

Interaction between Amyloid Beta Toxicity and the PI3K Pathway in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is the most common disease causing dementia. Amyloid beta (A β) is well known to play the most important roles in the pathogenesis. A β induces neuronal cell death and neuroinflammation. It has been published that A β affects numerous intracellular signaling pathways. The phosphatidylinositol-3-kinase (PI3K) pathway associated with neuronal cell survival and various neural stem cell functions. In this review, the interaction between A β and the PI3K pathway will be discussed.

Keywords: Alzheimer's disease; Amyloid beta; PI3K; Neurons; Neural stem cells

Abbreviations: PI3K: Phosphatidylinositol 3-kinase; GSK-3 β : Glycogen synthase kinase-3 β ; VEGF: Vascular endothelial growth factor; GS: Glycogen synthase; CoQ10: Coenzyme Q10; P: Phosphorylated form; Ser: Serine

Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disease that is the cause of 60% to 70% of cases of dementia. The most common early symptom is difficulty in remembering recent events. As the disease advances, symptoms can include problems with language, disorientation (including easily getting lost), mood swings, loss of motivation, not managing self-care, and behavioral issues. Though AD has been studied for over several decades, there are still crucial problems in its diagnosis, prevention and treatment.

When it comes to pathogenesis, however, amyloid beta (A β) has been considered as a main factor: namely, A β monomers, A β oligomers, and A β fibrils play very important roles in the pathogenesis of AD [1]. Once A β monomers start to form oligomers in the brain, astrocytes and microglial cells become activated and a lot of inflammatory cytokines are released by A β oligomers. Subsequently, abnormal protein-folding activities, mitochondrial dysfunction, and neuronal cell death are followed. As the result, neurodegenerative change of AD is started in the brain [2].

The Amyloid Cascade Hypothesis and its Weakness in AD Patients

The amyloid cascade hypothesis is still one of the most reliable pathophysiological processes of AD until now. It is well known that A β oligomers provoke oxidative stress and cytotoxicity, so there is growing interest in using antioxidants to treat this disorder. To be more detailed, A β produces hydrogen peroxide (H₂O₂) through metal ion reduction, with expression of thiobarbituric acid-reactive substances, and this mechanism is probably caused by hydroxyl radicals as well as nitro-oxidative stress [3-5]. These processes are well known to induce the damage of neuronal cells and neural stem cells. Therefore, it is clear that some of the cytotoxicity of A β oligomers is associated with oxidative stress.

In the basis of this amyloid cascade hypothesis, numerous clinical trials for AD using anti-amyloid treatment have been performed, but all of the anti-amyloid treatment that reached Phase III clinical trials

has failed even though some of them effectively clear Ab deposits [3]. These failures have raised questions about the role of A β and anti-amyloid treatment in AD, and then, we might have to consider other pathophysiological processes of AD and other strategies for its treatment.

The PI3K Pathway in Neurons or Neural Stem Cells

The phosphatidylinositol 3-kinase (PI3K) pathway is known to be important in neuronal cell survival. It is the major intracellular signal pathway responsible for the transmission of anti-apoptotic genes and the control of cell survival, and it is activated by some neuroprotective signals [6,7]. This pathway also plays a key role in control of oxidative stress and adult neurogenesis [8] and a pivotal role in control of amyloid metabolism and tau phosphorylation in AD brains [9-12]. Describing in detail of the PI3K pathway, various neuroprotective signals activate PI3K, and then activated PI3K phosphorylates its downstream target, Akt/protein kinase B. Phosphorylated Akt (pAkt) directly affects Bcl-2 associated death promoter (BAD)/Bcl-2, caspase 9, I κ B kinase, and Forkhead-related transcription factor. pAkt also inhibits GSK-3 β by phosphorylating it at Ser9. Glycogen synthase kinase-3 β (GSK-3 β) involves in glycogen metabolism, regulates the function of metabolic, structural, and signaling proteins, such as activator protein-1, cyclic AMP response element binding protein, nuclear factor of activated T cells, heat shock factor-1, and β -catenin. Activation of GSK-3 β , which activates the mitochondrial death pathway, increases the release of cytochrome c from mitochondria. Released cytochrome c activates caspase-9 and caspase-3, and cleaves PARP, resulting in apoptosis [13,14]. Thus, inactivation of the phosphorylated GSK-3 β by pAkt is important for neuronal cell survival. In addition, it was reported that the PI3K pathway is essential for the self-renewal of embryonic stem

