

NICOTINIC α_7 RECEPTOR AS A NEW TARGET FOR TREATMENT OF CANNABIS ABUSE

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Cannabis abuse is a wide spread phenomenon in western societies especially among teenagers and young adults. Although physical dependence may be mild, psychological dependence to cannabis may be strong and require medical treatment. Thus, the discovery of new molecular tools to reduce the psychotropic and rewarding effects of cannabis is of primary importance to produce effective therapies. Here, we investigated whether selective antagonists for nicotinic receptor acetylcholine subtypes reduced the abuse-related effects of THC. In rats discriminating injections of 3 mg/kg i.p. of delta-9-tetrahydrocannabinol (THC), the main active ingredient in cannabis, from injections of saline, the selective α_7 nicotinic acetylcholine receptor antagonist methyllycaconitine (MLA) (1-5.6 mg/kg i.p.), but not the selective heteromeric non- α_7 nicotinic acetylcholine receptor antagonist dihydrobetaerythroidine (DHBE) (1-18 mg/kg i.p.) significantly antagonized the discriminative effects of THC without altering rates of responding. In addition, MLA but not DHBE reduced intravenous self-administration of the synthetic cannabinoid CB1 receptor agonist WIN55,212-2 (12.5 and 25 μ g/kg/inj) under fixed-ratio schedules (FR1 and FR5). Finally, MLA but not DHBE decreased THC-induced dopamine elevations in the shell of the nucleus accumbens (NAc). Altogether our results indicate that blockade of α_7 nicotinic receptors reverses abuse-related behavioral and neurochemical effects of cannabinoids. Importantly, MLA reversed the effects of cannabinoids at doses devoid of depressant or toxic effects, further pointing to α_7 nicotinic acetylcholine antagonists as potentially useful agents in the treatment of cannabis abuse in humans.