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Dorsal hippocampal NMDA receptors mediate the interactive effects of arachidonylcyclopropylamide and MDMA/ecstasy on memory retrieval in rats

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ABSTRACT

A combination of cannabis and ecstasy may change the cognitive functions more than either drug alone. The present study was designed to investigate the possible involvement of dorsal hippocampal NMDA receptors in the interactive effects of arachidonylcyclopropylamide (ACPA) and ecstasy/MDMA on memory retrieval. Adult male Wistar rats were cannulated into the CA1 regions of the dorsal hippocampus (intra-CA1) and memory retrieval was examined using the step-through type of passive avoidance task. Intra-CA1 microinjection of a selective CB1 receptor agonist, ACPA (0.5–4 ng/rat) immediately before the testing phase (pre-test), but not after the training phase (post-training), impaired memory retrieval. In addition, pre-test intra-CA1 microinjection of MDMA (0.5–1 μg/rat) dose-dependently decreased step-through latency, indicating an amnesic effect of the drug by itself. Interestingly, pre-test microinjection of a higher dose of MDMA into the CA1 regions significantly improved ACPA-induced memory impairment. Moreover, pre-test intra-CA1 microinjection of a selective NMDA receptor antagonist, D-AP5 (1 and 2 μg/rat) inhibited the reversal effect of MDMA on the impairment of memory retrieval induced by ACPA. Pre-test intra-CA1 microinjection of the same doses of D-AP5 had no effect on memory retrieval alone. These findings suggest that ACPA or MDMA consumption can induce memory retrieval impairment, while their co-administration improves this amnesic effect through interacting with hippocampal glutamatergic-NMDA receptor mechanism. Thus, it seems that the tendency to abuse cannabis with ecstasy may be for avoiding cognitive dysfunction.

1. Introduction

Patterns of polydrug use among young people are becoming increasingly alarming (Sala and Braida, 2005). Among poly-drug users, co-abuse of cannabis with drugs such as 3,4-methylenedioxy-methamphetamine (MDMA or ecstasy) or cocaine is very common (Aberg et al., 2007; Schulz, 2011). A great deal of previous research indicated that various factors may be the reasons of co-abuse of cannabis and MDMA. For example, cannabis consumption has been reported to decrease MDMA-induced anhedonia, depression (Parrott, 2000; Parrott et al., 2004), somatic symptoms, aggressive behaviors (Milani et al., 2005) and acute hyperthermia (Morley et al., 2004). On the other hand, exposure to polydrug use has been shown to cause an additive dopamine release in the nucleus accumbens (Tizabi et al., 2007), which may be an important reason for the tendency toward the co-abuse of the drugs. The mesolimbic dopaminergic reward system, which is the main target of abused drugs, originates from ventral tegmental area (VTA) and projects to the nucleus accumbens (Nac), the hippocampus and the amygdala (for review see Clay et al., 2008). A large body of evidence shows that the hippocampus plays a critical role in many aspects of the addictive processes (Eisch and Harburg, 2006) and drug-induced cognitive dysfunction may be related to the alterations in adult hippocampal neurogenesis (for a review, see Venkatesan et al., 2007).

Cannabis is the most prevalent drug of abuse that exerts its effects via cannabinoid CB1 and CB2 receptors which are members of the

Abbreviations: ACPA, Arachidonylcyclopropylamide; ANOVA, Analysis of variance; CA1, cornus ammonis; CB1, Cannabinoid receptor type 1; CB2, Cannabinoid receptor type 2; CP-55,940, (−)-cis-3-[2-Hydroxy-4-(1,1-dimethylheptyl)phenyl]-trans-4-(3-hydroxypropyl)cyclohexanol; D-AP5, D-(−)-2-amino-5-phosphonopentanoic acid; Δ^9–THC, Delta9-tetrahydrocannabinol; GABA, gamma-aminobutyric acid; GTP, Guanosine triphosphate; LTP, long-term potentiation; MDMA, 3, 4-methylenedioxy-N-methylamphetamine; Nac, Nucleus accumbens; NMDA, N-methyl-D-aspartic acid; SEM, standard error of mean; VTA, Ventral tegmental area; WIN 55,212-2, WIN55,212-2 mesylate; 5-HT, 5-Hydroxytryptamine.

