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# Cognitive impairment induced by MDMA (Ecstasy) involves cannabinoid CB1 receptors

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(±)-3,4-Methylenedioxymethamphetamine (MDMA, Ecstasy) is a synthetic analog of methamphetamine (MAP), and its abuse is becoming a serious issue worldwide. Clinical findings suggest that its protracted withdrawal syndrome includes such psychiatric disorders as panic attack, insomnia and anxiety, as well as memory impairment. Recently, we have reported that cannabinoid CB1 receptors (CB1Rs) are involved in the expression of the withdrawal syndrome of morphine and MAP-seeking behavior. Judging from these findings, it is suggested that the cannabinod system may be activated upon withdrawal from various types of dependence-producing agents. In this study, we examined whether chronic MDMA induces cognitive impairment upon withdrawal in mice, and the involvement of the cannabinoid system with CB1R knockout [CB1 (-/-)] mice. Mice were administered MDMA 10 mg/kg, i.p., once daily for 7 days, followed by a 7-day withdrawal period with a novel object recognition test conducted on days 1 and 7. MDMA-treated mice showed significant impairment of task performance on both days during the withdrawal period, however, when MDMA was co-administered with a CB1R antagonist, AM251, cognitive impairment was not seen on withdrawal day 7. Furthermore, a single administration of AM251 during the withdrawal period significantly attenuated impairment. Although there was no difference between saline-treated wild-type (+/+) and CB1 (-/-) mice in the object recognition task performance, withdrawal from MDMA did not induce any cognitive impairment in CB1 (-/-) mice. In summary, this study showed that repeated MDMA induced cognitive impairment upon withdrawal via the activation of CB1Rs. The finding suggests the possibility that a CB1R antagonist may serve as therapy for MDMA withdrawal syndrome.