Amylin Receptors

Subjects: Neurosciences

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Amylin Receptors peptide amylin polypeptides

1. Amylin Receptors

Amylin, a peptide hormone with 37 residue units, has been linked as a putative target for cognitive damage and glycemic irregularities in relation to Type 2 diabetes mellitus (T2DM) and obesity [1]. Amylin, or islet amyloid polypeptide (IAPP), is secreted along with insulin by the pancreatic β-cells [2]. These pancreatic polypeptides form a class of calcitonin (CT) peptide family and share a similar structure with CT, adrenomedullin, and CT gene-related peptide (CGRP). Receptors whose binding unit comprises CT and RAMP (receptor activity modifying protein) form the base of amylin receptors (AmRs). AmRs are a heterodimer made by combining CTR subunit (calcitonin receptor) and one of the RAMP members (RAMP1, RAMP2, or RAMP3)., Three types of amylin receptors have been identified, namely AMY_1, AMY_2, and AMY_3. CTR is a type of GPCR, and its binding affinity with amylin can be modified in the presence of RAMPs [3]. In this scenario, the hetero structures of either the CTR and RAMP1 or CTR and RAMP3 have been considered to favorably bind with amylin to mediate physiological functions in the brain. Both CTR and RAMPs manifest in the brain including hippocampus, cortex, and locus coeruleus, the regions most associated with AD [4].

2. Specifics

The amylin polypeptides that accumulate within T2DM pancreatic islets have similar physiological properties with amyloid beta peptides deposited in the brains of AD patients. Both diseases share pathogenic similarities including amyloid aggregation, inflammation, oxidative stress and neurotoxicity [5]. At cellular level, both Aβ peptide and IAPP (islet amyloid polypeptide) uses amylin receptor to express their biophysical effects leading to cytotoxicity. The process of cytotoxicity is achieved by activating GPCR and inducing the common intracellular pathways including, the signal transduction mediators such as protein kinase A, MAPK, protein kinase B, and cFos. Thus, AMY3 receptor (amylin-3 receptor) may serve as a therapeutic target for the action of Aβ peptide for the treatment of AD [6][7]. The effect of Aβ appears to take place via the amylin receptor in the cell, showing direct interaction between Aβ oligomer and amylin receptors. Indeed, the action of the two peptides can regulate the neuronal activity at cellular and synaptic level by activating the amylin receptor. However, the prolonged exposure of the receptor to the peptides results in apoptosis via the signal transduction pathways (**Figure 6**).