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GTP-binding protein coupled receptors (Demuth and Molleman, 2006). In view of the fact that the rat hippocampus has a high density of cannabinoid CB1 receptors (Iversen, 2003) and that the pre-synaptic cannabinoid CB1 receptors modulate different neurotransmitters release, it seems that hippocampal endogenous cannabinoid system plays a critical role in learning and memory processes (Han et al., 2012). The cannabinoid receptor agonists have been shown to impair long-term potentiation (LTP; a candidate mechanism for memory formation) in the rat hippocampal slices (Terranova et al., 1995; Han et al., 2012) probably via inhibition of glutamate release induced by the activation of pre-synaptic cannabinoid CB1 receptors (Schlicker and Kathmann, 2001). A considerable amount of literature has been published on the functional interaction between cannabinoid and other neurotransmitter systems including glutamatergic and serotonergic systems. For example, Rey et al. (2012) using mice lacking CB1 receptors showed that the biphasic effect of cannabinoids on anxiety responses may be mediated by the CB1 receptors on cortical glutamatergic terminal. Melis et al. (2004) also pointed to the involvement of endocannabinoids in presynaptic inhibition of glutamatergic transmission to the ventral tegmental area dopaminergic neurons which may prevent neuronal excitability and synaptic transmission.

MDMA as an amphetamine derivative plays a modulatory role in different physiological functions such as memory formation (Sprague et al., 2003), anxiety (Maldonado and Navarro, 2000) and rewarding processes (Vidal-Infer et al., 2012). The effects of MDMA on the cognitive processes are various and depend on factors such as dose and the duration of exposure (Broening et al., 2001). It has generally been viewed as a monoaminergic agonist and modulates serotonin (5-hydroxytryptamine or 5-HT) release (Thomasius et al., 2003). To better understand the effect of MDMA on serotonergic neurotransmission, Mueller et al. (2013) showed that MDMA oral administration in a single dose can induce neurochemistry deficits of serotonin. This consumption will therefore cause long-term cognitive deficits (Schilt et al., 2008). It is important to note that MDMA produces an acute and rapid enhancement in the release of serotonin from the storage vesicles (Riegert et al., 2008; Capela et al., 2009) leads to a reduction in serotonin uptake sites and degeneration of serotonergic axons in certain brain areas (Ricaurte et al., 2000). Further research has shown that systemic administration of neurotoxic doses of MDMA decreases serotonergic axon density and aberrant swollen varicosities in the frontal cortex of rats (Adori et al., 2011). On the other hand, the enhancement of serotonin concentration in the hippocampus following MDMA exposure (Gudelsky and Nash, 1996) has been mediated via 5-HT1A transporters (Hasler et al., 2009) which are present in large numbers in the cortex, the hippocampus (Varnäs et al., 2004). Also, it has been shown that MDMA administration decreases GABA and increases glutamate release in the dorsal hippocampus (Anneken et al., 2013). It seems that MDMA-induced augmentation of hippocampal glutamate efflux may be mediated through a serotonergic mechanism (Anneken and Gudelsky, 2012). Considering that NMDA receptors mediate the acquisition of the conditioned rewarding effects of MDMA (García-Pardo et al., 2015), neurochemical MDMA effects on the brain may be explained, in part, by the interaction of MDMA with NMDA receptors.

