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Effect of adolescent exposure to MDMA and cocaine on acquisition and reinstatement of morphine-induce CPP

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Abstract

It is well known that an elevated percentage of ecstasy users also consume cocaine. Recently, it has been reported that a high frequency of heroin smokers first consumed heroin under the effects of ecstasy with the hope of reducing the stimulant effects of the latter drug. The aim of the present study was to evaluate the effect of exposure to MDMA and cocaine during adolescence on morphine-induced conditioned place preference (CPP) and reinstatement in adulthood. In the first experiment, adolescent mice were exposed to six injections of MDMA and three weeks later their response to the reinforcing properties of 40 mg/kg of morphine was evaluated using the CPP paradigm. All the treatment groups developed the same magnitude of morphine-induced preference and, after CPP was extinguished, it was restored in all the groups with a priming dose of 10 mg/kg of morphine. Only mice that had been treated with 10 or 20 mg/kg of MDMA had their morphine-induced preference reinstated after receiving only 5 mg/kg of morphine. In the second experiment, adolescent mice were similarly treated with six administrations of cocaine (25 mg/kg) or cocaine plus MDMA (5, 10 or 20 mg/kg), and their response to morphine-induce CPP was evaluated three weeks later. Similarly to the first experiment, all the groups developed a preference for the morphine-paired compartment, but this preference was not reinstated with a priming dose of 10 mg/kg of morphine following extinction, as was the case among the control animals. These results lead us to hypothesize that periadolescent MDMA exposure alters responsiveness to the rewarding properties of morphine, highlighting MDMA as a gateway drug whose use may increase the likelihood of dependence on other drugs.

Keywords: Cocaine; Conditioned place preference; MDMA; Mice; Morphine; Relapse

1. Introduction

MDMA (3,4-methylen-dioxy-methamphetamine) or ecstasy is an illicit recreational drug consumed by many teenagers and young adults. Ecstasy users are more likely to take other drugs than non-MDMA users, with 90% of MDMA users and only 13.8% of non-MDMA users reporting having consumed other illicit substances. Specifically, cocaine has been reported as being used by 43.8% of MDMA users (The National Survey on Drug Use and Health, 2004; Wish et al., 2006). This pattern is also observed in Spain, where cocaine is used by about 60% of ecstasy abusers (DGPNSD, Encuesta Estatal sobre Uso de Drogas en Enseñanzas Secundarias, 2004). Ecstasy users who do not consume any other illicit psychoactive drugs would seem to be uncommon (Rodgers, 2000). A number of reports have highlighted how an elevated proportion of heroin smokers recognize that they first consumed heroin hoping to decrease the stimulant effects of ecstasy (Gervin et al., 1998; 2001). These users also report taking more ecstasy tablets per night and consuming this drug more frequently than those who had not taken opiates (Gervin et al., 2001).

The repeated, intermittent administration of a variety of potentially addictive drugs produces persistent increases in their

Abbreviations: MDMA, 3,4-methylen-dioxy-methamphetamine; CPP, conditioned place preference; DA, dopamine; VTA, ventral tegmental area; PD, postnatal days; Pre-C, pre-conditioning; Post-C, post-conditioning; cAMP, cyclic adenosine monophosphate; CREB, cAMP response element-binding; mRNA, messenger ribonucleic acid; NAc, nucleus accumbens; Pro-Dyn, pro-dynorphin.

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incentive motivational properties (Lett, 1989; Manzanedo et al., 2005; Shippenberg and Heidbreder, 1995). This phenomenon is known as sensitization. The neural changes that underlie behavioural sensitization are thought to contribute to the development of the compulsive patterns of drug seeking and drug craving that characterize addiction (Robinson and Berridge, 1993; for review, see Stewart and Badiani, 1993). Sensitization to the locomotor-activating effects after repeated MDMA administration has been widely demonstrated in rats (Herin et al., 2005; Kalivas et al., 1998; Modi et al., 2006; Ramos et al., 2004; Spanos and Yamamoto, 1989) and mice (Itzhak et al., 2003). Moreover, these augmented effects are known to affect the actions of other drugs. Repeated treatment of adult rats with MDMA has been reported to increase cocaine-induced motor activity and promote the subsequent acquisition of cocaine self-administration (Fletcher et al., 2001), which highlights the crossover effects of these two drugs. However other studies have failed to identify similar crossover effects between MDMA and amphetamine or methylphenidate (Modi et al., 2006).

