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Amylin and its G-protein-coupled receptor: a probable pathological process and drug target for Alzheimer's disease

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Abstract

G-protein-coupled receptors (GPCRs) are shown to be involved in Alzheimer's disease (AD) pathogenesis. However, because GPCRs include a large family of membrane receptors, it is unclear which specific GPCR or pathway with rational ligands can become effective therapeutic targets for AD. Amylin receptor (AmR) is a GPCR that mediates several activities, such as improving glucose metabolism, relaxing cerebrovascular structure, modulating inflammatory reactions and potentially enhancing neural regeneration. Recent studies show that peripheral treatments with amylin or its clinical analog, pramlintide, reduced several components of AD pathology, including amyloid plaques, tauopathy, neuroinflammation and other components in the brain, corresponding with improved learning and memory in AD mouse models. Because amylin shares a similar secondary structure with amyloid- β peptide (A β), I propose that the AmR/GPCR pathway is disturbed by a large amount of A β in the AD brain, leading to tau phosphorylation, neuroinflammation and neuronal death in the pathological cascade. Amylin-type peptides, readily crossing the blood brain barrier (BBB), are the rational ligands to enhance this GPCR pathway and may exhibit utility as novel therapeutic agents for treating AD.

Keywords

Alzheimer's disease; G-protein-coupled receptors (GPCRs); Amylin; Amylin receptor (AmR); therapeutics

Introduction

The number of Alzheimer's disease (AD) patients is rapidly increasing in the US and globally (Mayeux and Stern, 2012). AD is a neurodegenerative disorder characterized by the

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accumulation of proteinaceous aggregates and neurofibrillary lesions composed of amyloid- β peptide (A β) and phosphorylated tau (pTau) proteins, respectively, in addition to non-specific components, such as neuroinflammation and neuronal death in the brain (Holtzman et al., 2012). Currently, only few medications are prescribed for AD, and their effects are modest and do not modify the underlying disease process. In addition, clinical trial drugs against a single component of AD pathology, A β , seem to only have modest effects on the disease (Holmes et al., 2008; Karran and De Strooper, 2016; Selkoe, 2013). The need for alternative and effective targets for the AD drug discovery is evidentiary.

Amylin is a gut-brain axis hormone. Using AD animal models, two independent laboratories have demonstrated that peripheral treatments with amylin or its analog, pramlintide, reduced the core AD pathology and neuroinflammation and improved cognitive impairment (Adler et al., 2014; Zhu et al., 2015; Zhu et al., 2017b). However, for decades amylin has been considered as a foe for AD due to self-aggregation properties (Qiu and Zhu, 2014). This review will present different perspectives but emphasize the research data and knowledge on amylin as a neuroprotective hormone. It is proposed that the beneficial effects of amylin type peptides for AD are via amylin G-protein-coupled receptors (GPCRs); when amylin aggregates, it fails to bind to this receptor (Figure 1). For more detailed review on amylin aggregation in AD, the readers should refer to another review by DeToma et al. (DeToma et al., 2012).

Amylin: a gut-brain hormone for energy homeostasis in brain

Amylin (also known as islet amyloid polypeptide, or IAPP) is a 37-amino acid peptide hormone belonging to the calcitonin gene peptide superfamily including calcitonin (CT), calcitonin gene-related peptide (CGRP) and adrenomedullin (Lutz, 2013; Wimalawansa, 1997). While amylin is mainly produced and secreted by β -cells in the pancreas (Westermarck et al., 1987), its expression occurs in other locations, such as the gut (Mulder et al., 1994), the sensory nervous system and brain (Mulder et al., 1995). Amylin is stored together with insulin in dense core secretory granules in the pancreas (Lukinius et al., 1989). It is secreted in response to diet/nutrient intake (Vine et al., 1998) and exercise (Kraemer et al., 2002) stimuli and displays a profile similar to that of insulin. The amylin gene is encoded on chromosome 12 and highly conserved in mammals during evolution (Chang et al., 2004; Nishi et al., 1989), and its gene polymorphism is associated with amyloid pathology in the brain and cognitive decline in AD (Roostaei et al., 2016).

Is amylin-mediated G-protein-coupled receptor/pathway disturbed in AD?

