Developmental effects of $\beta2^{V287L}$ nAChR subunit on pyramidal neuron morphology in the neocortex

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Abstract:
Mutant nAChR subunits can be linked to epileptic syndromes, like Autosomal Dominant Sleep-related Hypermotor Epilepsy (ADSHE). Mice expressing the ADSHE-linked $\beta2^{V287L}$ subunit during development (P0-P15) show a reduction of the early excitatory input onto pyramidal neurons (Py), a delay in the GABAergic shift and a reduction of the excitatory input onto fast-spiking GABAergic neurons in the adult prefrontal cortex (PFC). These alterations are the possible substrate of spontaneous sleep-related seizures in the adult transgenic (TG) mice, which are absent if $\beta2^{V287L}$ expression is prevented by conditional knock-out.

Since alterations of Py morphology often accompany a dysfunctional microcircuit, we investigated it by staining 300 µm-thick brain slices with the Golgi-Cox method. We analysed the dorsolateral PFC (dlPFC, 2.58 -1.14 mm from Bregma) and the primary somatosensory cortex, barrel field (SS1bf, 0,26-0,02 mm from Bregma) as control region from 4 wild type (2 ♀ and 2 ♂) and 4 transgenic mice (3 ♀ and 1 ♂; all aged > P60). Sections were imaged by acquiring Z-stacks and from 4 to 17 neurons for each of II-III and V cortical layer were taken into consideration for both regions in each mouse.

Sholl analysis was performed to quantify the complexity of dendrite arbors: in dlPFC layer II-III the ramification peak at around 50 µm from the soma was significantly reduced in Py from TG mice (t-test, p-value < 0.5), as well as the number of distal ramifications in layer V (t-test, p-value < 0.5); differently, no genotype difference ware measured in SS1bf. The number of dendritic spines was manually counted every 10 µm from the soma to obtain the spatial profile of spine density over the dendrite length and a significant reduction was found in distal spine density (distance > 60 µm from the soma; t-test, p-value < 0.5) of layer II-III Py in the SS1bf of TG mice. In both genotypes the dendritic spine density is significantly higher in dlPFC than in SS1bf, whereas no difference was found in the overall dendrite length between wild type and TG mice.

We can conclude that mutant nAChR subunits can be involved in the developmental maturation of dendrites and dendritic spines of Py in the neocortex, with important effects on the network properties and pathogenic implications.