Intrabody-mediated postsynaptic recruitment of CaMKIIα improves memory

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Title
Intrabody-mediated postsynaptic recruitment of CaMKIIα improves memory

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Abstract
Long-term potentiation (LTP), the selective strengthening of specific synapses based on recent activity, has widely been accepted as the biological mechanism responsible for learning and memory. N-methyl-D-aspartate receptors (NMDARs) play a critical role in LTP, which when activated, result in a surge of postsynaptic intracellular calcium levels. The calcium rise during LTP results in the activation of Ca2+/calmodulin-dependent kinase II alpha (CaMKIIα), which consequently enacts multiple cellular effects that ultimately result in the strengthening of synaptic connections. Previous work has examined the effects of CaMKIIα overexpression in rat hippocampi on spatial memory, however, significant but limited improvement in memory was noted. Thus, we have hypothesized that selectively increasing CaMKIIα levels at NMDAR-enriched postsynaptic regions could improve the efficiency of learning and memory formation. We previously have developed and validated a novel genetically encoded intrabody, termed VHHAN1 (VHH Anti-GluN1), and demonstrated VHHAN1’s ability to direct cytosolic proteins to NMDARs in vivo. Here, we generated an adeno-associated virus (AAV) expressing a VHHAN1-CaMKIIα fusion protein, which was stereotaxically injected and expressed in the mouse hippocampus. The mice were then exposed to fear conditioning experiments, where VHHAN1-CaMKIIα-expressing mice demonstrated significantly improved contextual fear memory (more than 2-fold) with no significant changes in cued memory in comparison to non-injected and CaMKIIα-overexpressing mice. Brain slices of mice were then prepared and subjected to immunohistochemistry to confirm VHHAN1-mediated CaMKIIα local enrichment in postsynaptic regions. This specific application of the VHHAN1 intrabody may serve as a valuable potential therapeutic strategy to improve memory formation in memory disorders including Alzheimer’s disease.

Word Count: 250

Key Words
- Learning & Memory, Long-Term Potentiation, Hippocampus, Synaptic Plasticity, Fear memory, NMDAR, Intrabody, Adeno-associated Virus