Implications of GPCRs in Alzheimer's

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Abstract

G-protein coupled receptors, or GPCRs, are a large, diverse group of receptors found in all eukaryotes. GPCRs, as their name suggests, interact with G-proteins in the cell in order to carry out a variety of cellular responses. Most of these cellular responses are related to sensory functions such as pheromone signaling, taste, light perception, and other processes in the brain (Azam et al., 2020). For this reason, GPCRs are a very promising target for drugs that treat disorders affecting these processes. These disorders include many neurodegenerative CNS disorders, such as Alzheimer's disease. While many current drugs and therapies treat symptoms of these disorders, drugs that target GPCRs more directly would focus on the cause of the disorders at their roots (Huang et al., 2017). Insight into the mechanisms involved in signal transduction pathways in disorders such as those in Alzheimer's would lead us to new discoveries that could alter the course of these and many other disorders of the CNS.

Why are Receptors Important?

The neurons in your brain, as well as other cells in your body, are constantly sending signals in all directions to any neuron that will listen and respond. These neighboring cells need a way to "listen" to these communications and interpret them in meaningful ways so that the cell can respond accordingly. An example of one way that the cell does this is through receptors. When a cell fires, it releases a signaling molecule – typically a hormone or a neurotransmitter – called a ligand, which then binds to the receptor. While some signals do result in direct cellular responses, such as in the case of a ligand binding to an intracellular receptor, signals usually initiate some type of cellular response through a series of steps called a signal transduction pathway (Brooker et al., 2022). This pathway consists of a series of changes that lead to the production of a secondary signaling molecule which can lead to various cellular responses, such as altering enzymatic activity, altering protein function, or altering the function of transcription factors which activate gene expression – essentially turning a gene on or off. The proper functioning of any receptor is vital to the normal everyday bodily processes that are happening constantly in your body.

What are GPCRs?

One especially important group of receptors that are specifically relevant in the neuropathology realm are GPCRs, or G-protein coupled receptors. To put things into scope, there are over 370 non-sensory GPCRs currently identified, and 90% of those 370 receptors are expressed in the brain (Azam et al., 2020). GPCRs are a remarkably diverse group of receptors that bind a vast variety of different signaling molecules, and therefore perform a variety of difference functions in your body and brain. In the brain, they are responsible for things like taste and appetite, pheromone signaling and mood, vision and light perception, immune regulation, and more general functions like cognition and synaptic transmission (Huang et al., 2017). It is for this reason that regulation of GPCRs is a common target for drugs that treat disorders of such functions.

How are GPCRs Structured?

Being able to answer questions about how something is structured can often give us some clue as to how it works. GPCRs typically have seven domains, or segments, that are membrane-spanning, meaning that they wind back and forth across the plasma membrane of the cell. They also contain extracellular loops that contain components that stabilize the structure. GPCRs interact with G-proteins, named for their ability to bind to GTP and GDP. The G-protein is a lipid-anchored protein, which means that it is attached to the intracellular side of the membrane and consists of an alpha subunit and a β/gamma dimer. In its inactivated state, the G-protein binds GDP (Brooker et al., 2022).

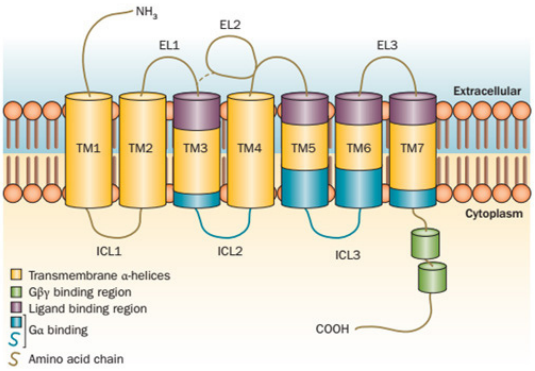

Figure 1. Schematic Diagram of GPCR Structure (Neumann et al., 2014).

How do GPCRs Function?

Now that we have a basic understanding of how the GPCR and G-protein are structured, let us examine how they function to carry out cellular responses when they are functional. To begin the signal transduction pathway, a ligand, or signaling molecule such as a hormone, peptide, or growth factor binds to the extracellular portion of the receptor. This causes a conformational change which allows the receptor to bind to a G-protein. Once bound to the receptor, the G-protein a subunit and β/g dimer separate, releasing GDP. This allows the alpha subunit to bind GTP.

The two components of the G-protein can both play separate, very important roles in eliciting cellular responses. For example, the a subunit can activate enzymes in the cell that lead, in a chain reaction, to the increased or decreased production of important energy sources such as glucose. The b/g dimer is also important, as it can play a role in the regulation of ion channels (Brooker et al., 2022).

