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Review

The role of PI3K/AKT pathway and its therapeutic possibility in Alzheimer's disease

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Alzheimer's disease (AD) is the most common form of dementia. Although uncountable clinical trials have been done to develop the treatment of AD, there are a couple of drugs that can be used only for symptomatic treatment. Therefore, many studies based on the amyloid cascade hypothesis and the tauopathy hypothesis are still ongoing. After the failure of numerous huge Phase III clinical trials, arguments on those hypotheses have arisen and efforts to establish other possible therapeutic strategies based on diverse plausible mechanisms associated with AD have been done as well. One of the new therapeutic targets for AD is the phosphatidylinositol 3-kinase (PI3K)/AKT pathway. In this review, questions on the two hypotheses, the definition of the PI3K/AKT pathway, the relationship between the pathway and AD, and the possibility of the modulation of the pathway as a new therapeutic strategy for AD will be discussed briefly.

Key words: Alzheimer's disease; Phosphatidylinositol 3-kinase; AKT; Amyloid beta; Tau

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INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia in the world. As the overall population is getting older worldwide, the number of patients with AD is incredibly increasing, so AD has become one of the most important health problems [1-4]. According to the official announcement of the Korean Government in 2013, the number of patients with dementia was more than half a million people in 2012 and the social cost for the care of dementia patients was expected to be more than 17 billion dollars in 2020. Nevertheless, the critical thing is that there is no definite treatment for AD yet except symptomatic treatment using some drugs. This means that the symptoms of AD will be aggravated as AD patients are getting old. This devastating feature is making people worry about AD and lots of studies on it have been done so far. Since amyloid cascade hypothesis was suggested [5,6], it has been in the center of studies on AD. Although most clinical trials based on this hypothesis have failed, it is still considered as one of the most convincing pathogenic mechanisms on AD. However, there are other movements to find other critical pathogenic mechanisms such as tauopathy [7], metabolic syndrome [8,9], and so on.

Due to technical development, lots of signaling pathways have been found to be important for cell survival. One of them is the phosphatidylinositol 3-kinase (PI3K) and AKT (also known as protein kinase B) pathway. The PI3K/AKT pathway is well known to promote survival and growth in response to extracellular signals including insulin, insulin-like growth factor (IGF), and so on. In many stressful conditions, the pathway is inhibited and then it is involved in cell death. Describing in detail, ischemia in the brain and oxidative stress inhibit the PI3K/AKT pathway in neurons and neural stem

cells and then induce cell death, so there have been a lot of studies to develop the way to protect neurons and neural stem cells by activating the pathway [10-13]. This phenomenon also happens in amyloid-induced cell death [14,15]. Considering the importance of the PI3K/AKT pathway in cell survival and growth, finding a good way to activate the pathway might be another option for the treatment of AD.

In this review, I will discuss the current issue about the problem of the amyloid cascade hypothesis, take a look at the PI3K/AKT pathway in detail, and describe the role of the PI3K/AKT pathway in AD. Last but not least, I will suggest the therapeutic possibility of the modulation of the PI3K/AKT pathway in AD.

Questions on the amyloid cascade hypothesis as a pathogenic mechanism of AD

Until recently, one of the most well-known hypothetical pathogenic mechanisms is the amyloid cascade hypothesis. Since 1991 when John Hardy and David Allsop proposed the hypothesis [16], most studies about AD have been performed based on it. The hypothesis says that the mismetabolism of amyloid precursor protein (APP) to amyloid beta (Aβ) 42 provokes the pathogenesis of AD. Aβ42 is naturally aggregated from monomers to form plaques. Initially, neuritic plaques were suggested to instigate further pathological events, such as the formation of neurofibrillary tangles (NFTs), the disruption of synaptic connections, the reduction of neurotransmitters, death of neurons, and finally dementia [16]. This hypothesis was strengthened based on the results showing that the vast majority of mutations causing familial early onset AD increase Aβ42 and that animal models of AD with pathogenic mutations of APP and presenilin 1 have increased Aβ42 and amyloid plaques [17,18]. Contrary to the initial suggestion, however, neuritic plaques are now thought to be the end product but not the cause. Meanwhile, Aβ itself was reported to be neurotoxic through inhibition of Wnt and insulin signaling [19,20], activation of the c-Jun N-terminal kinase (JNK)/Stress-activated protein kinases (SAPK) pathway [21], activation of microglia cells leading to the expression of pro-inflammatory genes, an increase in reactive oxygen species [22], and so on. After the finding that soluble oligomers of Aβ impair synaptic plasticity and memory [23], however, these forms are currently emphasized to be one of the casual factors for AD because amyloid oligomers are known to induce diverse toxicities such as activation of apoptotic signal, abnormal ion flow, activation of NMDA receptor, synaptic dysfunction, oxidative stress, synapse loss, increased glycogen synthase kinase (GSK)-3β, and Tau phosphorylation [24-27].

