested, satiety, energy homeostasis, and newer signaling mechanisms associated with amylin action are thought to be largely regulated via the central nervous system (CNS), as will be detailed in the sections to follow.

2. AMYLIN AND THE AMYLIN RECEPTOR

Amylin is 37 amino acid (aa) peptide, a part of the calcitonin family alongside calcitonin (Calc), two Calc related genes (aCGRP and bCGRP) and adrenomedullin (AM) [60]. Amylin is packaged and co-released with insulin in 1:100 (15:1, insulin: amylin molar) ratio from β-islet cells of the pancreas after a meal consumption [61, 62].

Amylin has an important role in energy homeostasis systemically and centrally and acts as a satiety hormone [63-66]. For example, amylin serves an important glucoregulatory role by limiting insulin release from the pancreas [64, 67]. Similarly, amylin inhibits local glucagon secretion in the liver, stomach, and intestine, slowing gastric emptying and, thus, nutrient absorption [63, 64, 68-70]. In the CNS, amylin is known to sensitize leptin signaling [71, 72], thus, serving an important role in energy homeostasis acutely, during meals, and longer-term, through the hypothalamic processes. These findings have been further validated in animal models in which amylin is genetically deleted [72-75].

2.1. Amylin Receptor Expression & Signaling

Amylin does not have a cognate receptor but rather signals through the native calcitonin receptor (CalcR), a class B, seven transmembrane spanning G-coupled protein receptor (GPCR). Specificity to amylin is conferred by the heterodimerization of CalcR with one of three receptor activity modifying protein (RAMPs 1-3) [76]. Thus, the amylin receptor (AMYR) is accepted to be CalcR complexed with a RAMP [59, 76-81]. There are two isoforms of CalcR, alpha and beta [82, 83], as well as three known isoforms of RAMPs, named RAMP1, -2 and -3, providing a highly complex signaling network through AMYR subtypes: AMYR1a, AMYR1b, AMYR2a, AMYR2b, AMYR3a and AMYR3b [79, 83, 84].

The different components that make up the AMYR have been reported in both the periphery, namely, the kidney, testes, skeletal muscle, pancreas, liver, stomach, small intestine, osteoclasts, and in dorsal root ganglia [85, 86], as well as the CNS. Radioligand binding studies suggest the brain to be a region of the highest level of amylin binding within the body [87]. Of note, early studies found amylin binding sites within the CNS in 1993, roughly six years before AMYR was fully characterized [59, 81]. To this end, dense binding sites were originally characterized within the area postrema (AP), nucleus accumbens (NAc) and the hypothalamus. These brain regions are linked to amylin's regulation of satiety. Additional sites of amylin of binding as well as amylin uptake, confirmed amylin-labeled radioactivity include: ventral tegmental area (VTA), hypothalamus, NAc, subfornical organ (SFO), amygdala, bed nucleus of the stria terminalis (BNST), locus coeruleus, thalamus pons, medulla, hippocampus, striatum, as well as frontal, occipital and parietal lobes [59, 85, 88-96].

CalcR and all three RAMPS have been shown to co-localize in hindbrain and midbrain areas such the Nucleus Tractus Solitarii (NTS) within the brain stem and the lateral parabrachial nucleus (LBPN), part of the pons within the midbrain [59, 90-94]. Additionally, different RAMP subtypes are known to localize to different areas. For example, along with CalcR, RAMP1 has been found in the area AP, ventromedial hypothalamus (VMH) and the NAc, caudate putamen and olfactory tubercles [91, 92, 97-99]. On the other hand, RAMP3 has been reported within the AP, dorsal thalamus, and SFO. In humans, RAMP2 is primarily expressed in the vasculature, and knockout of RAMP2 is lethal [77], thus, it is less commonly studied. Together, these data suggest that RAMPs may confer regional and signaling specificity. Importantly, the study of AMYR signaling *in vivo* is further complicated by the fact that no AMYR conformation is 100% specific to amylin binding [81, 82], and the fact that RAMPs are known to complex with nine different receptors, not just CalcR [100, 101]. Similarly, since CalcR signals for its native ligand calcitonin, unless it is coupled to RAMPs, knockout strategies for either RAMPs or CalcR are not useful to determine AMYR signaling mechanisms [58, 102].

