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LTD deficit in α7 neuronal nicotinic receptor (α7*) knockout mice is strain dependent

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Schizophrenia is a mental disorder characterized by insufficient filtering of external stimuli as well as other cognitive deficits. The prevalence of this disorder (~1%) and evidence of its heritability give reason to investigate the genetics and functional neuronal interactions which may contribute to schizophrenia. The alpha 7 neuronal nicotinic receptor is thought to play a role in the development or expression of schizophrenia. Postmortem brain tissue from schizophrenics has fewer alpha-bungarotoxin binding sites – indicative of alpha 7 nicotinic receptors – than age-matched control individuals. It has been proposed that schizophrenic patients smoke at high levels and with disproportionately high incidences in order to compensate for the lack of these receptors. Furthermore, schizophrenics exhibit abnormal auditory gating, an endophenotype of the disorder, and administration of nicotine i.v. normalizes gating to auditory stimuli. Since cognitive deficits are frequently observed in schizophrenics, we hypothesized that mice which lacked the alpha 7 nicotinic receptor might mimic some of schizophrenic phenotypes, including deficits in synaptic plasticity. Previously we investigated long-term potentiation (LTP) in hippocampal slices from mice which lacked the alpha 7 nicotinic receptor gene (knock outs, KO), and we compared those data with that from wild type (WT) slices. We found that high-frequency stimulation induced less LTP in KO mice than in WT mice, but this difference depended on the background genotype; the deficit was apparent in C3H mice, but not in mice with the C57 background genotype. We have now examined another form of synaptic plasticity – long-term depression (LTD) – from these animals. In order to observe this effect, we tested mice at 13–19 days of age. Low-frequency stimulation (LFS; 1 Hz, 15 min, 900 pulses) evoked ~30% LTD in WT mice of the C3H background for up to 1 h after LFS. Similarly to LTP data, C3H mice lacking the alpha 7 receptor exhibited a deficit in LTD (essentially no LTD); Het mice were intermediate, exhibiting a small degree of LTD. Preliminary data also indicated that in mice of the C57 background, there was only a slight, nonsignificant difference in the LTD observed for KO vs. WT hippocampal slices (LTD: WT ≥ KO). Future experiments will determine whether the LTP and LTD deficit in C3H mice lacking the alpha 7 receptor is due to a developmental alteration or a dynamic, acute effect of the KO, which can be inhibited in WT mice by the appropriate nicotinic antagonist, or which can be overcome in KO slices by a nicotinic agonist.

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Lynx1 balances neuronal activity through nicotinic acetylcholine receptor modulation

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Maintenance of the level and function of nicotinic acetylcholine receptors (nAChRs) during development and adulthood is essential for proper circuit function. The action of lynx1, a prototoxin with structural similarity to α-bungarotoxin, manifests itself at both circuit and network levels on nicotinic systems. Removal of the molecular brake provided by lynx1 can lead to nicotinic receptor hypersensitivity—larger direct nicotinic responses, slowed desensitization kinetics, and enhanced sensitivity to nicotine. As a consequence of nAChR hypersensitivity, lynx1 knockout (KO) mice display increased levels of Ca^{2+} in neurons, enhancements in synaptic efficacy, and improved learning and memory functions. Studies on such hyperactive nicotinic receptors can reveal cholinergic-dependent processes with increased clarity. For instance, adult lynx1KO mice display heightened ocular dominance plasticity after the normal close of the critical period, suggesting that lynx1 acts as a molecular brake over the cholinergic system to suppress plasticity in the adult brain. nAChRs have been implicated in neuronal maturation and loss of synaptic lability, which appear to be correlated with the onset of lynx1 expression. α4β2 and α7 nAChRs in particular are known to regulate the excitatory/inhibitory balance. Our hypothesis is that lynx1 controls excitatory/inhibitory balance by regulating the number and localization of nAChRs. This modulation may occur through intracellular mechanisms or via cell surface gating interactions. Using high-resolution live cell imaging of nAChRs labeled with fluorescent proteins we have monitored receptor movement and localization in the presence and absence of lynx1. Total internal reflection microscopy (TIRF) data indicate that lynx1 increases the plasma membrane to ER ratio of nAChRs. Mobile fluorescent puncta were analyzed by creating kymographic representations of time-lapse TIRF images. lynx1 caused a 96% increase in mobile puncta, indicating that lynx increases nAChR mobility. We are also employing immunohistochemical and western blot analyses to monitor the state of neuronal maturation. These data indicate that lynx1 influences nAChRs to maintain excitatory/inhibitory balance in neuronal circuits. Thus, these data indicate how a prototoxin may function, at an intracellular level, to alter the level and localization of nAChRs, with profound implications on cellular and circuit function.

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2.7

Altered spine configuration in CA1 hippocampal basilar dendritic spines in alpha7 nAChR knockout mice

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The alpha7 nicotinic acetylcholine receptor (nAChR) is known to be involved in cognition and memory functions. The mechanisms underlying the learning-related functions of the alpha7 nAChR are not well-understood. The receptor is widely expressed in the