Pharmacology, Biochemistry and Behavior 167 (2018) 9–16

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Effects of para-methoxyamphetamine (PMA) on agonistic encounters between male mice

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ARTICLE INFO

Keywords:
PMA
MDMA
Agonistic encounters
Aggression
Anxiety
Mice

ABSTRACT

Para-methoxyamphetamine (PMA) is a synthetic drug chemically similar to the recreational drug 3,4-methylenedioxy-methamphetamine (MDMA or "ecstasy") and often replaces MDMA in tablets that show an "ecstasy" logo. PMA displays a higher toxic potential than MDMA, but the behavioral profile of PMA has been scarcely studied in animal models. Here we evaluated the effects of PMA (2, 4, 8, and 12 mg/kg, i.p.) on agonist encounters between male mice using an ethopharmacological approach, the isolation-induced aggression model. Likewise, since PMA and MDMA share common mechanisms of action, we compared the behavioral profile of PMA with that induced by MDMA (8 mg/kg, i.p.) which behavioral effects in this model are well characterized. Individually housed mice were exposed to anosmic standard opponents 30 min after drug administration. The encounters were videotaped and evaluated using an ethologically based analysis. PMA (all doses) significantly reduced offensive behaviors (threat and attack), however, a detailed behavioral analysis suggests that the observed antiaggressive effect seems to be unspecific, showing a complex dose-dependent behavioral profile. Thus, antiaggresive actions observed after the administration of the lowest dose were accompanied by increases in social investigation, avoidance/flee behaviors and non-social explorations, together with a reduction of digging behavior. This pattern reflects both approach-contact behaviors and avoidance-flee behaviors. From 4 mg/kg to 12 mg/kg, the increase in social investigation previously observed disappears, and there is a slight increase in immobility, together with a different behavioral pattern that suggests anxiogenic effects of PMA, similar to those reported after the administration of MDMA. The higher doses of PMA exhibit a behavioral profile very similar to that observed in animals treated with MDMA, with the exception of the immobility produced by PMA. These findings show for the first time the non-specific antiaggressive profile of PMA in the model of aggression induced by isolation in male mice.

1. Introduction

Para-methoxyamphetamine (PMA) is a synthetic drug of the phenethylamine family. It is classified as an emphathogenic substance with hallucinogenic properties (Matsumoto et al., 2014), being very similar in its chemical composition to the recreational drug 3,4-methylenedioxy-methamphetamine (MDMA or 'ecstasy'). In recent years, PMA has appeared on the drug market as a result of creative inventiveness of producers of psychoactive substances, who aimed at PMA replacing MDMA as a less expensive and more available product. In fact, MDMA is often substituted by PMA in "ecstasy" tablets, mimicking some of the psychological effects of MDMA, although consumers are not aware of the substances ingested (European Monitoring Centre for Drugs and Drug Addiction, 2003). Like other illicit substituted amphetamines, PMA has been suggested to have an abuse potential (Dukat et al., 2002).

Numerous cases of intoxication have been documented and fatal cases involving PMA have been described (Rojek et al., 2016). PMA induces toxicity at lower doses than MDMA (Lurie et al., 2012). Clinical symptoms specific to PMA poisoning include life-threatening hyperthermia, breathing difficulties, tachycardia, rhabdomyolysis, and acute renal failure (Caldicott et al., 2003). In the scarce studies conducted in laboratory animals, PMA has shown cardiovascular alterations in dogs (Cheng et al., 1974), hyperthermia on a high ambient temperature (Daws et al., 2000), hallucinogen properties (Winter, 1994), and disruption of operant behavior (Smythies et al., 1967) in rats. A slight motor activity stimulation, lower than that induced by MDMA, has also been reported (Daws et al., 2000; Romero et al., 2006).

