β2-V287L nicotinic receptor subunit expression reduces glutamate release on fast-spiking neurons in layer V prefrontal cortex

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Abstract: ADSHE is a familial focal epilepsy characterized by hypermotor seizures, typically arising from the frontal lobe during non-REM sleep.
About 10-15% of ADSHE patients carry mutations on genes coding for heteromeric nicotinic receptor (nAchR) subunits. Our work focused on the effects of β2-V287L mutation, conditionally expressed in a murine model under control of the tetracycline promoter (TET-off system). Transgene expression during early development (E1-P15) has been established to be crucial for the occurrence of spontaneous epileptic seizures and conditional silencing at later stages was not able to revert the pathological phenotype. Therefore, as literature indicates that nAChRs activity is involved in the processes of dendrite harboring and synapse refinement during neocortex development, the expression of mutant isoforms of these receptors may lead to permanent circuital anomalies and to the alteration of the excitatory/inhibitory balance.
To test this hypothesis, patch clamp experiments were performed to identify possible electrophysiological alterations induced by β2-V287L expression in prefrontal cortex (PFC) slices of adult mices.
Our data show that β2-V287L nAChRs expression reduced EPSC frequency in fast-spiking (FS) layer V neurons of the frontal area 2 (Fr2) compared to control animals, as a result of a reduction in glutamate release probability.
Since FS interneurons play a central role in the control of pyramidal neuron activity (through a feedforward inhibition mechanism), a reduction in glutamatergic input on FS interneurons can lead to the hyperactivation of pyramidal neurons and consequently to the generation of seizures.
Further investigations based on both electrophysiological and biomolecular methods will be critical to better characterize possible PFC circuitry impairments, which may be responsible for the excitatory and inhibitory tone imbalance typical of this pathology.