Amylin readily crosses the blood brain barrier (BBB) (Banks and Kastin, 1998; Banks et al., 1995; Olsson et al., 2007). A large body of data has documented the physiological actions of this peptide for both gastrointestinal and central nervous systems (Hay et al., 2015; Roth et al., 2013). Amylin receptor (AmR) is one type of GPCR and is composed of the calcitonin receptor (CTR) complexed with different receptor-activity-modifying proteins (RAMPs) (Gebre-Medhin et al., 1998; Hay et al., 2015). CTR and RAMPs are expressed in the brain, including the regions related to AD like locus coeruleus, cortex and hippocampus (Nakamoto et al., 2000; Young, 2005a). Individual RAMPs have been disrupted, revealing a

range of phenotypes in the mouse models. Heterodimers between the CTR and RAMP1 or RAMP3 have been shown to preferentially bind amylin to mediate physiological functions in the brain (Christopoulos et al., 1999).

GPCRs are known to be involved in numerous key components in AD pathogenesis, such as A β generation and pTau formation, and in neurotransmitter systems, including neuroinflammation. Glutamatergic, serotonergic, adrenergic and peptidergic neurotransmitter systems in the brain are disrupted in AD and deserve further exploration against AD (Thathiah and De Strooper, 2011). Acetylcholine levels are low in the AD brain, and muscarinic acetylcholine receptors (a class of GPCRs) have been implicated in the pathophysiology of AD (Wess et al., 2007). However, the effects of acetylcholine esterase inhibitors, which increase acetylcholine levels in the brain, are only modest in delaying cognitive decline and do not modify the underlying AD pathology in clinical use. Because multiple GPCRs share common components in secondary signal pathways, key GPCRs specific for AD pathogenesis have yet to be identified. Probably unspecific GPCR drugs have only modest effects. Because of the complexity of GPCR signaling, the rational design of ligands with increased specific efficacy and attenuated side effects may become the standard for drug development (Maudsley et al., 2007).

A recent study found that amylin gene polymorphism is associated with AD (Roostaei et al., 2016). Independent studies found that elderly who had AD or mild cognitive impairment (MCI) had lower concentrations of plasma amylin than controls (Adler et al., 2014; Zhu et al., 2015). Since amylin shares secondary structures with A β and tau (Kurnellas et al., 2013), I propose that amylin, with its AmR, is the key GPCR pathway disturbed by the AD pathology, and if so, a drug agonizing or enhancing amylin or amylin receptors could affect several key components in AD pathology and improve cognitive impairment. There are studies providing evidence to support that amylin and A β mediate different intracellular signal transduction. For example, despite the fact that amylin and A β bind to the same amylin receptor (Fu et al., 2012), while amylin and pramlintide increase intracellular cAMP, an important secondary messenger for learning and memory, A β 1-42 does not influence intracellular cAMP (Gingell et al., 2013). Additionally, amylin activates the extracellular-signal regulated kinase 1/2 (ERK1/2) pathway by inducing the phosphorylation of ERK1/2 (pERK) (Potes et al., 2012); in contrast, A β decreases pERK in neurons, leading to the generation of toxic tau phosphorylation and fragments (Reifert et al., 2011).

Amylin treatment reduces the core AD pathology in AD mouse models

A β aggregation and amyloid plaques are identified as hallmark pathology in the AD brain and have been thought to be key elements in early stage AD pathogenesis leading to the formation of tauopathy and neuroinflammation (Hardy and Selkoe, 2002). Amylin is shown to be an effective drug target, which can hold or delay the whole pathological cascade of AD (Zhu et al., 2017b).

Amylin and amyloids

Amylin and A β share several features, including similar β -sheet secondary structures (Lim et al., 2008), binding to the same amylin receptor (Fu et al., 2012) and being degraded by

(Bennett et al., 2003; Qiu et al., 1998; Shen et al., 2006) or bound to insulin-degrading enzyme (IDE) (de Tullio et al., 2013).

