Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com

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

Mercedes Martín-López*, Ana T. Muela, María Cavas, José Francisco Navarro

Department of Psychobiology, Faculty of Psychology, Campus de Teatinos s/n, University of Málaga, 29071 Málaga, Spain

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 mo-

* Corresponding author.
Email address: mmmartin@uma.es (M. Martín-López)

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 xxx

tor 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 (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, threat, attack, avoidance/flee, defence/submission and immobility (for a more detailed description see Manzaneque and Navarro, 1999; Navarro et al., 2008). Only the behavior of the isolated animal was assessed and the analysis was carried out by a trained experimenter 'blind' to the treatment administered to the experimental subjects.

2.4. Statistical analysis

The data obtained for time spent, frequency, and latency of each behavioral category were analyzed. All data was first checked for non-normality by applying the Shapiro-Wilk test. When non-normality of the data could not be rejected, homogeneity of variances was assessed through the Levene's test. Since data were not normally distributed or homogeneity of variances could be rejected, the overall Kruskall-Wallis test was applied. Subsequently, appropriated paired comparisons were performed using the two-tailed Mann-Whitney *U* test. A value of $p < 0.05$ was considered statistically significant.

3. Results

The effects of acute administration of PMA and MDMA on agonistic interactions between male mice are shown in Table 1 (medians with ranges). Kruskal-Wallis analysis showed that there were significant differences in the behavioral categories of body care, digging, non-social exploration, social investigation, threat, attack, avoidance/flee and immobility ($p < 0.05$–$p < 0.01$) in almost all parameters evaluated (T: time; F: frequency, and L: latency). Paired comparisons using the two-tailed Mann-Whitney *U* test revealed that, compared with the vehicle group, mice treated with PMA showed a decrease in frequency and time spent in the categories of body care (8 and 12 mg/kg, $p < 0.05$), digging (2 mg/kg, $p < 0.05$, T; 4–12 mg/kg, $p < 0.01$, T and F), threat, and attack (all doses, $p < 0.01$). These decreases were accompanied by a significant delay of the onset latency parameter (digging: 4–12 mg/kg; threat and attack: all doses; $p < 0.01$). In contrast, time spent in non-social exploration, avoidance/flee (all doses; $p < 0.01$), immobility (4–12 mg/kg; $p < 0.01$) and social investigation behaviors (2 mg/kg; $p < 0.01$) were significantly increased in animals treated with PMA compared to animals receiving the vehicle. In the same sense, animals treated with PMA showed an increase in the frequency of these behaviors with the exception of non-social exploration. PMA (12 mg/kg) increased the time spent in defence/submission but this increase did not reach statistical significance. Finally, the latency of the first avoidance/flee behavior was significantly shorter after PMA treatment (all doses, $p < 0.01$) than after vehicle.

Mice treated with MDMA (8 mg/kg) exhibited a significant reduction in body care, digging, threat, and attack behaviors ($p < 0.01$; T and F) as well as in the behavioral category of social investigation ($p < 0.05$; T). An increase in time spent in non-social exploration and avoidance/flee behaviors ($p < 0.01$) was also observed. MDMA increased defence/submission behaviors but no statistically significant differences were reached. With respect to the latency of each behavioral category, the onset latency for avoidance/flee behaviors was shorter in animals receiving MDMA than in those receiving physiological saline ($p < 0.01$), while social investigation behaviors delayed their onset in the MDMA group compared to the control group ($p < 0.01$).

Paired comparisons between MDMA treatment group and PMA treatment ones show no significant differences in offensive behaviors (threat and attack), showing all animals had a reduction in these behaviors. Main differences were observed between animals receiving MDMA and those treated with the lowest dose of PMA (2 mg/kg). Thus, an increase in frequency and in time spent in body care behaviors ($p < 0.01$), digging ($p < 0.01$), and social investigation ($p < 0.01$; T) were observed in animals treated with 2 mg/kg of PMA, while a reduction in non-social exploration ($p < 0.01$; T) and avoidance/flee behaviors ($p < 0.01$; T and F) was also detected. Animals receiving 4 mg/kg of PMA spent more time in body care behavior category ($p < 0.01$; T and F) and social investigation ($p < 0.05$; T), while reduced time spent in non-social exploration ($p < 0.01$) compared to animals treated with MDMA. Paired comparisons between the MDMA group and PMA at 8 or 12 mg/kg showed significant differences in immobility, which T and F were increased after PMA treatment ($p < 0.05$), and non-social exploration, where a reduction in T was observed ($p < 0.05$). A summary of the main results observed in the study is presented in Table 2.

4. Discussion

The present study analyzes for the first time the effects of PMA administration on aggression in isolated male mice. The results indicate that PMA (2–12 mg/kg) treatment produces a drastic reduction in aggressive behavior (threat and attack); however, a more detailed behavioral analysis suggests that the observed antiaggressive effect seems to be unspecific, and shows a complex dose-dependent behavioral profile. In the same way, MDMA (8 mg/kg) administration shows a non-specific antiaggressive action, with increases in non-social exploration and avoidance/flee behaviors accompanied by a reduction in social investigation, digging, and body care, without affecting immobility. This behavioral profile has previously been described as anxiogenic (Maldonado and Navarro, 2001; Navarro and Maldonado, 1999, 2004).

