α6* Nicotinic receptors modulate lateral habenula circuits and control nicotine addictive behaviors

The habenula, consisting of medial and lateral parts, is a critical regulator of aversion signaling. Previous studies have demonstrated that the medial habenula-interpeduncular nucleus pathway is important for nicotine aversion and intake. To date however, there has been no evidence for either functional nicotine acetylcholine receptors (nAChRs) in the lateral habenula (LHb) or a role for LHb in nicotine-related behaviors.

We used patch-clamp recordings from acutely prepared rat brain slices to examine the actions of nicotine on membrane potential, spike firing, and GABAergic as well as glutamatergic transmissions in LHb, and to identify the nAChR subunits involved. We then determined the functional effects of LHb nAChR blockade in nicotine-induced conditioned place preference.

Activation of nAChRs induced membrane depolarization and strong and robust increases in firing frequency and glutamatergic synaptic currents in LHb neurons, all of which were blocked by α-conotoxin MII, an antagonist selective for α6* nAChRs. We also showed that GABAergic afferents to LHb contain α4β2* nAChRs that are more sensitive to nicotine than nAChRs on LHb neurons or on glutamatergic afferents, and desensitize more rapidly. Furthermore, intra-LHb infusion of α-conotoxin MII potentiates the acquisition of nicotine-induced conditioned place preference, but impairs its expression.

Taken together, these findings demonstrate that α6* nAChRs within the LHb enhance LHb activity and play a crucial role in nicotine-induced addictive behaviors.

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