APP, PSEN1, PSEN2, and BACE1 Genes on the Pathogenesis of Alzheimer's Disease and Inhibition Strategies

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Background

Many abnormalities have been found in the brains of patients who had neurodegenerative diseases such as Alzheimer's disease. One of the most notable abnormalities has been observed at the cellular level, namely clusters of toxic proteins called beta-amyloid plaques (Aß). These plaques, as well as neurofibrillary and tau tangles, have been the focus of research for a very long time, with multiple treatments targeting them. Although none of these treatments have really worked, and the underlying cause of Alzheimer's disease is still unknown, it is still good to know about these proteins and how they play into the disease.

In a previous article, a basic analysis of the role of amyloid-beta (Aß) plaques and Tau protein tangles in the progression of Alzheimer's disease was explored. A solid understanding of how proteins contribute to the disease is important because the article will focus on more of the causes of why these proteins came to be. Although some combinations of letters and numbers, such as PSEN1, may sound daunting, this article hopes to break it down and act as a gentler introduction to the inner workings of the disease.

What Is APP?

Amyloid Precursor Proteins (APP) are proteins that can be broken down into Aß plaques that could damage the brain and have toxic effects on its cellular environment. Found wedged between the plasma membranes of cells, APP is a transmembrane protein expressed in neurons. APP plays an important role in synapses, the connections between neurons. Specifically, APP was observed to be vital for the structural integrity of neuronal extensions (dendrites) and the proper functioning of synaptic connections (Tyan et al., 2012). However, mutations in both APP and enzymes involved in its function can cause plaques that could prove harmful to the brain.

Harmful Cleavage of APP

APP undergoes regular cleavage in cellular efforts to maintain homeostasis. The cleavage of APP produces beneficial fragments and molecules that facilitate cell signaling (Hartmann, 2013). However, mutations can occur in both APP and the enzymes that cleave APP, leading to the formation of plaques.

Usually, two processes occur when APP is cleaved: the amyloidogenic and nonamyloidogenic pathways. In the nonamyloidogenic pathway, which does not harm the brain, α-secretase, an enzyme, initiates cleavage and produces sAPPα. Since sAPPα is both harmless and soluble, it does not build up or create plaques. Researchers also associate sAPPα with increased electrical activity, suggesting sAPPα may benefit the brain. The cleavage leaves an 83-amino acid chain (C83) in the membrane, and ɣ-secretase later processes C83 without harmful effects (Chen et al., 2017).

On the other hand, the amyloidogenic pathway starts with ß-secretase, another enzyme produced by the BACE1 gene, beginning the cleaving. When ß-secretase makes the cut, a 99-amino chain (C99) is left. However, because the C99 offers a specific order that allows for the formation of Aß plaques, when ɣ-secretase cleaves C99, multiple Aß are produced and set free into the extracellular matrix, which allows for those insoluble proteins to build up (Chen et al., 2017). With BACE1, elevated levels were correlated with higher levels of plaques. Furthermore, mutations along the BACE1 gene can lead to the continued dysfunction of ß-secretase.

Some of those enzymes were subjected to mutations in genes, which could be an underlying cause for the formation of Aß plaques. Let's explore these mutations.

Presenilin

Presenilin genes (PSEN) encode proteins (enzymes) involved in the cleavage process. Specifically, PSEN1 and PSEN2 are important components in the ɣ-secretase process, and mutations could potentially speed up and facilitate the pathogenesis of Alzheimer's disease. PSEN1 and PSEN2 are genes that provide the information to create presenilin-1 and presenilin-2 proteins through protein synthesis.

PSEN1

PSEN1 plays a critical role in the production of presenilin-1 proteins. Presenilin-1 proteins are important in their role in ɣ-secretase. Specifically, presenilin-1 is a subunit of the ɣ-secretase enzyme, with presenilin-1 carrying out the cleavage. However, when mutations occur within this gene, the presenilin-1 proteins are incorrectly produced, which leads to abnormal cleavages and functions. Mutations accounted for 70% of Alzheimer's cases and were found to play an integral role in the overproduction of Aß plaques (MedlinePlus, n.d.-a).

Furthermore, mutations in PSEN1 can contribute to calcium metabolism dysfunction (Bagaria et al., 2022), which could compound or exacerbate malfunctions in astrocyte regulation of calcium ions. Astrocytes and their influence on calcium balance in the brain are explored in a previous article on this site.

PSEN2

PSEN2 is notable in its role of processing Aß plaques. PSEN2 mutations can prove harmful, as they interrupt the processing of these plaques. Although relatively rare, accounting for 5% of cases, a mutation in PSEN2 creates a phenomenon where Aß is overproduced and is

unable to be broken down, therefore causing aggregation and may contribute to Alzheimer's disease (MedlinePlus, n.d.-b).

Inhibition Strategies

Based on this research and information, treatments have been directed at those genes and enzymes to try to inhibit their function and slow plaque buildup. One such treatment being explored involves selective inhibition of ɣ-secretase and the presenilin-1 protein. Because inhibition of ɣ-secretase could prove detrimental to other functions, inhibition strategies have focused on the PSEN1 gene, which encodes the cleaving subunit. One of the better treatments in this approach was MRK-560. MRK-560 was found to bind to PSEN1 rather than the other complexes of the enzymes, providing a viable route to inhibit the specific complex that seemed to be causing the problem. (Serneels et al., 2023)

Inhibition strategies for BACE1 and the ß-secretase enzyme are also underway. In a study conducted on mice, the genetic deletion of BACE1 was able to decrease the rate of Aß production (Vassar, 2014). However, the mice also experienced side effects such as seizures and other issues. BACE1 deletion may also hurt humans. However, this acts as further confirmation that BACE1 is indeed involved in the Aß production, and it remains to be seen if there is any safe way to suppress Aß production without said side effects.

Conclusion

While progress has been made in understanding the roles of APP, PSEN1, PSEN2, and BACE1 in Alzheimer's, effective and safe treatments require more information and a nuanced approach to inhibit harmful pathways while preserving essential physiological functions.

Continued research into these genetic and enzymatic processes will be important in developing therapies that can cure the progression of Alzheimer's disease.

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