In vitro studies, which confer most of our understanding of AMYR signaling, demonstrate that ligand binding to the AMYR activates adenyl cyclase and phospholipase C path-

ways ($G\alpha_s$ and $G\alpha_q$, respectively) [80, 103-105]. Either cascade is known to drive ERK phosphorylation (pERK), which has been established as a key signaling molecule in AMYR action [103, 106, 107]. When comparing–the main AMYR subtypes, AMYR1 and AMYR3 have been reported to have similar binding affinity and dose-dependent response signaling for amylin [108]. However, some studies have shown a more diverse signaling pattern depending on the cascade activated and the cell type studied. For example, both AMYR1 and AMYR3 were shown to increase second messenger cAMP twenty-fold in Cos7 cells at similar doses. However, activation of these two receptor subtypes only led to a three to five-fold increase in intracellular Ca^{2+} and ERK phosphorylation (pERK) in Cos7 and HEK293 [105]. Moreover, this study also reported that AMYR3 preferentially signaled for through Gq, driving an increase of Ca^{2+} and pERK, over AMYR1 in Cos7 cells, but not HEK293 cells. Such studies highlight the complex nature of AMYR signaling, even *in vitro*.

Antagonists for the members of the calcitonin family (*i.e.*, AC413, AC66, $CGRP_{8-37}$, AC187, AC253) have been widely used to address the action of the AMYR. These antagonists are typically N-truncated isoforms of the native agonists that competitively inhibit receptor activation [109]. The most commonly used antagonist within this family, AC187, is modeled after salmon CT (sCT), where aa 35-37 are homologous to rat amylin. sCT is known to activate AMYR second to CalcR (64); additionally, sCT and amylin share a 30% aa sequence similarity [110]. However, AC187 is missing the disulfide bridge found in amylin that is thought to be the biologically active portion of these peptides within the calcitonin family [111]. AC187 is found to be equally potent as an antagonist of AMYR1a and AMYR3a receptor subtypes, suggesting it cannot discriminate between the two [58, 102, 112]. Together, these data emphasize the need for developing new AMY receptor pharmacology to deepen the mechanistic understanding of this hormone peptide.

3. AMYLIN CENTRAL NERVOUS SYSTEM FUNCTION

3.1. Hindbrain Amylin Function

Canonical amylin signaling within the CNS was first linked to the AP [103, 113, 114], a nucleus within the medulla oblongata, critical in the integration of neural inputs from the peripheral nervous system that allows larger peptides, like amylin, to access the CNS. AMYR activation within the AP reduces feeding behavior *via* the initiation of meal ending signals [115, 116]. This effect is reversed by antagonist delivery [117, 118]. Amylin also serves as a modulator of energy intake through the regulation of glucagon secretion, processes that are reversed by delivery of the AC187 antagonist, particularly as they pertain to glucagon secretion [119], food consumption [120], and inhibition of gastric emptying largely suggested to be mediated through vagal stimulation from AP outputs [63, 65, 121].

The CalcR and RAMP3 subtype most prominently colocalize within the AP to form the AMYR3 [93, 122]. AMYR3 has been suggested to play a key role in amylin-mediated effects on glucose regulation and satiety signaling, shown by altered glucose sensitization and decreased inter-meal duration in the RAMP3 KO mouse [104]. These findings seem to be restricted to AMYR3, as Zhang and colleagues (2011) showed that over-expression of RAMP1 does not alter feeding behaviors in mice [123]. However, as mentioned before, these results need to be weighed with caution since knockout or over-expression RAMPs may be driving changes beyond amylin signaling.