Based on these hypotheses, uncountable clinical trials targeting Aβ have been performed. Some of them are going to be described. Solanezumab, a monoclonal IgG antibody designed to lower the level of Aβ in the brain, has been being used in the clinical trials for AD patients [28,29]. Although they did not show definite effect of solanezumab on AD, a subgroup analysis showed its possibility for the treatment of patients with mild AD [28], so a further clinical trial to confirm the effect of solanezumab in mild AD patients is ongoing. Another phase 1 clinical trial for immunotherapy targeting Aβ was completed with GSK933776 [30], but further clinical trials have not yet been started. Besides, AN1792 [31] and Bapimeuzumab [32], which were developed for immunotherapies to reduce Aβ, were tested in several clinical trials for AD patients, but all of them did not reach the primary endpoint or were ceased due to severe adverse effects. Several different drugs reducing Aβ with different mechanisms were also tried for the treatment of AD patients, but all of them unfortunately failed to show efficacy so far: namely, Tramiprosate (a small and orally-administered compound that binds to soluble Aβ and reduces amyloid aggregation and subsequent deposition) did not confirm any efficacy in a randomized, double-blind, placebo-controlled, multi-center study [33]; Tarenflurbil, a selective Aβ42-lowering agent, did not slow cognitive decline or the loss of activities of daily living in patients with mild AD in a phase 3 trial [34]; Semagacestat, a small-molecule-secretase inhibitor reducing Aβ, did not improve cognitive status and patients receiving the higher dose had significant worsening of functional ability [35]; Avagacestat, an arylsulfonamide-secretase inhibitor did not demonstrate efficacy and was associated with adverse dose-limiting effects [36]; and intravenous immune globulin (IVIG) was reported not to show any efficacy in a phase 2 and 3 study evaluating safety and effectiveness of IVIG for the treatment of mild-to-moderate AD[37]. Although there are still ongoing clinical trials targeting Aβ, all these failures led us to think about other pathogenic mechanisms as therapeutic targets.

Most of all, tauopathy is the leading hypothetical pathogenic mechanism of AD next to the amyloid cascade hypothesis. Many reports have supported that hyperphosphorylation of Tau is the main component of neurofibrillary tangles, which are strongly correlated with duration and severity of AD [38]. Tau proteins in neurons are the major microtubule-associated proteins which stabilize microtubules [39,40]. Six

tau isoforms are known to exist in the brain and they are classified depending on their number of binding domains: three isoforms with three binding domains vs. the other three with four binding domains. The binding domains, located in the carboxy-terminus of the protein, are positively charged and bind to the negatively charged microtubule. In terms of stabilization of microtubules, the isoforms with four binding domains are better than those with three binding domains. The isoforms are a result of alternative splicing in exons 2, 3, and 10 of the tau gene. However, when tau becomes abnormally hyperphosphorylated, the positive charge of the proteins disappears and then they are detached from microtubules and aggregated with each other forming neurofibrillary tangles [41]. During the process, misfolded and oligomeric tau by abnormal hyperphosphorylation is well established to induce neurotoxicity, death of neurons, and then dementia [42]. Therefore, a few studies have been done to prevent abnormal hyperphosphorylation of tau in AD [43,44], although clinical trials targeting hyperphosphorylated tau are much less when compared with the ones targeting Aβ and some of them did not show clinical benefit either [44]. Moreover, lots of clinical trials targeting diverse mechanisms had been done and all of them failed to show any efficacy: Atorvastatin and Simvastatin did not show any difference between the treatment group and the control group in AD patients [45,46]; non-steroidal anti-inflammatory drugs were tried to prevent or delay the onset of AD but the result was also negative [47]; rosiglitazone, the peroxisome proliferator-activated receptor-agonist, was tested for the treatment of mild to moderate AD but it also failed [48]; and so on. Considering all these failures, it is not easy to find the way to treat AD but it is necessary and cannot be given up. One of the new targets for AD is the PI3K/AKT pathway.

