

Inhibition of Monoacylglycerol Lipase Reduces the Reinstatement of Methamphetamine-Seeking and Anxiety-Like Behaviors in Methamphetamine Self-Administered Rats.

Abstract

Background: Methamphetamine is a highly addictive psychostimulant with reinforcing properties. Our laboratory previously found that Δ 8-tetrahydrocannabinol, an exogenous cannabinoid, suppressed the reinstatement of methamphetamine-seeking behavior. The purpose of this study was to determine whether the elevation of endocannabinoids modulates the reinstatement of methamphetamine-seeking behavior and emotional changes in methamphetamine self-administered rats. Methods: Rats were tested for the reinstatement of methamphetamine-seeking behavior following methamphetamine self-administration and extinction. The elevated plus-maze test was performed in methamphetamine self-administered rats during withdrawal. We investigated the effects of JZL184 and URB597, 2 inhibitors of endocannabinoid hydrolysis, on the reinstatement of methamphetamine-seeking and anxiety-like behaviors. Results: JZL184 (32 and 40 mg/kg, i.p.), an inhibitor of monoacylglycerol lipase, significantly attenuated both the cue- and stress-induced reinstatement of methamphetamine-seeking behavior. Furthermore, URB597 (3.2 and 10 mg/kg, i.p.), an inhibitor of fatty acid amide hydrolase, attenuated only cue-induced reinstatement. AM251, a cannabinoid CB1 receptor antagonist, antagonized the attenuation of cue-induced reinstatement by JZL184 but not URB597. Neither JZL184 nor URB597 reinstated methamphetamine-seeking behavior when administered alone. In the elevated plus-maze test, rats that were in withdrawal from methamphetamine self-administration spent less time in the open arms. JZL184 ameliorated the decrease in time spent in the open arms. Conclusion: We showed that JZL184 reduced both the cue- and stress-induced reinstatement of methamphetamine-seeking and anxiety-like behaviors in rats that had self-administered methamphetamine. It was suggested that a decrease in 2-arachidonoylglycerol in the brain could drive the reinstatement of methamphetamine-seeking and anxiety-like behaviors.