3.2. Hypothalamic Amylin Function

Amylin effects on long-term energy homeostasis, as well as additional regulation of satiety mechanisms, are also mediated through AMYR signaling in the hypothalamus [124]. A transporter-mediated mechanism enables amylin crossing across the BBB [96, 125] and allows amylin effects in brain regions independently of AP mechanisms.

A key area in long-term energy regulation and body weight is the VMH. These aspects are primarily regulated *via* peripheral adiposity input signals. Similarly, amylin shows positive effects on overall energy balance and increases energy expenditure [120, 126, 127]. In this regard, amylin is proposed to regulate energy expenditure by increasing brown adipose tissue activity mediated through the sympathetic nervous system. Mediation of sympathetic output in combination with amylin ability to reduce meal size is suggested to be the key component of amylin signaling ability to reduce adiposity [127]. This effect is blocked by AMYR antagonist administration, which markedly increases body adiposity [120]. Such changes are also seen in a human RAMP1 overexpression mouse model [128]. Specifically, Coester *et al.* (2020) reported that RAMP1 over-expressor male mice showed increased fat mass deposits, despite displaying similar body weights to controls. Female RAMP1 KO did not show changes in fat mass; however, they showed altered plasma leptin levels compared to controls. This work suggests that AMYR1 may be important for these amylin mechanisms [129].

In fact, it has been hypothesized that functional amylin and leptin signaling are both required for these actions, suggesting a synergistic relationship. To this end, leptin sensitivity is lost during the obese and diabetic states, leading to the loss of satiation and accumulation of fat mass over time; however, amylin administration in combination with leptin in obese mice shows additive results on fat-specific weight loss over amylin or leptin therapy alone [72, 114, 130]. Furthermore, AMYR knockdown within the VMH results in reduced pSTAT3 signaling, whereas amylin gene knockdown mice have significantly less LepR mRNA within the VMH, as well as overall leptin insensitivity [71, 72], collectively elucidating important amylin sensitizing effect on leptin.

Another important downstream target of leptin and amylin activation within the hypothalamus is proopiomelanocortin (POMC), a precursor protein important for satiety and body weight management that counteracts the orexigenic actions of agouti related peptide/ neuropeptide Y (AgRP/NPY) neurons [124, 131, 132]. The activation of POMC neurons within the ARC, causes POMC to be converted to one of several end products, including melanocyte-stimulating hormones (MSHs), corticotrophin (ACTH), and endorphins (*i.e.*, β-endorphin). MSH subtype alpha (αMSH) activates the melanocortin receptor subtype 4 (MC4R) receptors to mediate satiety [133, 134].

A functional MC4R circuit has been suggested for amylin actions on satiety as $MC4R^{K314X/K314X}$ mice, a receptor loss-of-function model, showed a loss of responsiveness on feeding behaviors upon AMYR agonist therapy compared to WT mice [135]. More specifically, both LepR and AMYR have been suggested to trigger JAK/STAT3 or ERK signaling cascades within POMC neurons, respectively, to drive such effects [71, 124].

Altogether this body of work highlights the amylin actions in mediating metabolic homeostasis processes. Importantly, however, amylin's actions extend beyond metabolic regulation to other processes that are relevant to aging and AD development, discussed in the section below.

4. AMYLIN LEVELS AND ALZHEIMER'S DISEASE

The current literature on amylin signaling is conflicting regarding its role in AD pathogenesis. On one end, amylin has been hypothesized to drive AD pathogenesis. As the name suggests, amylin is an amyloid peptide that aggregates *in vivo* during pathological states, thus, it is not surprising that its discovery was in aggregates in the pancreas of T2DM patients as well as diabetic cats [61, 136, 137]. Interestingly, amylin oligomers and plaques have been reported to be present in temporal lobes and within arteriole walls of both diabetic and non-diabetic patients with AD, as well as cognitively unimpaired patients. These aggregates have been reported to be mixed amylin- Aβ plaques or amylin-only plaques [138-140]. Amylin fibrils, like Aβ, are toxic to β-islet cells in late stage T2DM, as well as neurons *in vitro* [141-143]. Recent work suggests that amylin may be serving as a seeding mechanism for amyloid beta in diabetic patients, thus further linking T2DM to AD and supporting the traditional view of amyloid aggregation as a '*gain of toxic function'* mechanism in disease etiology [138, 144].