The effects of PMA on brain neurotransmission are similar to those of MDMA, thus, PMA increases serotonin (5-hydroxy-tryptophan or 5-HT) release from the synaptic terminal and blocks its reuptake (Callaghan et al., 2005; Golembiowska et al., 2016); it also acts upon noradrenergic and dopaminergic terminals but in a lesser proportion

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https://doi.org/10.1016/j.pbb.2018.02.002
Received 26 September 2017; Received in revised form 9 February 2018; Accepted 12 February 2018
Available online 14 February 2018

(Daws et al., 2000; Golembiowska et al., 2016; Matsumoto et al., 2014), and can also delay the metabolism of these monoamines by inhibition of monoamine oxidase (MAO) (Matsumoto et al., 2014; Stanley et al., 2007).

Some studies have proposed that PMA is more potent than MDMA at increasing 5-HT release and blocking its uptake in rat corpus striatum and cerebral cortex (Green et al., 1995; Tseng et al., 1976), or has similar potential (Romero et al., 2006). Nevertheless, a recent "in vivo" study indicates that the potency with which these compounds increase 5-HT levels seems to depend on the region studied. Thus, Golembiowska et al. (2016) found that PMA was less potent than MDMA promoting the release of 5-HT in nucleus accumbens and frontal cortex and higher in the striatum.

Recently, the reinforcing effects of PMA have been described in the zebrafish (Ponzoni et al., 2016a). In rats, it has been previously suggested to have an abuse potential (Dukat et al., 2002). Ponzoni et al. (2016a) found that low doses of the drug show reinforcing properties in the Conditioned Place Preference (CPP) test, suggesting an abuse potential for PMA. Additionally, hallucinatory behavior consisting on appearance of "trance-like" behavior following the administration of the highest dose was also reported. Both reinforcing and hallucinatory effects were prevented by simultaneous administration of ritanserin, a $5\text{-HT}_{2A/C}$ receptor antagonist. In the same zebrafish model, a prosocial action in the shoaling preference test and anxiolytic actions in the light-dark and novel tank tests have also been described (Ponzoni et al., 2016b).

Serotonin is, to date, the neurotransmitter most closely linked to aggressive and violent behavior across different species (de Boer, 2018). In fact, current treatment for patients displaying impulsive aggression includes the use of substances that increase 5-HT levels, most frequently selective serotonin reuptake inhibitors (SSRIs) (Coccaro et al., 2015), or monoamine oxidase A (MAOA) inhibitors (Raj, 2004). However, these treatments affect global serotoninergic neurotransmission, and may trigger several undesired side effects given the multiplicity of behaviors and physiological processes modulated by this neurotransmitter (for a review see Hale et al., 2012).

In contrast to PMA, the effects of MDMA on agonistic behaviors have been widely studied, and an antiaggressive effect of MDMA has been reported in the resident-intruder test (Miczek and Haney, 1994), isolation induced aggression model (Maldonado and Navarro, 2001; Navarro and Maldonado, 1999, 2004) and in social interaction models (Machalova et al., 2012; Morley and McGregor, 2000). However, this antiaggressive effect shown by MDMA seems to be nonspecific, since it is accompanied by other behaviors that suggest an anxiogenic effect of the drug (Machalova et al., 2012; Maldonado and Navarro, 2001; Navarro and Maldonado, 1999).

To our knowledge, the effects of PMA on agonistic or aggressive behavior have not been analyzed yet. The aim of the present study is to examine, for the first time, the behavioral effects of PMA (2–12 mg/kg, i.p.) administration in agonistic encounters between male mice using the isolation-induced aggression model. PMA shows similarities in its mechanism of action to MDMA, and the effects of MDMA administration have been studied using this experimental model (Maldonado and Navarro, 2001; Navarro and Maldonado, 1999, 2004). In order to better characterize the behavioral profile of PMA, we study the effects of a wide range of doses of PMA and compared them with those induced by the administration of a well-characterized, standard dose of MDMA (8 mg/kg).