Sensitization phenomena at developmental ages are not well understood, as important ontogenetic changes in the neurobiological systems, which underlie the development of sensitization, are common and might in turn be responsible for variations in the level of vulnerability to drugs as age progresses (Laviola et al., 1995). Age-related differences in psychostimulant sensitization profiles have been described for cocaine and amphetamines (Laviola et al., 1995, 1999). Although adolescent rats show an increase in the conditioned reinforcement of cocaine after treatment with MDMA (Aberg et al 2007; Fone et al., 2002), a recent report has shown that they are less vulnerable to MDMA-induced sensitization, only developing this response to MDMA when administered with a high dose and within a narrow margin of time (Aberg et al., 2007).

The aim of the present study was to evaluate if adolescent exposure to MDMA or MDMA plus cocaine affects the rewarding actions of morphine. Adolescent animals were employed in view of the fact that ecstasy is consumed mostly by teenagers and young adults (Observatorio Europeo de Drogas y Toxicomanias, 2005). Furthermore, the elevated percentage of ecstasy users who also consume cocaine has prompted us to study the co-administration pattern. Adolescent mice were exposed to two daily administrations of MDMA or MDMA plus cocaine over three days (six doses in total), and their response to the reinforcing properties of 40 mg/kg of morphine was evaluated three weeks later using the conditioned place preference paradigm. Since this opiate is presently employed by many MDMA users in order to relieve the psychostimulant effects of ecstasy, it is of relevance to evaluate whether such users are subject to an increase in the well-known addictive properties of morphine and to study susceptibility to relapse into morphine abuse.

2. Material and methods

2.1. Subjects

A total of 146 male mice of the OF1 strain were acquired from Charles River (Barcelona, Spain) at 21 days of age (10–13 g). They were housed in groups of 4, in plastic cages (25 cm × 25 cm × 15 cm), under the following conditions: constant temperature (21 ± 2 °C), a reversed light schedule (white lights on: 07.30–19.30 h), and food and water available ad libitum, except during the behavioural test. All procedures involving the experimental animals complied with national, regional and local laws and regulations, and were in accordance with European Community Council Directives (86/609/EEC, 24 November 1986).

2.2. Drugs

Animals were injected i.p. with morphine (Laboratorios Alcaliber, Madrid, Spain), MDMA (SIGMA-ALDRICH Laboratories, Spain) and cocaine hydrochloride (Laboratorios Alcaliber S A, Madrid, Spain), in a volume of 0.01 ml/g. A control group was injected with physiological saline. All compounds were diluted in physiological saline (0.9% NaCl), which was also used as a vehicle, and administered i.p.

2.3. Apparatus

Four identical plexiglas boxes were employed, consisting of two equal size compartments (30.7 cm long × 31.5 cm wide × 35.5 cm high) that were separated by a grey central area (13.8 cm long × 31.5 cm wide × 35.5 cm high). The walls of the compartments differed in colour (black versus white) and had distinctive floor textures (fine grid in the black compartment and wide grid in the white one). Four infrared light beams at the entrance to each of the box's compartments and six in the central area enabled the position of the animal and its crossings from one compartment to the other to be recorded. The equipment was controlled using an IBM PC computer and MONPRE2Z software (CIBERTEC, SA, Spain).

2.4. Experimental procedure

2.4.1. 1st experiment: effect of MDMA exposure on morphine-induced CPP, extinction and reinstatement

After an acclimatizing period of 8 days, animals were divided into different groups. Pre-treatment consisted of two daily administration (every 12 h, at 8 am and 8 pm) over three days (6 injections in total, from PD29 to 31) of physiological saline (Sal, $n = 15$) or MDMA (5, 10 or 20 mg/kg) (M5, $n = 21$; M10, $n = 19$; M20, $n = 17$). Three weeks after pre-treatment had finalized, the morphine-induced CPP procedure was initiated (postnatal day 52). A more detailed description of the experimental procedure is presented in Table 1. A dose of 40 mg/kg of morphine was selected on the basis of previous studies that demonstrated that animals presented a more stable and robust CPP when they received a high dose of this drug (Ribeiro Do Couto et al., 2003), without exhibiting any sedative effects (Manzanedo et al., 1999, 2001).

Place conditioning, consisting of three phases, was carried out during the dark cycle, following an unbiased procedure of initial spontaneous preference (Manzanedo et al., 2001; Ribeiro Do Couto et al., 2003). During the first phase, which represented pre-conditioning (Pre-C), mice were allowed access to