The monoacylglycerol lipase inhibitor JZL184 attenuates methamphetamine-seeking behaviors in methamphetamine self-administered rats

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Methamphetamine (METH) is a highly addictive psychostimulant with reinforcing properties. We previously found that the cannabinoid CB_1 receptors drive reinstatement of METH-seeking behaviors. The purpose of this study was to determine whether the activation of endocannabinoids regulates the reinstatement of METH-seeking behaviors. Rats were tested for reinstatement of METH-seeking behaviors following METH self-administration and extinction. We investigated the effects of JZL184 or URB597, inhibitors of endocannabinoid hydrolysis, on the reinstatement of METH-seeking behaviors. JZL184 (40 mg/kg, i.p.), an inhibitor of monoacylglycerol lipase, significantly attenuated both the cue- and footshock-induced reinstatement of METH-seeking behaviors. URB597 (3.2 mg/kg, i.p.), an inhibitor of fatty acid amide hydrolase, attenuated only cue-induced reinstatement. On the other hands, we also investigated the effect of the inhibitors of endocannabinoid hydrolysis on cognitive function using the novel object recognition task in mice. The recognition index level in the test did not change in JZL184-treated mice. However, URB597 significantly decreased the recognition index level. These findings suggested that JZL184 might have potential as a new therapeutic agent with anti-craving effect, without amnestic effects, in METH addiction.