WHAT IS THE PI3K/AKT PATHWAY?

The PI3K/AKT pathway is known to play pivotal roles in survival, growth, proliferation, and migration of cells. Various kinds of growth factors and signals, such as epidermal growth factor (EGF), Sonic hedgehog (SHH), insulin-like growth factor 1 (IGF-1), insulin, and calmodulin, binding to a receptor tyrosine kinase activate cell surface receptors phosphorylating PI3K. Activated PI3K phosphorylates phosphatidylinositol (PI) (3,4)-bisphosphate (PIP2) to PI (3,4,5)-trisphosphate (PIP3). Next, this PIP3 stimulates AKT, a serine/threonine kinase, by interaction with these PI docking sites [49,50]. AKT is the direct and most important effector of the PI3K/AKT pathway. It is reported that activated AKT affects as many as 100 different substrates that are important in cellular signaling. Among them, the most well-known and important one is GSK-3β, directly inducing tau phosphorylation. Activated AKT phosphorylates GSK-3β at serine 9. This phosphorylation inhibits GSK-3β. To know the significance of the inhibition of GSK-3β, it is necessary to discuss the roles of active GSK-3β. GSK-3 is a proline-directed serine/threonine kinase inactivating glycogen synthase. It has two isoforms and the beta form (GSK-3β) is involved in energy metabolism, neuronal cell development, and body pattern formation [51]. When it comes to AD, GSK-3β is important because it phosphorylates tau proteins and induces detachment of tau proteins from microtubules, as described above.

In addition to the PI3K/AKT/GSK-3β pathway, the PI3K/AKT/mechanistic target of the rapamycin (mTOR) pathway is also highly emphasized in cell survival. Just like the PI3K/AKT/GSK-3β pathway, activated AKT activates mTOR. Activated mTOR works as an atypical serine/threonine protein kinase regulating cell growth, cell proliferation, cell motility, cell survival, protein synthesis, autophagy, and transcription [52]. mTOR is present in two distinct complexes: mTOR complex 1(mTORC1) including mTOR, Raptor, GβL, and DEPTOR and mTORC2 with mTOR, Rictor, GβL, Sin1, PRR5/Protor-1, and DEPTOR. mTORC1 is inhibited by rapamycin and is known to be a master growth regulator. Diverse nutritional and environmental cues activate AKT as described above and then activated AKT activates mTORC1. Activated mTORC1 promotes cellular growth by phosphorylating substrates potentiating anabolic processes such as mRNA translation and lipid synthesis, or limit catabolic processes such as autophagy, while mTORC2 promotes cellular survival by activating AKT. Therefore, mTOR signaling has been emphasized in cancer, cardiovascular disease, and diabetes [53]. Nowadays, this pathway is also stressed in various neurological diseases including AD.

THE ALTERATION OF THE PI3K/AKT PATHWAY IN AD

As described above, the PI3K/AKT pathway is important in AD just like other neurological diseases. Based on our previous studies, the PI3K/AKT pathway is inhibited by Aβ and its recovery by diverse ways is helpful for the prevention of Aβ toxicity [14,15,54]. This finding is also supported by many

other researchers [55-57]. In other words, Aβ oligomers inhibit the PI3K/AKT pathway and the inhibition of the PI3K/AKT pathway induces neuron death and eventually dementia.

