

BETA-2 AND ALPHA-4, BUT NOT ALPHA-7, SUBUNITS OF THE NICOTINIC RECEPTOR WITHIN THE VTA ARE NECESSARY AND SUFFICIENT FOR NICOTINE REINFORCEMENT

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Tobacco consumption and exposure have been shown to have significant negative health effects, making the identification of the molecular mechanisms involved in nicotine reinforcement of primary importance to produce effective therapies. Nicotine is known to sustain self-administration (SA) behaviour in laboratory animals while the ventral tegmental area (VTA) of the midbrain is considered one of the neuroanatomical substrates through which nicotine exerts its reinforcing and dependence-producing actions. Nicotine binds to neuronal nicotinic acetylcholine receptors (nAChRs), a heterogeneous family of pentameric ligand-gated ion channels composed of twelve α and β subunits (α_2 - α_{10} and β_2 - β_4), which potentially assemble in multiple combinations with a broad range of pharmacological and electrophysiological properties. Among these nAChR subunits, the beta-2 (β_2), alpha-4 (α_4) or alpha-7 (α_7) are thought to play crucial yet differential roles in mediating the addictive properties of nicotine. In the present study, we evaluated acute nicotine (0.025, 0.075 and 0.15 mg/kg/inf) intravenous SA in drug-naïve mice knockout for either the beta2 (β_2 -KO), the alpha4 (α_4 -KO) or the alpha7 (α_7 -KO) subunit, in wild-types (C57BL/6J, WT mice) and in KO mice in which the deleted nAChR subunit has been re-expressed selectively in the VTA by stereotaxic injections of lentiviral re-expression vectors. Results showed that, contrary to respective WT groups showing dose-dependent nicotine SA, both β_2 -KO and α_4 -KO mice lack responsiveness to nicotine. However, when the β_2 or the α_4 subunit was reintroduced into the VTA of β_2 -KO or α_4 -KO animals, responsiveness to nicotine was restored, suggesting that the rewarding effects of nicotine are entirely restored by reintroduction of these receptor subunits into cell bodies of the VTA. Conversely, α_7 -KO mice promptly self-administer nicotine intravenously at the same extent as the WT group, demonstrating that this specific subunit is not crucial for the expression of the acute reinforcing properties of nicotine. Altogether, these findings demonstrate that nicotine produces its motivational effects through β_2 - and α_4 - rather than α_7 -containing nAChRs, suggesting a functional dissociation between nAChR neural substrates within the VTA that mediate its acute reinforcing effects. As activation of β_2 - or α_4 -nAChRs in the VTA is sufficient per se to make nicotine rewarding, drugs selectively targeting such receptor subunits might be useful in reducing nicotine addiction.