The Beta 3 subunit of the nicotinic acetylcholine receptor (nAChR) is required for nicotine withdrawal but nicotine reward

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The □3 subunit of the nicotinic acetylcholine receptor (nAChR) is not widely distributed in the brain, but it is expressed in brain regions important in drug dependence and reward including the ventral tegmental area, substantia nigra, nucleus accumbens and medial habenula. In addition, receptors containing the □3 subunit have been implicated in dopamine release from terminals in the mouse striatum. Human genetic studies suggest that allelic variation in *CHRNB3* is associated with smoking dependence vulnerability. Nevertheless, surprisingly little is known about the role of □3-containing nAChRs in nicotine dependence and reward. A recent study reported that oral nicotine consumption in the two-bottle choice paradigm was decreased in □3 KO mice. In this study, we assessed nicotine dependence behaviors in □3 wildtype (WT) and knockout (KO) male and female mice. We first evaluated nicotine reward in the conditioned place preference (CPP) test and then measured nicotine withdrawal signs after chronic exposure to the drug. WT mice and □3 KO mice were tested for nicotine preference in unbiased CPP test for a 5-days procedure. Nicotine-induced CPP did not differ between □3 KO and WT mice. Consistent with these findings, levels of nicotine intake were similar in WT mice and □3 KO mice across a broad dose-range in the intravenous nicotine self-administration procedure. For the withdrawal studies, mice were continuously infused with 24 mg/kg/day of nicotine using surgically implanted osmotic mini-pumps for 14 days. Mini-pumps were removed at day 15, and withdrawal signs (somatic signs, hyperalgesia, anhedonia using the sucrose preference test and anxiety-like behaviors using the light dark boxes) were collected at 24-h intervals for three days following spontaneous withdrawal of nicotine. Our results showed that □3 KO mice displayed similar somatic symptoms and hyperalgesia compared to the WT mice but showed significant absence in affective (anhedonia and anxiety-like behaviors) withdrawal signs in nicotine-dependent mice. These observations demonstrate that the □3 nicotinic subunits does not seem to influence nicotine reward and reinforcement but instead plays an important role in nicotine withdrawal. These results may contribute to our understanding of brain molecular mechanisms underlying nicotine dependence.

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