Using AD mouse models, 5XFAD and Tg2576, we investigated the effects of amylin and its clinical analog, pramlintide, on AD pathogenesis (Zhu et al., 2015). Chronic intraperitoneal (i.p.) injections in AD mouse models with either amylin or pramlintide reduced the amyloid burden and lowered the concentrations of A β in the brain. Independently, Adler et al. used pramlintide to treat another AD mouse model (Adler et al., 2014), SAMP8, which has increased amounts of A β correlating with age-related decline in learning and memory (Flood and Morley, 1998). Both teams discovered that amylin-type treatments significantly improved learning and memory in the different AD mouse models using different behavior tests. Our research demonstrated that amylin treatment reduced the amyloid burden in the brain by removing A β from the brain in AD mouse models (Zhu et al., 2015). A translational study using human subjects demonstrates that a single injection of pramlintide, an amylin analog, similarly induced a surge of A β in plasma in AD patients (Zhu et al., 2017a). Amylin and A β have consistently been positively associated in plasma in humans (Qiu et al., 2014), suggesting that the more amylin in blood crossing the BBB, the more A β moved out of the brain into the blood.

Amylin and tauopathy

The benefits of amylin treatment for AD are beyond reducing amyloid burden only in the brain. Recently, we conducted studies to investigate the amylin effect on tauopathy, another major component of AD pathology, by using AD mouse models (Zhu et al., 2017b). It was shown that amylin treatment reduced the phosphorylation and aggregation of tau in the brain. Two identified pathways lead to tau phosphorylation, CDK5 and GSK3 β (Lee and Tsai, 2003). Mechanistic studies have shown that amylin treatment decreased levels of CDK5 and p25 proteins for the p35-p25-CDK5 pathway for AD (Baumann et al., 1993; Tsai et al., 1994; Tsai et al., 1993) but did not influence the GSK3 β pathway in the brain. Again, AC-253 and AC-187 blocked the inhibitory effects of amylin on the tau protein-phosphorylating pathway of p35-p25-CDK5. Amylin also shares similar secondary structures with tau protein as well as A β (Kurnellas et al., 2013). These data demonstrate that amylin treatment through its receptor could play a role in reducing neurotoxic p25 levels, which attenuate pTau production and aggregation, and in reducing tauopathy formation in the AD brain.

Amylin and neuroinflammation

Neuroinflammation through microglial cells may play an important role linking brain AD pathology and cognitive decline (Griffin et al., 1989; Mattiace et al., 1990; McGeer et al., 1987; Overmyer et al., 1999; Paresce et al., 1997; Rogers et al., 1988; Rozemuller et al., 1986). However, no effective drug has yet been developed to target neuroinflammation in the brain. Our research examined whether peripheral treatment with amylin influenced neuroinflammation in the AD brain (Wang et al., 2017; Zhu et al., 2017b). Two well-documented markers for activated microglia, i.e., ionized calcium-binding adaptor (Iba-1) (Paquet et al., 2014; Zotova et al., 2013) and CD68 (Arnold et al., 2000), were examined in the brains of AD mouse models by immunostaining for the effects of amylin treatment on

neuroinflammation in the AD brain. While amylin treatment significantly reduced the number of Iba-1+ microglia cells at the cortex, thalamus and hippocampus, amylin treatment modestly but significantly reduced the number of CD68+ microglia at the cortex region in AD mouse models (Wang et al., 2017; Zhu et al., 2017b). The expression levels of inflammatory cytokines IFN γ and IL-1 β were also reduced by amylin treatment.

Amylin and dysregulation of energetic metabolism in AD

Despite of the hallmark of AD pathology including amyloids and tauopathy in the brain, multiple studies have demonstrated that metabolic diseases, including type 2 diabetes, obesity and chronic inflammation, increase AD risk (Merlo et al., 2010; Schrijvers et al., 2010; Walker and Harrison, 2015), suggesting dysregulation of energetic metabolism in AD pathology. Despite that the preclinical studies demonstrate amylin's beneficial effects as a single drug treatment in AD mouse models (Adler et al., 2014; Zhu et al., 2015), as an adipokine, it is possible that the role of amylin works with other adipokines, leptin and ghrelin, in adipoinular axis to inhibit apoptosis and inflammation processes and, thus, generate protective responses in the AD brain (Folch et al., 2013).