The above evidence, however, is contested by studies showing negative correlations between amylin levels and disease pathogenesis. For example, Adler *et al.* (2014) showed that plasma amylin levels were negatively correlated with cognitive impairment [145]. Both mild cognitive impairment (MCI) and AD patients showed significantly lower levels of circulating amylin than age-matched control subjects. These findings were confirmed by others [146] (after adjusting for APOE4 allele, diabetes, stroke, kidney function and lipid profile [147]. An additional study from Zhu and colleagues [148] found that plasma amylin levels and AD risk might fall on an inverted U-shaped curve, where lower and extremely high plasma amylin concentrations were associated with increased AD risk, whereas high plasma amylin did not show this relationship. Interestingly, this study also reported that plasma amylin concentrations shared a positive correlation with temporal gray matter volume [149]. Collectively, this work suggests that, at least at the level of circulating amylin, the relationship is one that is beneficial, not pathogenetic, thus supporting a "*loss of native function"* mechanism of pathogenesis in conditions such as T2DM, as well as AD.

4.1. Amylin Receptor Modulation in AD Models: Cognition

Several animal studies using native amylin preparations or non-aggregating forms of amylin (pramlintide acetate) [150], which shows similar pharmacokinetics and pharmacodynamics as human amylin [108], support these conclusions. Of note, pramlintide acetate therapy has shown beneficial outcomes in T2DM patients receiving insulin therapy, such as improving glycemic index, increasing weight loss in obese patients, and improving cognitive decline [151]. Of importance, and in addition, pramlintide lowers postprandial glucagon in T2DM patients [152] without inducing hypoglycemia [153]. These benefits also extend to cognition and mitigating AD-related pathogenesis.

Adler *et al.* (2014) found that a five-week chronic infusion of pramlintide in SAMP8 mice (a model of accelerated aging) improved novel object recognition, a hippocampal formation dependent memory test. These benefits were linked to increased expression of antioxidant enzymes and synaptic markers, including synapsin I and CDK5 [145]. This group extended this work to an APP/PS1 AD mouse model [154], where they showed that pramlintide therapy rescued hippocampal spatial memory deficits [155]. Additional studies have confirmed these findings in other mouse AD-mouse models. Both human amylin and pramlintide, in 5XFAD and Tg2576 mice, improved Y maze and MWM performance [156], an aspect that was demonstrated to be AMYR dependent [157].

As initially discussed, however, whether amylin receptor activation is beneficial or detrimental in AD is controversial. This is evidenced by data demonstrating that blocking receptor activation, thus inhibiting amylin function, is beneficial in AD pathogenesis. AC253 or cyclic AC253(cAC253) antagonists reportedly improved T-maze and MWM in 8 mos. TgCRND8 AD mice [56, 158]. AC253 and cAC253 were suggested to improve memory deficits through increased synaptic markers, synapsin I and synaptophysin [56, 158]. Kimura and colleagues (2016) demonstrated that high doses of (50nM) human amylin induce long-term depression (LTD) in CA1 hippocampal slices of older TgCRND8 mice, suggesting that amylin receptor antagonism would result in benefits [159]. However, it is important to note that the high dose and advanced stage of pathology in these mice could have confounded the resulting conclusions. Interestingly, the same authors reported that pramlintide application to CA1 in hippocampal slices induced long-term potentiation (LTP), important for memory formation, compared to controls, and suggested that pramlintide served an antagonist function, an aspect that is not well supported, at least *in vitro* [108].

