β2-containing neuronal nicotinic receptors (nAChRs) in neocortex development and sleep-related epilepsy.

Marta Cerina[1], A. B. Zeynali[2], F. Gullo[1], A. Amadeo[2], A. Becchetti[1]
E-mail: m.cerina2@campus.unimib.it
[1] Department of Biotechnology and Biosciences, University of Milano-Bicocca, 20126 Milano, Italy
[2] Department of Biosciences, University of Milano, 20133 Milano, Italy

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Abstract:
Autosomal Dominant Sleep-related Hypermotor Epilepsy (ADSHE) is a rare form of epilepsy which can be caused by mutations in the subunits of heteromeric nAChRs. The 'gain-of-function' β2V287L mutation, when expressed in conditional mouse strains up to P15, permanently disrupts the glutamatergic input to fast-spiking (FS) parvalbumin (PV)-expressing GABAergic cells, in layer V of the prefrontal cortex. This suggests that β2V287L alters the maturation of glutamatergic synapses on FS neurons, leading to lifelong hyperexcitability because of impaired recurrent inhibition of pyramidal excitatory neurons.

Since nAChRs regulate the NRG/ErbB4 pathway, i.e. a critical modulator of synaptic maturation of FS neurons, we investigated this pathway through immunostaining in brain slices of adult mice carrying or not β2V287L. In layer V of mutant mice, we observed an increase of NRG1+ synapses, along with a selective decrease of the glutamatergic NRG1+ synapses contacting PV+ GABAergic cells. We hypothesize that mutant nAChRs may overactivate the NRG/ErbB4 pathway, possibly leading to an exhaustion of powerful glutamatergic input to layer V GABAergic neurons.

To investigate the underlying cellular mechanisms occurring during synaptogenesis, we used electrophysiological techniques such as patch-clamp and Micro Electrode Arrays (MEAs) to record the electrophysiological activity of postnatal mouse cortical cultures, treated with cholinergic agonists and inhibitors of the NRG/ErbB4 pathway up to 14 days *in vitro*. Preliminary results confirm a selective regulation of glutamatergic synapses on FS neurons, highlighting potential molecular targets that could counteract the epileptogenic process during synaptogenesis.