Since cerebral glucose metabolism is probably perturbed in the AD brain (Johnson et al., 2012), amylin is also an important hormone regulating glucose metabolism in the body (Min et al., 2011; Roth et al., 2013). Because amylin crosses the BBB, it may mediate these functions in brain. Indeed, amylin treatment influences several brain gene transcriptions, including ATP5B related to glucose metabolism. Amylin and pramlintide increased intracellular cAMP levels, an important secondary messenger of GPCRs for glucose metabolism and for learning, memory and mood (Gingell et al., 2013). Additionally, amylin activates the extracellular-signal regulated kinase 1/2 (ERK1/2) pathway by inducing the phosphorylation of ERK1/2 (pERK) (Potes et al., 2012). A study showed that amylin treatment increased glutamate release to levels sufficient to cause cell firing (Fukuda et al., 2013); this may be necessary for restoring learning and memory in AD (Danysz and Parsons, 2012).

Amylin and neuroprotection

Amylin has been proposed to play a role as a trophic factor (Potes and Lutz, 2010), for example, for osteoblast growth (Cornish et al., 1998). Amylin infusion enhanced neurogenesis in the hippocampus and the area postrema in the brain of rodents with ovariectomy and improved their immobility in forced swim tests (Trevaskis et al., 2010). Studies demonstrate that pramlintide-treated mice had increased expression of the synaptic marker synapsin I (Adler et al., 2014) and adding pramlintide reversed A β induced depression of hippocampal long-term potentiation (Kimura et al., 2016). Whether the neuronal protective activity of amylin under pathological insults can be beneficial to induce neuroregeneration in AD requires further investigation.

Elucidating the mechanism of amylin effects on learning and memory for AD

Both the molecular and cellular experiments have been conducted to elucidate the mechanism of amylin treatment for AD. Protection effects of amylin on cortical neurons are inhibited by adding the antagonists, AC253 or AC187, highly suggesting that AmR mediated this beneficial effect of amylin for AD (Zhu et al., 2017b). Because the C-terminals of AC253 and AC187 have almost identical sequences as the C-terminal of amylin, our study shows that AC253 alone reduced the AD pathology and improved learning and memory in AD mouse models, and some in vitro studies suggest beneficial effects against A β (Jhamandas et al., 2011; Kimura et al., 2012). Thus, it is likely that AC253 and AC187 may play the role of partial agonists for AmR and display both agonistic and antagonistic effects depending on the presence of the full ligand amylin (Zhu et al., 2017b).

Using a cell-based model of the BBB, it was found that amylin enhanced A β transport across the BBB. This effect was inhibited by amylin receptor antagonists and RAMP3 knockdown, further suggesting a role of AmR in mediating A β transport out of the brain across the BBB (Mohamed et al., 2017). Additionally, amylin treatments enhanced the A β brain-to-blood clearance likely by relocating low density lipoprotein receptor-related protein 1 (LRP1) from the cytosol to the membrane at the BBB. These studies provide a new avenue for the treatment and diagnosis of AD (Qiu and Zhu, 2014).

Using weighted gene co-expression network analysis (WGCNA), we discovered that peripheral amylin treatment has the transcriptome-wide targets in the brain of an AD mouse model. Specifically, amylin treatment influenced two modules of gene expressions 1) related to neuroinflammation that included a hub gene of CD68 and 2) related to mitochondrial function that included a hub gene of ATP5B (Wang et al., 2017). Using human data, we found that orthologues of these hub genes, including CD68 and ATP5B, strongly correlated with neurofibrillary tangles in the AD brain and with Mini-Mental Status Examination scores. Using a microglial cell line, BV-2, we found that CD68 expression stimulated by LPS was downregulated by adding low concentrations of amylin. In contrast, CD68 expression was not influenced by the media addition of a high concentration of amylin (Wang et al., 2017). In the activated microglia cells, we validated that the amylin-induced attenuation of CD68 expression is mediated by binding to AmR by knocking-down the amylin receptor.

