cell bodies and synaptic terminals, may be important for cholinergic sensitization of arousal and reward circuits.

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2.3

Alpha2* nicotinic acetylcholine receptors as a therapeutic target for memory enhancement

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GABAergic interneurons have a central role in the control of synaptic plasticity and hippocampus-dependent learning, and many of these interneurons express nicotinic acetylcholine receptors (nAChRs). However, it is largely unknown how activation of nAChRs on different interneuron subtypes influences hippocampal circuit activity or the induction of long-term potentiation (LTP) and long-term depression (LTD), which are considered to be cellular substrates of learning and memory. The α2* nAChR, the most sparsely expressed nAChR subtype in the brain, is selectively found in a subset of GABAergic interneurons in the stratum oriens/alveus. We have investigated the consequences of α2* nAChR activation on circuit activity and the induction of LTP and LTD. We found that it causes an increase in the frequency of spontaneous inhibitory postsynaptic currents in pyramidal cells in a glutamate-receptor-independent and Na^+ channel-dependent manner. Furthermore, dual whole-cell recordings from α2* nAChR-containing interneurons and pyramidal cells showed that pairs are synaptically connected. These results suggest that activation of α2* nAChRs causes GABA release onto postsynaptic membrane domains, affecting hippocampal circuit operation. We have also found that α2* nAChR-containing interneurons are continuously excited in the presence of nicotine and that Ca^{2+} entry through α2* nAChRs promotes the induction of *N*-methyl-D-aspartate receptor (NMDAR)-independent LTP in these interneurons. In addition, we found pathway specific effects of α2* nAChR activation. Hippocampal CA1 pyramidal cells, which provide the major output of the hippocampus, receive two major sources of excitatory synaptic inputs from the entorhinal cortex, the Schaffer collateral (SC) path and the temporoammonic (TA) path. Optical recordings with a voltage-sensitive dye showed that activation of α2* nAChRs enhances excitatory neural activity along the SC path, whereas activation of α2* nAChRs increases hyperpolarization along the TA path. Accordingly, activation of α2* nAChRs promotes the induction of NMDAR-dependent LTP at the SC path, but suppresses LTP induction at the TA path. In contrast, activation of α2* nAChRs has no significant effect on LTD induction at the SC path and facilitates LTD induction at the TA path. Our work shows that the α2* nAChR subtype is an important component of hippocampal circuitry and potentially serves as a switch for gating information flow and synaptic plasticity by exciting a subset of GABAergic interneurons in the stratum oriens/alveus. It is potentially involved in nicotine-induced cognitive enhancement, and appears to be an attractive new target for improving memory.

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2.4

Plasticity of prefrontal attention circuitry: Upregulated muscarinic excitability in response to decreased nicotinic signaling following deletion of α5 or β2 subunits

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Acetylcholine in the medial prefrontal cortex is critical for attention, an effect mediated by the ionotropic nicotinic and the metabotropic muscarinic families of cholinergic receptors. Corticothalamic pyramidal neurons in layer VI of the medial prefrontal cortex express cholinergic receptors of both families and play an important role in attention through their feedback projections to the thalamus. Response to acetylcholine in medial prefrontal layer VI pyramidal neurons is primarily mediated by α4β2α5 nicotinic receptors. Mice lacking either the accessory α5 subunit [1] or the ligand-binding β2 subunit [2] show weaker attentional performance. However, the presence of muscarinic cholinergic receptors in these neurons raises the possibility of plasticity in their cholinergic response. Here, we investigate the combined effects of nicotinic and muscarinic cholinergic receptors on the excitability of corticothalamic layer VI pyramidal neurons using whole-cell recordings in acute brain slices of the prefrontal cortex. We focus in particular on how cholinergic excitation of these layer VI neurons is altered by genetic deletion of either the α5 or β2 nicotinic receptor subunits. We find that mice lacking the α5 subunit have significantly reduced nicotinic receptor mediated responses to acetylcholine, whereas the response is absent in mice lacking the β2 subunit. However, despite showing similar differences across genotypes in terms of the magnitude of cell depolarization, the increase in action potential firing observed in response to acetylcholine application is not weakened in α5 or β2 knockout mice when both nicotinic and muscarinic receptors are activated. As suspected, muscarinic receptor mediated responses to acetylcholine in α5 and β2 knockout mice are significantly enhanced when compared to wild type mice. This change is mediated by a functional increase in muscarinic M1 receptor signaling, with a small muscarinic M3 receptor component in most layer VI pyramidal neurons. Our findings suggest that disrupting nicotinic receptor function can fundamentally alter the mechanisms and timing of excitation in prefrontal attentional circuitry. Ongoing work will attempt to pharmacologically dissect downstream mechanisms contributing to the observed muscarinic plasticity.

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