Regulation of nicotinic receptor subtypes by nicotine: in vivo studies

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Nicotine, the main psychoactive component of cigarette smoke, has two main effects that contribute to addiction: its reinforcing or rewarding properties, and the aversive abstinence syndrome that develops when it is withdrawn. These behavioural effects are due to the neural adaptations induced by the interactions between nicotine and the neuronal nicotinic acetylcholine receptors (nAChRs) in the mesolimbic and habenulo-interpeduncular pathways.
We studied the effects of treatment of mice with different alpha4 and beta2 subunit expression (wild-type [WT], heterozygotes [HT] and null mutants [KO] for each gene) with one of four doses of nicotine (0, 0.25, 1.0 or 4.0 mg/kg/h for 14 days) and analysed the nAChR expression in different brain areas after nicotine exposure and during nicotine withdrawal. We determined that chronic nicotine exposure increased nAChRs in a dose-dependent and saturable manner in the WT and HT mice, but not in the alpha4 or beta2 KO mice, thus indicating that the increase was mainly due to the alpha4/beta2* nAChR subtype. The magnitude of the increase varied in different brain regions; in the cortex, nicotine not only increased the expression of the alpha4/beta2* subtype, but also favoured the formation of the receptors with the (alpha4)2(beta2)3 stoichiometry. Furthermore, we found that in vivo nicotine up-regulates the alpha3beta2*-nAChR subtype, while had no effect on the alpha3beta4-nAChR subtype.
Nicotinic stimulation of dopamine secretion in the mesolimbic pathway is essential for the reinforcing effects of nicotine, but other neurotransmitter pathways such as glutamatergic neurons are also involved in the motivational effects of nicotine. We found that non-contingent chronic nicotine treatment has different effects on nAChR and glutamate receptor (GluR) expression in the mesocorticolimbic pathway. In particular, nicotine up-regulated beta2-containing nAChRs in the striatum, midbrain and prefrontal cortex, and its withdrawal led to rapid decrease in the levels of these receptors; differently, the effects of nicotine exposure and withdrawal on GluRs were region- and subtype-specific with many alterations in GluRs developing slowly after nicotine withdrawal and peaking at withdrawal day 14. Alterations in glutamatergic transmission after cessation of chronic nicotine treatment may be persistent and contribute to the long-lasting alterations in brain neurochemistry and behavior observed after chronic nicotine exposure