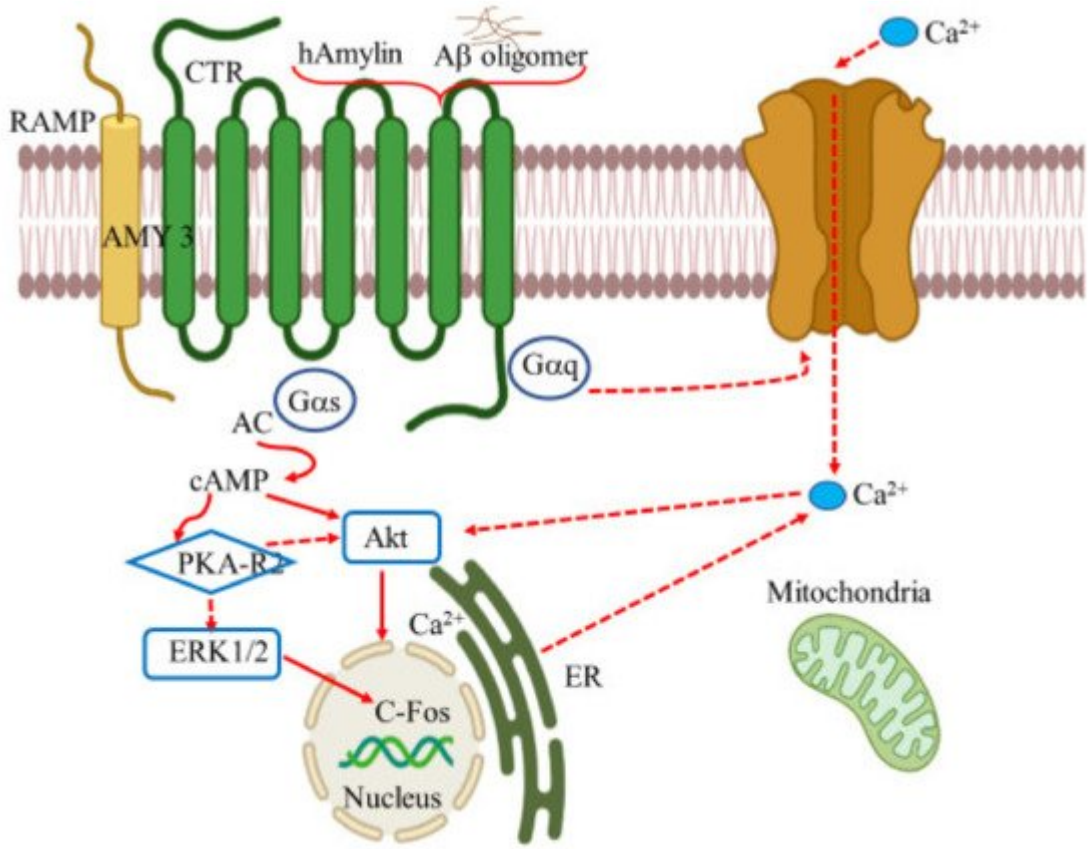

Figure 6. The AMY_3 is a heterodimeric complex of calcitonin receptor and receptor activity modifying protein 3. In AD, Amyloid β (Aβ) peptide activates AMY_3 subtype receptors by promoting multiple intracellular signaling pathways which is demonstrated in the above figure. The interaction of Human amylin (hAmylin) and Aβ together leads to activation AMY_3. The activation of AMY3 stimulates G-Protein Gαs which further control the adenylate cyclase (AC), followed by an increase in cellular cAMP. Binding of cAMP to the PKA regulatory subunits (R_2) induces dissociation of the tetrameric PKA holoenzyme, resulting in activation of PKA catalytic subunits. cAMP-activated PKA is involved in the regulation of Erk1/2 activities. The triggering of the ERK1/2 pathway may cause uneven distribution of Ca^{2+} trigger the dysfunction of the endoplasmic reticulum (ER) and mitochondria and result in cell death. In addition, cAMP stimulates Akt which further leads to transcription factor cFos expression. Created with BioRender.com.

Other approaches have suggested the beneficial role of amylin receptors antagonists as a promising therapeutic agent in AD. The depressant effects of Aβ (1-42) and human amylin on hippocampal long-term potentiation (LTP) were blocked by the application of AC253, an antagonist developed for the treatment of T2DM, in the APP transgenic mouse model [8]. Likewise, the amylin receptor antagonist, AC253, has also been reported to block the electrophysiological effects of Aβ on human fetal neurons (HFNs). It has also been observed that expression of amylin receptors is correlated with amyloid burden. The down regulation or blocking of amylin receptor using siRNA in HFNs is considered to provide protection to the neurons from Aβ induced apoptotic cell death [9].

In humans, lower concentration of the pancreatic hormone amylin has been connected with cognitive impairment [10]. The administration of increased levels of amylin in the murine mice model of AD reduced the Aβ in the brain

with significant behavioral improvement [11]. Similarly, in another study APP transgenic mice received an intraperitoneal injection of amylin and pramlintide, an analog of amylin, successfully reducing the level of Aβ by removing the peptide from the brain. Further, in Morris water maze and Y maze tests, the animal showed remarkable improvement in learning and memory functions [12]. Amylin's utility is not limited to minimizing the Aβ peptide in the brain but has also been shown to diminish tauopathy and brain inflammation in two animal models of AD. Subsequent administration of human amylin remarkably decreased cerebral Aβ and reduced tau proteins, insoluble tau, and Iba1 and CD68 (inflammatory markers). Amylin and its receptors, in this case, are thought to influence the CDK5 signaling by decreasing the active form of CDK5, p25, by reducing the tau phosphorylation [13]. Indicating, that amylin can also act as a potential therapeutic approach for ameliorating neurodegeneration and cognitive defects in AD.

Amylin's role remains ambiguous. Some studies portray it as a critical component to reduce amyloid beta peptides and restore cognitive functions. Other studies consider it a causative factor for neurotoxicity and long-term potentiation in the hippocampus. Lim et. al. proposed that the action of human amylin, unlike rat amylin, has strikingly similar neurotoxic features to those shown by Aβ peptides. In this study, they proposed that both the human amylin (hamylin) and amyloid-β peptides were toxic to hippocampal and cortical neurons [14]. The toxic effect of hamylin in rat hippocampal neurons were reported to be concentration dependent and thought to occur via transient receptor potential cation channel subfamily V member 4 (TRPV4) channels. At high concentration of human amylin, these polypeptides activated the TRPV4 channel, which subsequently depolarized the local membrane and allowed a high calcium influx into the cells resulting in neuronal dysfunction, inflammation, and neurotoxicity, thereby making TRPV4 a therapeutic interest for treating AD pathology [15]. Evidence from the studies indicate that amylin's role in neurodegeneration should not be neglected. The amylin analogue, pramlintide, along with the amylin receptors and their antagonists are significant factors that define AD's etiology, reduce the amyloid plaques in AD brain, and subsequently restore cognitive impairments.

Amylin receptor antagonists could be potential AD drug targets due to its presence in central nervous system cells and is directly associated with amyloid beta formation upon activation. In addition, no evidence supports the direct connection of amylin receptor function with other receptors such as dopamine and serotonin for its regulatory function.

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