Genetic manipulation of amylin receptor components in AD models suggests that amylin receptor activation may be detrimental in AD models. For example, a recent study from Patel *et al.* (2020) [160] demonstrated that depletion of amylin function via a 50% hemizygous CalcR knockdown in a TgCRND8 or 5XFAD rescued LTD and cognitive deficits in an MWM task observed in this mouse. However, it is important to note that the knockdown of the CalcR is not specific to amylin action.

4.2. Amylin Receptor Modulation in AD Models: AD Pathology

Amylin and Aβ, both being amyloids, possess similar secondary beta-pleated sheet structures and are both degraded by insulin-degrading enzyme (IDE) [143, 161]; because of this, it has been suggested that Aβ can bind to and signal through AMYR, specifically, AMYR3 [143, 162]. Aβ bind-

ing to AMYR has been proposed to be detrimental by 1) toxic intracellular signaling and 2) inhibiting amylin binding to its cognate receptor and driving accumulation of amylin extracellularly [162, 163]. Furthermore, Mousa *et al.* (2020) proposed that amylin and pramlintide alter γ-secretase subunits, increasing their translocation to lipid rafts and increasing total Aβ in TgSwDI mice [55]. However, it is important to note that while *in vitro* and *ex-vivo* work suggest benefits of AMYR blockade on amyloid-related parameters, *in vivo* studies using amylin receptor antagonists [56, 158] reported the lack of changes in Aβ burden nor APP processing.

Contrary to the above studies, others have reported that amylin and pramlintide administration reduce Aβ plaque burden, again supporting a neuroprotective action of amylin within the CNS. Patrick *et al.* (2019) saw that chronic pramlintide reduced plaque burden and formic acid-soluble fraction (fibrillar Aβ) $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ compared to APP/PS1 saline controls [155]. The same study showed that hippocampal and cortical ADAM10 protein expression was increased in pramlintide-treated mice compared to saline controls, concluding that mediation of alpha secretase could be a potential mechanism of action of pramlintide to reduce amyloidosis [155]. In parallel, Zhu *et al.* (2015) saw that both human amylin and pramlintide decreased Aβ plaque size and burden, and suggested decreased BACE1 activity as a mechanism due to findings that amylin treated Tg2576 mice had reduced CTFβ cleavage products, confirmed through decreased BACE1 activity [156]. Overall alteration of APP-processing enzymes may speak to amylin modulation of APP enzyme trafficking or availability, a theory that remains to be carefully tested.

Amylin administration has also been suggested to regulate Aβ clearance from the brain [156]. To this end, a single injection of either human amylin or pramlintide via IP or ICV leads to increased serum $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ 24 hours later in both mouse models, suggesting changes in Aβ efflux by amylin [156]. This mechanism of Aβ clearance has been proposed to be via AMYR activation within cerebral arteries, causing vasodilation, increasing cerebral blood flow, thus increasing Aβ efflux from the brain [164, 165].

Recent reports also suggest the ability of amylin to regulate tau pathology. For example, amylin has been shown to interact, via co-localization, with MAP2 and tau in hippocampal cells of individuals with AD, implicating negative protein-protein alterations that promote tau aggregation [166]. Conversely, Zhu *et al.* (2017) reported that amylin significantly decreased phosphorylated Ser396/Ser 404 Tau (PHF-1) and p25 in 3XFAD mice, compared to controls, thus reducing pathology. Additionally, this study also found that AC253 blockade of AMYR blocked these effects [157]. However, the relationship between amylin and tau and the impact of amylin receptor agonism or antagonism on tau pathology remains fully explored. Importantly, how such regulation or even which receptor subtype mediates Aβ and tau protein burden or clearance remains unknown.