The debate on whether amylin can be a therapeutic for AD

The perspective of aggregation

The beneficial effects of amylin might be surprising to some and thus the debate on whether amylin is beneficial or harmful for AD is ongoing. It is shown that human amylin causes neurotoxicity when the concentration is high to induce its aggregation, but rat amylin, which does not have aggregating character, does not induce neurotoxicity with the same concentration (May et al., 1993). More importantly, a recent paper demonstrates that low vs. high concentrations of amylin bind different receptors (Zhang et al., 2017). Thus the

potential benefits of amylin type peptides as a neuropeptide or a drug against neurodegeneration are probably through its cognate receptor, which is a different receptor from the one binding to aggregated amylin (Qiu and Zhu, 2014).

While I have no doubt that an extremely high concentration of human amylin leading to aggregation, it is worth to mention that the concentration (50 μ M) used to cause neurotoxicity in rat cortical neurons after two to four days' exposure (Jhamandas and Mactavish, 2012; May et al., 1993) is twenty times higher than the maximum concentration used in our neuronal culture. Our in vitro study showed that human amylin with a concentration from 10 ng/ml ($\sim$ 2.5 nM) to 10 μ g/ml ($\sim$ 2.5 μ M) was beneficial to antagonize the neurotoxicity caused by aggregated A β 1-42 in rat cortical neurons. The average fasting plasma amylin concentrations are in the range of 4–25 pmol/l in healthy humans (Nyholm et al., 1998), the peak of amylin in the amylin treatment we conducted for the mice was $\sim$ 1 nmol/l and the half-life of exogenous amylin or pramlintide is about 20–45 minutes *in vivo* (Colburn et al., 1996; Young, 2005b). Since MCI and AD patients have lower concentrations of plasma amylin than healthy controls (Adler et al., 2014; Zhu et al., 2015), the potential benefits of amylin type peptides with a physiological concentration as a neuropeptide should not be ignored.

A study found an accumulation of amylin amyloid in the cerebrovascular system in the AD brain (Jackson et al., 2013). The core structure of fibrils from amyloids in the AD brain is essentially the same as those in the pancreas of type 2 diabetes patients (Sunde et al., 1997). However, increasing evidence suggests that while pathological deposits are good diagnostic markers for disease, they are not actually the responsible pathological toxic species (Cohen et al., 2009). In this context, I would also argue that the strong tendency of amylin to aggregate may account for its presence in amyloid deposits but may not necessarily indicate its toxicity.

The perspective of neuropeptide for the lost functions in AD

There is no doubt that when a peptide aggregates, it can become toxic to the cells. However, if this peptide mediates important functions like amylin, its aggregation or the block of AmR by A β can lead to serious dysfunction in the AD brain. Thus providing a non-aggregating form of amylin to rescue the loss of functions should be another perspective for the AD drug development. The development of pramlintide for diabetes could be a good lesson for the drug development for AD.

Amylin amyloid deposits were first found in the pancreas in diabetic patients in 1901 (Opie, 1901) and amylin aggregates disrupt islet structure and contribute to β cell dysfunction in type 2 diabetes patients (Hoppener et al., 1994; Hull et al., 2004). However, the research on amylin as a gut-brain hormone resulted in and advanced an amylin analog, pramlintide, to be approved by FDA and became an effective drug for type 2 diabetes (Gebre-Medhin et al., 2000). Pramlintide has a favorable safety profile in clinical use. The most common side effect of pramlintide is nausea, which is certainly tolerable among type 2 diabetes patients. Many of these patients have amylin aggregation in the pancreas and still get benefits from the pramlintide treatment (Aronne et al., 2007).

The monomeric and aggregated amylin have different or even opposite effects on neuroinflammation through different mechanism. Trikha and Jeremic found that at low concentrations of amylin (100 μ M), the internalization of amylin monomers occurred through AmR. However, at high and cytotoxic concentrations, the internalization of amylin oligomers occurred through a macropinocytotic and amylin receptor-independent pathway leading to extracellular accumulation and cytotoxicity in pancreatic β cells (Trikha and Jeremic, 2013). Mice with disrupted RAMP1 genes exhibited dysregulated immune responses (Sexton et al., 2009), suggesting that monomeric amylin modulates inflammation by binding to its receptor. In another study, after unilateral adjuvant-induced inflammation, amylin expression was upregulated in innervating sensory neurons and was involved in the inflammatory response (Mulder et al., 1997). In inflammatory models characterized with vascular components, including mouse ear edemas induced by croton oil and acetic acid-induced peritonitis, amylin exerted anti-inflammatory activity (Clementi et al., 1995). However, aggregated human amylin has been shown to activate the inflammasome, NLRP3 (Masters et al., 2010). Aggregated amylin has been shown to stimulate microglial cells to secrete cytokines, including interleukin-6 and tumor growth factor- α , both of which have been related to AD pathology (Yates et al., 2000), leading to a proinflammatory stage of microglia cells (Srodulski et al., 2014). Almost all published studies on amylin and its effects on inflammation have examined aggregated amylin in AD (Srodulski et al., 2014) or used animal models with type 2 diabetes that caused amylin to aggregate (Despa et al., 2014). Our recent study shows that adding monomeric amylin with a low concentration through binding to AmR attenuate neuroinflammation in microglia cell line (Wang et al., 2017).

