LIFE SCIENCES SEMINAR

"Co-activation of selective nicotinic acetylcholine receptors improves hippocampal activity and memory in Alzheimer's disease"

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Understanding the neural mechanisms underlying cognitive decline is crucial for identifying viable biomarkers and developing disease-modifying therapies in Alzheimer's disease (AD). The hippocampal memory system is particularly vulnerable to cellular pathologies of AD. Neural oscillatory activity in the hippocampus plays important roles in memory formation. Importantly, in people at high risk of developing AD, abnormal oscillatory activity during hippocampal memory processes is detected decades before the onset of clinical disease. In animal models of AD, hippocampal oscillatory activity during memory processes is significantly reduced before amyloid plaque deposition, suggesting that decreased hippocampal oscillations are a precursor to AD. This decreased activity has thus been identified as a potential treatment target for improving cognition and, in the longer term, disease modification. Hippocampal oscillations are generated by circuits involving distinct subtypes of GABAergic inhibitory interneurons, and reduced activity in these cells is associated with decreased hippocampal oscillations and memory loss in AD. In the early stages of AD, beta-amyloid peptide (Aβ) is linked to reduced hippocampal oscillations via a decrease in GABAergic inhibition, consequently leading to cognitive impairment. Importantly, cholinergic deficiency is known to be a prime suspect for Aβ-induced inhibitory dysfunction. Therefore, enhancing cholinergic functions has been used to treat AD. However, non-selective cholinergic activation fails to reverse Aβ-induced inhibitory dysfunction and has only had a moderate level of success for AD treatment. In fact, we have revealed that Aβ selectively inhibits a subtype of nAChRs, α7- and α4β2-nAChRs, but not α3β4-nAChRs, in cultured hippocampal GABAergic interneurons and decreases inhibitory activity, which leads to abnormal activity in excitatory neurons. Moreover, co-activation of α7- and α4β2-nAChRs reverses the Aβ-induced adverse effects in cultured neurons. Most importantly, we have demonstrated that in vivo co-stimulation of α7- and α4β2-nAChRs reverses decreased hippocampal oscillatory activity during fear memory consolidation and improves fear memory in the mouse model of AD. Together, we suggest that Aβ reduces hippocampal GABAergic activity via selective inhibition of α7- and α4β2-nAChRs, leading to disruptions in hippocampal oscillations and memory loss in AD, thus selective co-activation of α7- and α4β2-nAChRs reverses the Aβ-induced pathological effects.

- **Date: 4:00PM, August 8(Monday), 2022**
- **Place: POSTECH Biotech Center #476**
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