The doses of PMA used in the present study were chosen attending to the scarce previous studies that have analyzed the behavioral effects of PMA in rodents. Significant effects upon behavior in male mice have been observed after the administration of 3 (Hitzemann et al., 1971), 10 (Hatoum and Davis, 1978), and 30 mg/kg of PMA (Glennon et al., 1988). In rats, different behavioral studies have evaluated the effects of PMA administration, using doses that range from 2 to 20 mg/kg (Bustamante et al., 2004; Daws et al., 2000; Jaehne et al., 2005; Romero et al., 2006). Golembiowska et al. (2016), examined the effects of PMA (5 and 10 mg/kg) and MDMA (5 and 10 mg/kg) on extracellular levels of 5-HT, DA, and its metabolites in frontal cortex, striatum, and nucleus accumbens in freely moving rats. In this study, similarly to MDMA (5 and 10 mg/kg), PMA increased the release of DA and 5-HT in rat striatum, nucleus accumbens, and frontal cortex, and enhanced both DA and 5-HT tissue content in nucleus accumbens and frontal cortex. Taken all these studies together, a range of doses was chosen for the present study, selecting 2, 4, 8, and 12 mg/kg. Likewise, we compared the effects of PMA with those induced by MDMA (8 mg/kg) administration in order to compare the effects of PMA and a well characterized dose of MDMA in the isolation-induced aggression model.

We predict that, based on the closeness in the pharmacological profile of PMA and MDMA, PMA administration will produce some behavioral effects similar to those induced by MDMA, affecting agonistic behaviors and behaviors related to anxiety.

2. Materials and methods

2.1. Animals

A total of 142 male mice of the OF.1 strain (Harlan, Barcelona, Spain) weighing 25-30 g on arrival at the laboratory were used. All animals were housed in groups of 5 for 7 days for adaptation to laboratory conditions under a constant temperature (21 °C ± 2 °C) and a reverse light–dark cycle (white lights on: 20:00–08:00). Food and water were available ad libitum (except during behavioral trials). After the adaptation period, the animals were randomly assigned to the different housing conditions. Half of the animals (71) were housed individually in transparent plastic cages for 30 days to be used as experimental (control and treated) animals. The other half continued in groups of 5 to be used as "standard opponents" and were rendered temporally anosmic by intranasal lavage with 4% zinc sulphate solution (Sigma Laboratories, Spain) administered 3 and 1 days before testing. This kind of opponent elicits attack but never initiates such behaviors (Brain et al., 1981). This experiment was carried out in accordance with the guiding principles for care and use of Laboratory Animals approved by the European Communities Council Directive of November 24, 1986 (86/609/EEC).

2.2. Drugs

PMA and MDMA were obtained from Sigma-Aldrich (Spain) and diluted in physiological saline (0.9% NaCl), which was also used as vehicle (0.1 mg/ml). PMA (2, 4, 8, and 12 mg/kg), MDMA (8 mg/kg) or vehicle was injected intraperitoneally (i.p.) in a volume of 10 ml/kg. The dose of MDMA was chosen considering previous studies with the same model of aggression (Maldonado and Navarro, 2001; Navarro and Maldonado, 1999, 2004). Due to the few behavioral studies carried out in rodents using PMA (Bustamante et al., 2004; Romero et al., 2006), a wide dose range (2–12 mg/kg) was used.

2.3. Behavioral test

Thirty minutes after drug administration, an isolated animal and a "standard opponent" were allowed to confront each other in a neutral cage (50 × 26 × 30 cm) for 10 min. Before the encounter, the animals were allowed 1 min of adaptation to this apparatus while separated by means of a plastic barrier. The agonistic encounters were conducted between the second and seven hours of the dark phase and videotaped under red illumination. After each encounter, the neutral cage was washed and the sawdust bedding was replaced. The tapes were analyzed using a microprocessor and a custom-developed program (Brain et al., 1989), which facilitated estimating time, frequency and latency allocated to ten broad behavioral categories: body care, digging, non-social exploration, exploration from a distance, social investigation,