Among about 100 targets of AKT, GSK-3β (the PI3K/AKT/GSK-3β pathway) and mTOR (the PI3K/AKT/mTOR pathway) are known to play pivotal roles in AD. First of all, GSK-3β is important in tau hyperphosphorylation. GSK-3β is a serine/threonine protein kinase adding phosphate molecules onto serine and threonine amino acid residues. It was initially discovered as a regulatory kinase for glycogen synthase [58], but the critical roles of GSK-3β have been reported in a number of diseases including AD. Active form of GSK-3β directly phosphorylates tau at multiple sites. The majority of them are located in 2N4R tau, which is encoded by exon 3 (2N) and has four binding domains (4R) [59]. Positive charge of tau is changed to negative charge by phosphorylation and it makes tau detach from microtubules and aggregate with each other. Microtubules, which tau is detached from, get their stability and important functions lost. It increases vulnerability of cells and finally induces cell death.

The PI3K/AKT/mTOR pathway is well known to interact with AD pathology in several aspects. Differently from the PI3K/AKT/GSK-3β pathway, the activation of the PI3K/AKT/mTOR pathway has been reported to be associated with AD: namely, mTOR signaling is hyperactive in AD brains. mTOR signaling has been reported to be closely related to the presence of soluble amyloid beta (Aβ) and tau proteins [60]. Contrary to the PI3K/AKT/GSK-3β pathway, it has been reported that Aβ increases p70S6K, a downstream target of mTOR known to have higher expression in neurons that eventually develop neurofibrillary tangles [61,62]. Moreover, mTOR hyperactivity is observed by injecting Aβ oligomers into the hippocampi of normal mice [63]. Considering all of these findings, the mTOR signaling pathway is thought to be one mechanism of Aβ-induced toxicity in AD. Increasing Aβ concentrations increases mTOR signaling, however, significantly large, cytotoxic Aβ concentrations ironically decrease mTOR signaling [64]. Thus, the role of the mTOR signaling in the amyloid hypothesis might be still controversial.

In case of tauopathy, there have been much less reports about the relationship of mTOR with tau proteins than Aβ, but p70S6K activation has been reported to promote tangle formation as well as mTOR hyperactivity through increased phosphorylation and reduced dephosphorylation [65]. In addition, mTOR is suggested to contribute to tau pathology by increasing the translation of tau and other proteins [66]. Although the relationship between tau proteins and mTOR is not yet conclusive, mTOR signaling seems to be involved in tauopathy.

THE THERAPEUTIC POSSIBILITY OF THE MODULATION OF THE PI3K/AKT PATHWAY IN AD

As described above, it looks obvious that the PI3K/AKT pathway is associated with the pathogenesis of AD even though it is not easy to say if it is good or bad because its effect can be different depending on downstream signaling pathways. My colleagues and I have studied to reveal the effect of the PI3K/AKT/GSK-3β on AD and to find the way to treat AD with the modification of the pathway. Speaking of the PI3K/AKT/GSK-3β pathway, Aβ enhances GSK-3β activity and then increases tau phosphorylation. These mechanisms contribute to neuronal cell death and dementia. Therefore, GSK-3β inhibition through the activation of PI3K/AKT can be another solution for the treatment of AD. We have reported that GV1001, which is a novel vaccine peptide mimicking Human telomerase reverse transcriptase (hTERT), donepezil, and coenzyme Q10 can block Aβ through the activation of PI3K and AKT and then the inhibition of GSK-3β [14,54,67]. Although the Phase II clinical trial using NP031112, a GSK-3β inhibitor, has not yet shown definite efficacy to AD patients, it showed that its usage was safe. The Phase III clinical trial with NP031112 might be being planned. Therefore, the way to activate the PI3K/AKT/GSK-3β could be another treatment option for AD.

Contrary to the PI3K/AKT/GSK-3β pathway, the way to inhibit the PI3K/AKT/mTOR pathway would be a new therapeutic strategy, although clinical trials have not yet been done with mTOR inhibitor for the treatment of AD.

Due to all these complexities of the PI3K/AKT pathway, it might be hard to establish the way to treat AD with the modulation of the PI3K/AKT pathway, but it is worth doing that when considering there is no cure for AD.

CONCLUSIONS

For the development of new therapeutic strategies for AD, there have been uncountable efforts so far. Although all these efforts were not successful, I am confident that these trials and errors will strongly contribute to the better treatment of AD. The PI3K/AKT pathway is so complicated, but it is quite

definite that the PI3K/AKT pathway plays pivotal roles in AD, so I think much more effort should be made to develop a new therapeutic strategy using the PI3K/AKT pathway.

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