4.3. Amylin Receptor Modulation in AD Models: Oxidative Stress & Inflammation

As mentioned previously, oxidative stress and inflammation commonly seen in T2DM and AD are detrimental to neuronal function, contributing to cellular damage and synaptic dysfunction [167, 168]. *In vitro* data also supports a potential antioxidant function for amylin [155]. Therefore, a mechanism of action of amylin/pramlintide associated with cognitive benefits in AD could also involve such a mechanism. To this end, within the CNS, pramlintide treated SAMP8 [145] and APP/PS1 mice [155] showed a profound impact on stress-related enzymes including hemoxigenase-1 (HO1) and glutathione (GPx) and manganese superoxide dismutase (MnSOD) *in vivo* and *in vitro*.

A well-known source of oxidative stress stems from inflammatory processes. In connection with this, Fu *et al.* (2017) demonstrated that AMYR activation may be involved in microglial activation. Both CalcR and RAMP3 were shown to be expressed in human fetal microglia, and their activation results in increased intracellular Ca^{2+}, an action associated with microglial activation. This effect was diminished by AMYR antagonism using cAC253. Nevertheless, like the findings for cognition and pathology, the above findings have also been contradicted. To this end, Wang *et al.* (2015) demonstrated that amylin attenuated LPS induction of CD68, a proinflammatory marker, in a microglia BV2 cell line. Additionally, knockdown of RAMP3, via siRNA, abolished amylin-mediated inhibition of CD68, suggesting that AMYR3 may be responsible for this relationship. *In vivo* work in the 5XFAD mouse showed lower expression of ionized calcium-binding adaptor molecule 1 (IBA-1) and diminished microglial activation. Importantly, co-administration of AC253 + amylin blocked this reduction of neuroinflammation, suggesting that AMYR activation may mediate anti-inflammatory pathways [157]. Together, while the data are conflicting, the presence of amylin AMYR in microglia suggests a direct inflammation regulatory role for this peptide that should be further explored.

CONCLUSION

The work described above supports a much more complex role for the peptide amylin than previously thought. Functions for this peptide expand beyond the traditional peripheral metabolic regulatory roles to include several CNS functions, such as long-term energy balance, reward functions, and, reviewed in detail here, cognitive functions and cellular endpoints associated with AD development (Table **1**). The most attention-grabbing aspect of amylin research in AD is the directly conflicting reports that amylin agonism and antagonism are therapeutically beneficial in the disease. To this end, studies support both a *'gain-of-toxic-function'* by amylin aggregation, either by providing a seed for Aβ [55, 56], or driving toxicity through its receptor [159, 162], as well as a beneficial effect of amylin or analog therapy [155-157, 164]. The latter supports the hypothesis that aggregation-mediated depletion of free amylin may lead to a *"loss of native function"*, an aspect that is supported by negative correlations between free amylin and AD in human studies [149, 155] (Fig. **1**).

The key to resolving some of these conflicts could lie in delving deeper into the complex amylin signaling pharmacology. This is particularly critical, given that amylin does not have its own receptor but rather signals through two subtypes of the calcitonin receptors when coupled to three potential modulating receptor proteins. Additional complexity is added to this already complicated system by the differential

Table 1. A condensed list of studies that evaluated amylin impact on cognition, amyloid and tau pathology, OS, inflammation, and signaling that utilized AD rodent and cellular models discussed within this review.

