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Behavioral effect of selective deletion of beta2 nicotinic acetylcholine receptors in neuropeptide Y expressing interneurons*

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Neuropeptide Y (NPY) is an abundant neuropeptide in the neocortex involved in numerous processes. NPY-expressing neurons differ in electrophysiological, molecular and morphological properties but overall, they are GABAergic interneurons (GINs). All cortical layers receive cholinergic inputs from the basal forebrain, which are crucial for cognition. Cholinergic receptors are differentially distributed across the cortex and the activation of nicotinic acetylcholine receptors (nAChRs) located on principal neurons and GINs modulates synaptic plasticity and behavior.

Functional consequences of the cholinergic activation of NPY-expressing cortical interneurons (NPY+GINs) have not been specifically clarified yet. By using the CRISPR/Cas9 approach, we deleted the most abundant beta2* subunit of nAChRs expressed by NPY+GINs in the prefrontal cortex (PFC) and investigated the effect on behavior.

By in situ hybridization, we characterized the expression of beta2* nAChRs on NPY+GINs. To induce a cell specific deletion of beta2* nAChRs, we crossed a mouse line expressing Cas9-GFP in a Cre-dependent manner with a NPY-Cre line. The resulting mice were injected with AAV vector carrying sgRNA targeting CHRN2, gene coding for beta2 nicotinic subunit, into PFC. Mutant mice and littermate controls, injected with scrambled gRNA, were tested in a battery of behavioral tasks including social preference task and novel object recognition. Immunohistochemical evaluation of neuronal markers and activity indicators showed changes in activation/inhibition balance in cortical circuits.

The successful induction of indels in CHRN2 gene in AAV-transduced cells was confirmed by FACS sorting followed by DNA sequencing. Mice with presumed deletion of nAChRs showed increased social interaction compared to controls.

The achieved efficiency of CRISPR/Cas9-induced indels in CHRN2 gene in NPY+GINs of the PFC was sufficient to induce behavioral changes in mice. Specifically, the increased sociability agrees with *Avale et al., 2011*.

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