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ANTI-"METHAMPHETAMINE-CRAVING" EFFECT OF A CANNABINOID CB1 RECEPTOR ANTAGONIST THROUGH NICOTINIC ACTIVATION IN THE PRELIMBIC CORTEX

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Objectives: We have reported that reinstatement of methamphetamine (MAP)-seeking/"craving" was attenuated by systemic administration of a cannabinoid CB1 receptor antagonist[3-4]and nicotine[1]. Recently, it was demonstrated that the prelimbic cortex (PrC) is important for expression of cocaine-induced behavioral sensitization. However, the interaction between cannabinoid CB1 and nicotinic receptors in the brain region in drug-seeking was not understood. Therefore, the present study clarified whether the attenuating effect of a cannabinoid CB1 receptor antagonist on the reinstatement would be due to the CB1 receptors in the PrC and involved in the nicotinic receptors.

Methods: Male Wistar/ST rats were surgically implanted catheters into the jugular vein and bilaterally guide cannulas into the PrC. Rats were trained to self-administer MAP (0.02 mg/infusion) in response to a light and tone (MAP associated-cues) under an FR-1 schedule in a daily session for 10 days. Then, extinction sessions under saline infusions without cues were conducted daily for 5 days. Reinstatement (drug-seeking) tests under saline infusions were carried out on day 6 of extinction and were induced by re-exposure to the cues.

Results: Systemic administration of a cannabinoid CB1 receptor agonist HU210 (32 microg/kg, s.c.) reinstates MAP-seeking. Intracranial HU210 (3.2-10 microg/side) into the PrC also reinstates MAP-seeking. On the other hand, intracranial administration of a cannabinoid CB1 receptor antagonist AM251 (10-32 microg/side) into the PrC attenuates reinstatement induced by MAP-associated cue. Furthermore, the attenuating effect of AM251 (32 microg/side) was blocked by intracranial administrations of a nicotinic antagonist mecamylamine (1.0-3.2 microg/side).

Conclusion: The attenuating effects of intracranial AM251 were blocked by intracranial mecamylamine. Recent study demonstrated inhibitory retrograde regulation of endocannabinoid in synapses[2]. Therefore, it is suggested that the attenuating effect of cannabinoid CB1 receptor antagonists on the reinstatement may be due to nicotinic activation followed by enhancement of acetylcholine release via blockade of cannabinoid CB1 receptors. Furthermore, these results strengthen the possibility of nicotinic activators as the "craving"-killers in MAP-dependence.

Referencess:

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