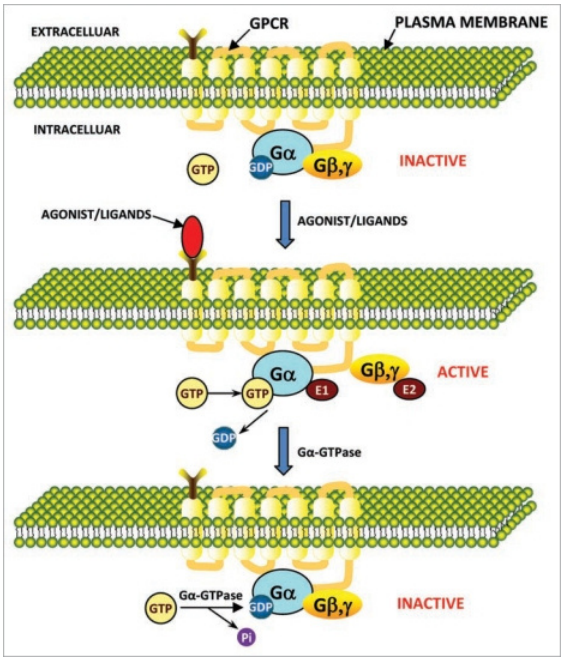

Figure 2. Diagram of General Signal Transduction Pathway of GPCRs (Tuteja, 2005).

How Do GPCRs Relate to Alzheimer's?

Alzheimer's disease (AD) is a neurodegenerative disorder associated with reduced cognitive function, loss of synapses, and neurofibrillary degeneration, or the formation of tangles of fibers within nerve cells, due to a buildup of plaques in the brain. These plaque buildups are accumulations of β-amyloid peptide (Aβ), which is formed from a protein called amyloid protein precursor (APP) (Zhao et al., 2016). As stated before, GPCRs are involved in the normal functioning of many important cellular processes in the brain. One example of this is demonstrated in GPCRs' role in the development of AD through the processing of APP.

GPCRs and the Regulation of APP Through BACE1 Downregulation

BACE1 is an enzyme that is essential for the processing of APP and generation of b-amyloid. In patients with AD, BACE1 has been found to be overactive, but not in excess (Zhao et al., 2016). Research suggests that GPCRs (specifically the M1 AChR, δ-opioid receptor, and A2A receptors) are involved in the regulation of BACE1 (Zhao et al., 2016). There are also a number of different proteins that are responsible for the regulation of GPCRs, and therefore may be responsible for regulating BACE1 activity. It has been shown that a loss of function in these enzymes is also connected to the progression of AD in some way or another (Zhao et al., 2016). For example, the upregulation of small GTPases such as RABs has been connected to cognitive impairment in AD (Ginsberg et al., 2010). Although there is evidence for a linkage of GPCRs to the regulation of BACE1, it is not currently known exactly the mechanism through which it is done.

GPCRs and the Regulation of APP Through Degradation of BACE1

Another possibility for a mechanism of regulation of APP by GPCRs is related to the degradation of BACE1. There is evidence that mAChR, which was previously mentioned as a possible component of BACE1 downregulation, could be involved in the degradation of BACE1 (Jiang et al., 2012). The mechanism through which this is done is not clear to researchers and is a continuing topic of discovery.

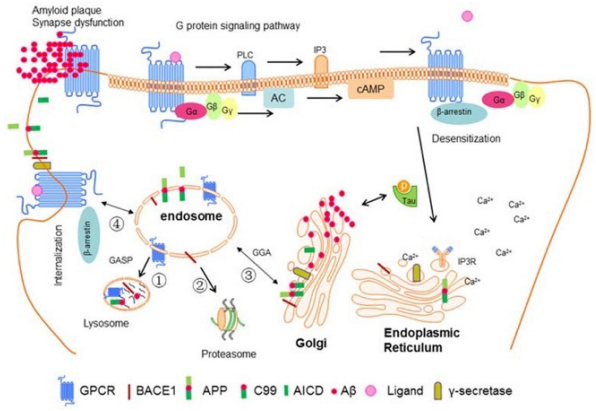

Figure 3. Proposed Signal Transduction Pathway and Interaction Between GPCR and BACE1 (Zhao et al., 2016).

Why is Determining These Mechanisms Hard, but Also So Important?

Currently, the drugs used for the treatment of AD only scratch the surface of the problem. Current treatments such as acetylcholinesterase inhibitors and memantine treat only the symptoms of AD. Acetylcholinesterase inhibitors simply inhibit the breakdown of acetylcholine, which is in short supply in the brains of AD patients. Similarly, memantine prevents excitotoxicity due to overstimulation (Huang et al., 2017). These treatments, while helpful, leave the root of the problem unchecked. If the mechanisms behind the role of GPCRs in the processing of APP are further studied, better therapies and even a possible cure for Alzheimer's may be on the horizon. The problem, however, is that there are a few difficult tasks standing in the way of our understanding of these mechanisms. First, inhibiting BACE1 would not come without side effects. Inhibiting BACE1 may prevent unnecessary Aβ production, but this does not come without consequences in application in the body. There is a strong possibility that BACE1 is related to the production of many other enzymes, so inhibiting it would affect enzymes that were not meant to be affected. This could lead to unwanted effects such as impaired spatial reference and working memory, as well as problems with temporal associative memory (Cole & Vassar, 2007).

Conclusion

Receptors in general are vital to the function of many bodily and brain processes. Even more specifically, GPCRs are vital to our understanding of the body, as they make up a large chunk of all receptors, especially in the brain. Further research into the functions of GPCRs and GPCR signal transduction pathways in relation to BACE1 and other enzymes would open the door, not only to potential treatments and maybe even a cure for Alzheimer's, but also to several treatments for CNS disorders such as Parkinson's and Huntington's disease.

Therefore, a partial, rather than full, inhibition of this enzymatic activity may be beneficial, although the percentage of BACE1 inhibition required to significantly delay amyloid pathology and the associated cognitive changes, remains to be determined.

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