Nicotinic receptors in cortical circuit development and sleep-related epilepsy.

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Abstract:

Mutant subunits of nicotinic acetylcholine receptors (nAChRs) can cause Autosomal Dominant Related Sleep-related Hypermotor Epilepsy (ADSHE), characterized by frontal seizures mainly arising during non-rapid eye movement (NREM) sleep. In mice, the ADSHE-linked gain-of-function mutation β2V287L permanently impairs the excitatory input on fast-spiking (FS) GABAergic cells in prefrontal cortex, by affecting the early maturation of glutamatergic synapses on FS cells. The ensuing impairment of recurrent inhibition of pyramidal neurons in the adult brain leads to lifelong seizures during sleep.

Little is known about how nAChRs regulate synaptogenesis in FS neurons. To reproduce the timing of synaptogenesis in vitro, we use postnatal mouse cortical cultures. Electrical maturation is studied by whole-cell patch-clamp methods, between the 1st and the 2nd week. In this way, we (i) characterize the cortical cell populations, including FS neurons, according to their firing pattern; (ii) evaluate the nAChR-dependent regulation of synaptogenesis, with special focus on the neuregulin/ErbB4 receptor pathway, known to modulate synaptic maturation of FS neurons; (iii) investigate the effect of β2V287L subunits on synaptogenesis.

Preliminary results from this study suggest that early nAChR hyperactivation could aberrantly stimulate glutamatergic transmission, especially on FS neurons. This may lead to long-term synaptic depression because of overstimulated presynaptic calcium signals, perhaps accompanied by a compensatory increase in synaptic density which was indeed observed in mice expressing the β2V287L nicotinic subunit.

Comprehending the mechanisms underlying the GABAergic maturation in the neocortex, whose derangement has a central role in ADSHE and other neurological diseases, would point to novel molecular targets that could rescue the epileptogenic process during synaptogenesis, opening new perspectives for treatment of genetic epilepsies.