Amylin Findings in Alzheimer's Disease Literature			
Study	**Model**	**Treatment**	**Findings**
Lim *et al.*, 2010	SHSY5Y	Fibular hAMY or Aβ	Increased cytotoxicity LDH Reduced mitochondrial oxygen consumption
Adler *et al.*, 2014	Human	----------	MCI and AD patients have significantly decreased plasma amylin compared to normal aging individuals
	SAMP8 mice	PRAM	PRAM increased Novel Object Recognition task PRAM increased synaptic markers PRAM increased Cdk5
Qui *et al.*, 2014	Human	----------	Amylin plasma positively correlated with verbal memory and vasoconstriction tasks
Zhu *et al.*, 2015	5XFAD & Tg2576	hAMY or PRAM	Reduced Aβ plaque size Increased CSF A$\beta_{1\text{-}42}$ Improved Y maze & MWM performance Tg2576 + hAMY only- decreased CTFβ
	Human	AD & Cognitively unimpaired	Plasma amylin positively correlates with A$\beta_{1\text{-}40}$ and A$\beta_{1\text{-}42}$
Soudy *et al.*, 2016	TgCRND8	AC253	AC253 improved T Maze and MWM performance No differences in Aβ pathology AC253 increased synaptic markers AC253 decreased microglia activation
	HEK293	AC253, cAC253	Blocked hAMY-induced cAMP (dose dependent manner)
Kimura *et al.*, 2016	TgCRND8	Fibular hAMY or Aβ	Depressed hippocampal LTP
		PRAM	Increased hippocampal LTP
Verma *et al.*, 2016	Humans (T2DM + AD)	---------	Neuronal amylin aggregates + decreased membrane integrity
	HIP rats	---------	
		Daily hAMY	Neuronal amylin aggregates + decreased membrane integrity
	C57BL6/J	Daily hAMY	Neuronal amylin aggregates + decreased membrane integrity
Tao *et al.*, 2018	Healthy elderly	PRAM	Single PRAM dose increased A$\beta_{1\text{-}42}$ efflux
Wang *et al.*, 2017	BV2 (microglia line)	Amylin	Amylin reduced LPS-induced Iba-1 & CD68 phagocytic microglial marker Amylin reduced amyloid and tau pathology
	5XFAD	Amylin	Amylin "corrected" mitochondrial gene expression (microarray)
Zhu *et al.*, 2017	5XFAD	hAMY or hAMY + AC253	hAMY reduced Aβ pathology; AC253 attenuated these results reduced tauopathy hAMY decreased p25
	3xTgAD	hAMY or hAMY + AC253	both models- hAMY reduced microglia activation, AC253 attenuated hAMY improved Y maze and MWM

(Table 1) contd….

Study	Model	Treatment	Findings
Fu *et al.*, 2017	5XFAD Human fetal micro-glia	cAC253, hAMY, AB cAC253, hAMY, AB	cAC253 reduced Aβ pathology hAMY & Aβ increased inflammation AC253 inhibited oligomeric hAMY and AB induced Ca^{+2} influx
Zhu *et al.*, 2019	Human	----------	Plasma amylin correlated with brain volume Plasma amylin concentration was correlated with AD-incidence on a U-shaped curve
Patrick *et al.*, 2019	APP/PS1 SHSY5Y	PRAM PRAM	PRAM improved MWM PRAM reduced Aβ pathology PRAM increased OS enzymes PRAM increased ADAM10 (CTX & HIPP), increased BACE1 (HIPP) Reduced OS-induced toxicity
Patel *et al.*, 2020	5XFAD TgCRND8	50% hemizygous CalcR KD	(both strains) Reduced Aβ pathology Improved MWM task
Mousa *et al.*, 2020	TgSwDI	Amylin, PRAM	Amylin and PRAM alter y-secretase subunits, increasing transportation to lipid rafts