There are some in vitro experiments suggesting that amylin can even inhibit A β aggregates in AD because amylin can form cross-interactions (Andreetto et al., 2010; Seeliger et al., 2012). Monomeric amylin and its analogs have been shown to inhibit the formation of A β aggregation in vitro (Andreetto et al., 2011; Sellin et al., 2010; Yan et al., 2013a; Yan et al., 2007; Yan et al., 2013b). Methylated amylin at the N-terminal region has been shown to be highly soluble and capable of inhibiting the aggregation of A β 40 (Sellin et al., 2010; Yan et al., 2013a; Yan et al., 2007; Yan et al., 2013b). Furthermore, A β -amylin hetero-oligomers have been shown to not be cytotoxic (Yan et al., 2013a); this aggregation may be another mechanism that acts to reduce amyloid pathology in the brain.

Conclusions

The gut-brain axis hormone amylin readily crosses the BBB and acts through a cognate receptor that might be able to exert wide-ranging effects on neuronal biology, especially neuroprotection in aging. Amylin could potentially impact AD in numerous ways by improving blood glucose, by causing weight loss, or by direct actions in AD. Because amylin mimics A β and tau structures (Kurnellas et al., 2013), I propose that amylin and its corresponding GPCR could be a key pathway that are disrupted by the accumulation of A β and pTau, especially the aggregated forms of them, in the AD brain (Figure 1). It is a reasonable argument that an effective drug target should be able to hold or delay the whole AD pathological pathway. Amylin or pramlintide may exhibit utility as a single novel therapeutic agent for targeting multiple indices of neurodegeneration in the AD brain. The

fact that diabetes is considered a risk factor for AD highlights yet another potentially beneficial action of the amylin cascade in AD. Ultimately, whether amylin type peptides can be a new and novel avenue of therapeutic for neurodegenerative diseases should only be concluded through a double blind, placebo controlled clinical trial in humans. The favorable safety profile of pramlintide suggests that pramlintide should be strongly considered for clinical testing as a repurposed amylin agonist for treating AD.

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Highlights

1. Amylin is a gut-brain axis hormone and amylin receptor (AmR) is a G-protein-coupled receptor (GPCR).
2. The AmR/GPCR pathway could be disturbed by a large amount of amyloid- β peptide ($A\beta$) in the Alzheimer's disease (AD) brain.
3. When amylin aggregates, it fails to bind to AmR/GPCR.
4. Peripheral amylin treatment reduces AD pathology in the brain, corresponding with improved cognition, in AD mouse models.
5. Providing exogenous amylin type peptides could be a novel therapeutic avenue for AD.

Figure 1. Proposed amylin receptor model for amylin's protective effects against the AD pathological process in the brain

Amylin receptor (AmR) is one type of GPCR and is composed of the calcitonin receptor (CTR) complexed with different receptor-activity-modifying proteins (RAMP)1 or RAMP3. Monomeric amylin binds to AmR, initiating a signal cascade that results in the activation of adenylate cyclase and converting ATP to cAMP. It is proposed that this amylin-AmR signal transduction is blocked or interfered by a large amount of A β in the brain because amylin and A β share similar secondary β -sheet structure and that aggregated amylin lose its ability to bind to its receptor. Thus providing exogenous amylin type peptides enhances the AmR signal transduction and reduces AD pathological cascade including amyloid burden, tauopathy and neuroinflammation.