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Nicotine-Conditioned Place Preference Requires Cannabinoid CB_2 Receptor

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The endocannabinoid system has long been known to play a role in the underlying mechanisms of drug reward and dependence. In particular, CB_1 receptor blockade reduces the rewarding effects of many drugs of abuse, including marijuana, morphine, ethanol, and nicotine. Recent work has also implicated the involvement of cannabinoid CB_2 receptors, in which CB_2 receptor agonists reduced cocaine self-administration, cocaine-induced hypermotility, and cocaine-enhanced extracellular levels of dopamine in the nucleus accumbens. Here, we evaluated whether CB_2 receptors also play a role in the nicotine dependence-related behaviors in mice.

Accordingly, we assessed the effects of CB_2 receptor agonists and antagonists as well as CB_2 null mice in the nicotine conditioned place preference (CPP) paradigm. For comparison, we tested the involvement of the CB_2 receptor on cocaine CPP to determine whether this receptor plays a similar role for both drugs. In this paradigm we determined preference score that was calculated for each animal as the difference between time spent in the drug-paired chamber on the post-conditioning day and time spent in the same chamber before conditioning (baseline). A positive number indicated a preference for the drug-paired side, whereas a negative number implied an aversion to the drug-paired side. A number of zero or near zero indicated no preference for either side. Results are shown as mean preference score ± SEM. Additionally, we used CB_2 (+/+) and (-/-) mice given seven days of exposure to nicotine via alzet mini pumps (24 mg/kg/day) to determine whether the CB_2 receptor is necessary for mecamylamine (2 mg/kg, s.c.)-precipitated withdrawal. Finally, we tested whether deletion of CB_2 receptors affects nicotine-induced hypothermia and antinociception (Merritt et al., 2008). The sample size in each group was $n \geq 6$. Data were analyzed with two-way ANOVA followed by Bonferroni post hoc comparison.

Nicotine (0.5 mg/kg, s.c.)-induced CPP (169±21 s) was dose-dependently blocked by the selective CB_2 receptor antagonist, SR144528 (3 mg/kg, i.p.) (-4±10 s) in wild type mice [$p<0.01$], and was absent in CB_2 (-/-) mice (28±16 s) [interaction of nicotine and genotype: $p<0.01$]. Conversely, the combination of the CB_2 receptor agonist O-1966, with a subthreshold dose of nicotine (0.1 mg/kg, i.p.), elicited increased preference scores following increasing doses of O-1966 (nicotine alone: 5±12 s, and nicotine plus respective doses of O-1966 (1, 3, 5, 10, 20 mg/kg): 15±28 s, 84±16 s, 101±21 s, 107±23 s, 78±26 s) [interaction of O-1966 and nicotine: $p<0.05$]. In marked contrast, O-1966 (20 mg/kg, i.p.) blocked cocaine (10 mg/kg, i.p.)-induced CPP in wild type mice (vehicle + cocaine: 179±18 s; O-1966 + cocaine: 39±16 s) [interaction of O-1966 and cocaine: $p<0.001$], while CB_2 (-/-) mice showed unaltered cocaine CPP (151±16 s)[interaction of cocaine and genotype: $p=0.7$]. CB_2 (+/+) and (-/-) nicotine-dependent mice showed almost identical precipitated withdrawal somatic and affective signs. Finally, deletion of the CB_2 receptor did not alter somatic, antinociceptive and hypothermic effects of acute nicotine administration (0.5, 2.5 mg/kg, s.c.).

Collectively, these results indicate that CB_2 receptors are required for nicotine reward as measured in the CPP test in the mouse, while it is not involved in nicotine withdrawal or the acute antinocieptive or hypothermic effects of nicotine. Moreover, these results suggest that CB_2 receptors play opposing roles in nicotine- and cocaine-induced CPP.

References:

Merritt LL et al, J Pharmacol Exp Ther 326(2):483-492, 2008.