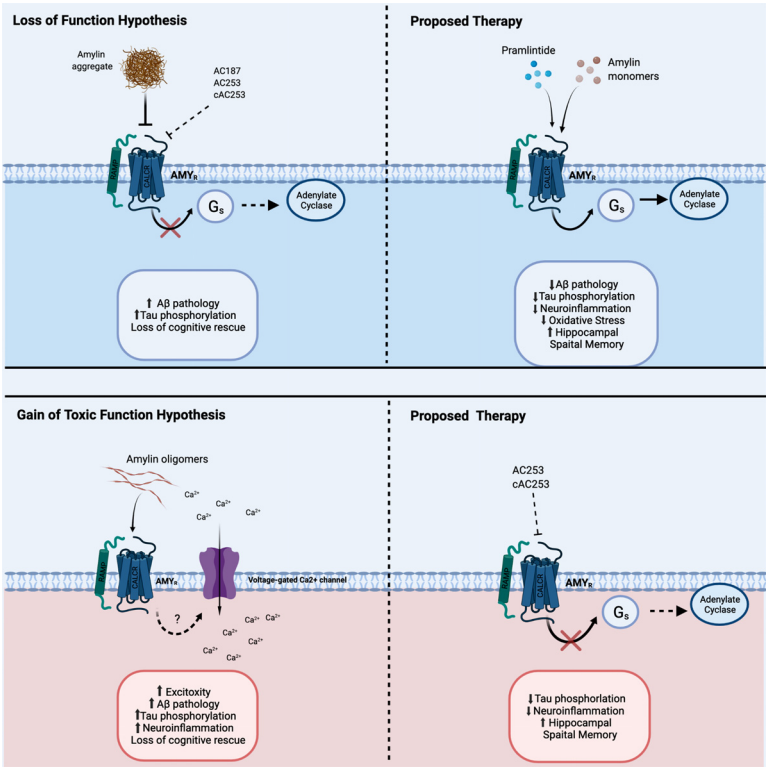

Fig. (1). The proposed signaling relationships between amylin, pramlintide (PRAM), and AMYR in AD as discussed throughout this review of the current literature. **Top Left**: Amylin aggregates (also mimicked by AMYR antagonist) may serve as a *"loss of function hypothesis"* of normal AMYR downstream signaling during Alzheimer's disease (AD) or metabolic dysregulation by blocking the receptor. It is proposed that due to this loss of amylin, there will be toxic consequences such as increased Aβ pathology, Tau phosphorylation and disruption of cognitive processes. **Top Right**: Proposed therapeutic approach signaling of amylin, PRAM and amylin as monomers activating AMYR in the brain leads to downstream adenylate cyclase activation to increase ERK signaling that leads to increased neuroprotective effects. **Bottom Left**: *"Gain of Toxic Function Hypothesis"*, higher concentrations or amylin oligomers/fibrils activating AMYR may cause the activation of Voltage-gated Ca^{2+} ion channels, to open leading to an excitotoxicity state due to chronic intracellular Ca^{2+} in state of disease or pathology, such as AD or Type II Diabetes. Bottom Right: Proposed therapy for this rationale is to block AMYR with antagonists that inhibit potential toxic downstream signaling. *Created with BioRender.com. (A higher resolution/colour version of this figure is available in the electronic copy of the article).*

expression of these combinations across regions within the CNS, all of which could have slightly different affinities for the ligand. Because of this complex receptor anatomy and the lack of a unique amylin receptor, the use of modern genetic tools to knock out a receptor becomes limited. Under genetic knockdown of calcitonin receptor or RAMPS one inherently disrupts both calcitonin and amylin signaling or any of the receptors that are modulated through RAMP binding, *i.e.*, calcitonin-like receptor and adrenomedullin receptor.

Together, the above highlights a key needed for "traditional" pharmacological studies, including detailed pharmacokinetics and pharmacodynamic studies of the native hormone, analogs, and existing antagonist in relation to each receptor subtype and CNS cell type. It also spawns for the development of novel pharmacology development in this area, one which utilizes modern computational modeling and high throughput techniques to understand how these peptides bind to each receptor subtype and activate or inhibit it. The development of specific antagonist for each receptor subtype based would allow for a much deeper understanding of amylin signaling *in vivo*.

Lastly, in relation to AD treatment, it will also become critical to determine the effects of such molecules under carefully controlled Aβ levels as well as carefully controlled measurements of aggregation, amyloid-beta processing, and degradation since one can impact the levels of the other. Together, however, the study of this pharmacological paradox is an opportunity to foster a deeper understanding of physiological amyloid functions and novel therapies in disease that is unfortunately devoid of pharmacological interventions beyond those aimed at lowering amyloid-beta.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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