The interactive role of dopamine D₁ and adenosine A₁ receptors in the nucleus accumbens on methamphetamine relapse

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Methamphetamine abuse is a global health problem, however the neuropharmacological mechanisms of its use and abuse are not well understood. Previous work has shown that dopamine and adenosine receptors are important for methamphetamine’s rewarding and reinforcing effects. The studies presented here examine the interactive role of dopamine and adenosine receptors in the nucleus accumbens (NAc) on the reinstatement of methamphetamine seeking following extinction. Rats were trained to lever press for methamphetamine in daily 2-hr self-administration sessions on a fixed-ratio-1 schedule for 10 consecutive days. Lever pressing was extinguished in at least 6 daily extinction sessions prior to reinstatement testing. We first assessed the effects of adenosine A₁ or A₂A receptor stimulation on reinstatement induced by a methamphetamine prime (1.0 mg/kg, i.p.). Systemic administration of the adenosine A₁ agonist, CPA, but not the adenosine A₂A agonist, CGS 21680, dose-dependently inhibited methamphetamine-induced reinstatement. We then assessed whether stimulation of dopamine D₁ or D₂ receptors in the NAc is sufficient to induce methamphetamine seeking. Micro-infusion of a dopamine D₁ agonist (SKF 81297), but not a dopamine D₂ agonist (quinpirole), exhibited a dose-dependent increase in methamphetamine seeking. We then identified whether SKF 81297-induced reinstatement would be altered by co-administration with an adenosine A₁ agonist (CPA) in the NAc. SKF 81297-induced reinstatement was blunted when CPA was co-administered in the NAc. Lastly, we evaluated the effects of an adenosine A₁ antagonist (DPCPX) administered into the NAc alone or in combination with SKF 81297. DPCPX had no effect when administered alone, but significantly enhanced SKF 81297-induced methamphetamine seeking. Collectively, these data suggest that dopamine D₁ and adenosine A₁ receptors in the NAc play an interactive role in methamphetamine-seeking behavior.

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