The main aims of this study were: (i) to examine the effects of microinjection of a selective CB1 receptor agonist (ACPA) or MDMA into the CA1 region of the dorsal hippocampus on memory formation in rats to show the possible role of this site in neurocognitive effects of cannabis or ecstasy consumption; (ii) to investigate the interactive effects of combined MDMA/ACPA administration on passive avoidance memory retrieval; and (iii) to assess whether this functional interaction between ACPA and MDMA can be affected by blockade of NMDA receptors in the dorsal hippocampus. Since the neurobiological basis of co-abuse tendency is poorly understood, this study makes a major contribution to research on memory performance induced by cannabis/ecstasy co-abuse.

2. Materials and methods

2.1. Animals

Male Wistar rats (from Faculty of Pharmacy, Tehran University of Medical Sciences) weighing 200–220 g at the time of surgery were used in this study. The animals were housed four per cage with free access to food and water. Cages were in a room with a temperature (22 ± 2 °C) and 12-h light/12-h dark cycle (lights on at 07:00 AM). All animals were allowed to adapt to the laboratory conditions for at least 1 week prior to the surgery and were handled for 5 min/day during this adaptation period. Trials were conducted between 10:00 AM and 02:00 PM. The experimental protocol was approved by the Research and Ethics Committee of the School of Medicine, Tehran University of Medical Sciences and was performed in accordance with institutional guidelines for the care and use of laboratory animals (NIH publications no. 80-23; revised 1996).

2.2. Surgical and microinjection

Ketamine-Xylazine (50 mg/kg and 5 mg/kg, respectively) was used for deep anesthesia in the animals. Using a stereotaxic apparatus, each animal was bilaterally implanted with 22-gauge guide cannulas which were 1 mm above the CA1 regions according to the atlas of Paxinos and Watson (2007). Coordinates for the CA1 regions of the dorsal hippocampi were: AP: −3.3; ML: ±2; DV-2.8. The cannula was fixed to the skull with two jewelers screw and dental acrylic. To prevent clogging, the stainless steel stylets (27 gauge) were used in the guide cannulas until the animals were given the injection. The rats were given 1 week to recover from the surgical procedure. For drug injection, the stylets were slowly removed from the guide cannulas and replaced with 27-gauge injection needles (1 mm below the tip of the guide cannula). The injection unit was attached with a polyethylene tube to a 2-μl Hamilton syringe. The injection lasted about 60 s and the cannula was left in place for 60 s after each injection to allow for diffusion and the stylet was then reinserted into the guide cannula.

2.3. Drugs

The drugs used in this study were ACPA (arachidonylcyclopropylamide; N-(2-cyclopropyl)-5Z, 8Z, 11Z, 14Z-eicosatertraenanmide), MDMA (3, 4-methylenedioxy-N-methylamphetamine) or ecstasy and D-AP5 [D-(_)-2-amino-5-phosphonopentanoic acid] (Tocris, Bristol, UK). ACPA dissolved in Tocrisolve™ (a soya oil and water emulsion) was obtained from Tocris and was diluted with sterile 0.9% saline. The other drugs were dissolved in sterile 0.9% saline just before the experiments and were bilaterally injected into the CA1 regions at a volume of 1 μl/rat (0.5 μl/each side). All control groups received sterile 0.9% saline, except for ACPA groups which received Tocrisolve™ with the same concentration as in the experimental solution (as vehicle). The time intervals of drug administrations and the drugs' doses were based on our pilot experiments and previous studies (Rezayof et al., 2011; Alijanpour et al., 2013; Tirgar et al., 2014).

2.4. Passive avoidance apparatus

The animals were trained and tested in a step-through type passive avoidance apparatus which consisted of two compartments, one light (white compartment, 20 cm × 20 × 30 cm) and the other dark (black compartment, 20 cm × 20 × 30 cm). The chambers were separated by a guillotine door (7 cm × 9 cm) in the middle of the dividing wall. Stainless steel grids (2.5 mm in diameter) were placed at 1-cm intervals (distance between the centers of grids) on the floor of the dark compartment. Intermittent electric shocks (50 Hz, 3 s, 1 mA) were delivered to the floor of the dark compartment by an insulated stimulator (Borj Sanat Co., Tehran, Iran). It is important to note that the paradigm of