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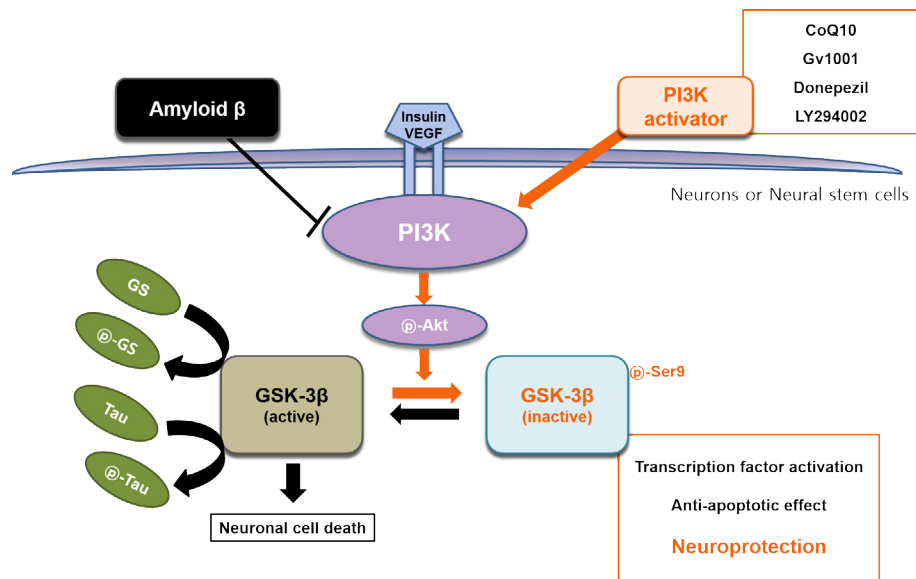


Figure 1: Interaction between the PI3K pathway and amyloid β in neurons or neural stem cells.

cells (ESCs) and activation of this pathway is significant for maintaining pluripotency in ESCs [15]. Several studies showed that the phosphatase and tensin homolog deleted on chromosome 10 (PTEN), an antagonist of PI3K, negatively regulates NSCs proliferation, survival, and self-renewal both in vivo and in vitro. Contrary to PTEN, components of the PI3K pathway were reported to be involved in the self-renewal of NSCs [16,17] (Figure 1).

Interaction between the PI3K Pathway and Amyloid β in Neurons or Neural Stem Cells

We have published that $A\beta$ induces neurotoxicity by inhibiting the PI3K pathway in neuronal cells or neural stem cells and a direct PI3K activator has neuroprotective effects through activation of the PI3K pathway in $A\beta$ -induced neuronal cell death and we also confirmed that several neuro-protectants protect those cells against $A\beta$ -induced injury by activating the PI3K pathway. For example, it was found in our previous study that Coenzyme Q10, Donepezil, GV1001, and LY294002 (a PI3K activator) protect against amyloid beta-induced neuronal cell death by activating the PI3K pathway [18-21]. In the other study, we also confirmed that Coenzyme Q10 restores $A\beta$ -inhibited proliferation of neural stem cells through the activation of the pathway [22]. Other previous studies have shown that abnormal activities of the PI3K pathway are found in people at risk of developing AD. These abnormal activities are known to be associated with an increased production of $A\beta$ and a decreased ability to clear $A\beta$, together resulting in excessive $A\beta$. Moreover, $A\beta$ has been also described to affect the activities of the pathway: $A\beta$ oligomers activate GSK-3 β blocking the activities of the pathway and increasing hyperphosphorylation of tau directly associated with cognitive decline [23-25].

Conclusion

In conclusion, because AD is a multifactorial disease and lots of pathogenic mechanisms are involved in AD, we need to investigate the molecular pathways associated with AD in much more detail. Based on the results, we should develop the new approaches for adjuvant therapies. One more important thing is that new therapies have to be started from the presymptomatic or early AD state considering that all

the clinical trials targeting full-blown or advanced AD have been failed. Taken together of our previous results, activation of the PI3K pathway can be one of new therapeutic strategies for AD. Thus, how to activate the PI3K pathway without any side effects should be developed for the treatment of AD patients and then its activation has to be used for AD patients in the presymptomatic or early state.

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