An exhaustive analysis of the behavioral repertoire exhibited by the animals during the agonistic encounters allows us to detect not only the antiaggressive effects of the drug, but also anxiolytic/anxiogenic effects and motor affectation by the administered substance (Brain et al., 1991; Gómez et al., 2017; Krsiak et al., 1984; Navarro et al., 2004). Thus, the antiaggressive effect observed after the lowest dose of PMA (2 mg/kg) administered is not specific. Although no motor impairment and no increase in the immobility category were shown, other behavioral categories were significantly affected, showing a complex behavioral profile of the drug at this dose. This complex behavior profile observed after the administration of 2 mg/kg of PMA comprises the display of behaviors that both approach and avoid the opponent. Time spent in social investigation was increased when compared to vehicle treatment. Social investigation includes behaviors where the animal approaches and physically contacts the opponent, and these behaviors are often considered as representative of a reduction of anxiety (Brain et al., 1991; File and Seth, 2003). An increase in social investigation together with the reduction of aggressive behaviors could reflect a prosocial-empathic action, described also in humans who have consumed similar compounds to PMA such as MDMA (Bedi et al., 2010; Nichols,

Table 1
Effects of the administration of para-methoxyamphetamine, PMA (2, 4, 8 y 12 mg/kg), on agonistic behavior in male mice.

Behavioral categories	Parameters	vehicle	MDMA	PMA			
			8 mg/kg	2 mg/kg	4 mg/kg	8 mg/kg	12 mg/kg
Body care	T[b]	8.8 (2–37)	1.9** (0–8)	11.1## (0 − 21)	14.3## (0–37)	3.9** (0 − 13)	3.7* (0–37)
	F[b]	6.5 (1–16)	1.5** (0–5)	5.5## (0 − 11)	6## (0–18)	1.5** (0–7)	2* (0–28)
	L	203 (43–305)	322.8 (127–600)	172.1 (68–600)	212.6 (22.7–600)	346.8 (105.4–600)	235.6 (42–600)
Digging	T[b]	16.1 (0–50.8)	0** (0–0.6)	1.3*## (0–26.2)	0** (0–8.1)	0** (0–4.7)	0** (0–1.7)
	F[b]	11 (0–29)	0** (0–1)	2## (0–15)	0** (0–5)	0** (0–5)	0** (0–2)
	L[b]	188.2 (69.7–600)	600** (252–600)	388.2# (14.6–600)	600** (117.5–600)	600** (95.2–600)	600** (231–600)
Non-social exploration	T[b]	357.4 (324–408)	509** (484–549)	439**## (348–522)	444.6**## (342–517)	438.3**## (347–528.9)	462.4**# (341–540)
	F	69 (55–92)	54 (32–83)	60 (35–72)	59.5 (39–71)	53.5 (38–75)	63 (37–75)
	L	0 (0.27.4)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–1.3)	0 (0–0)
Exploration from a distance	T	41.5 (8.4–61.1)	28.9 (7–52.8)	31.4 (9.5–71.8)	42.3 (16.2–86.6)	50.4 (22.6–101.3)	42.2 (5.9–113.8)
	F	43.5 (11–66)	27.5 (10–74)	33.5 (16–53)	33 (18–49)	31.5 (25–69)	37 (10–60)
	L	8.31 (0–47.5)	9.1 (2.7–32.9)	3.9 (0.9–21.7)	7.9 (2.2–40.8)	14 (0–87.9)	6.8 (1.7–130)
Social investigation	T[b]	40.6 (11.7–75.6)	15.7* (1.9–56.1)	86.7**## (19.9–148.6)	50.8# (11.8–137.5)	26.5 (9.7–128.8)	34.1 (15.7–76.3)
	F[a]	14.5 (5–33)	17 (2–36)	26** (12–41)	19 (5–36)	13.5 (4–29)	20 (10–44)
	L[b]	7.3 (2.7–28.8)	18.3** (10–68.6)	6.6## (3.3–19.9)	10.22# (4–141.1)	11.2 (4.2–236.3)	8.9# (2.6–45)
Threat	T[b]	112.8 (60.5–149.4)	0** (0–6.7)	0** (0–92.7)	0** (0–84)	0** (0–2.9)	0** (0–4.7)
	F[b]	77.5 (19–201)	0** (0–9)	0** (0–28)	0** (0–28)	0** (0–4)	0** (0–7)
	L[b]	59.2 (19–154.4)	600** (3.9–600)	600** (43.3–600)	600** (216.8–600)	600** (222.3–600)	600** (49.1–600)
Attack	T[b]	8.45 (0.2–36.3)	0** (0–0)	0** (0–37.7)	0** (0–48)	0** (0–0)	0** (0–0)
	F[b]	34.5 (1–162)	0** (0–0)	0** (0–9)	0** (0–9)	0** (0–0)	0** (0–0)
	L[b]	299.89 (53.2–530)	600** (600–600)	600** (248–600)	600** (350.7–600)	600** (600–600)	600** (600–600)
Avoidance/flee	T[b]	0.47 (0–4.3)	16** (4.9–30.5)	4.9**## (2.5–21.2)	10.4** (5.8–24.1)	11.6** (2.6–33.4)	9.5** (3.9–58.7)
	F[b]	0.5 (0–7)	17** (8–40)	6.5**## (3–24)	12.5** (6–26)	14** (3–34)	16** (5–44)
	L[b]	496 (3.7–600)	6.7** (3.2–50)	15.7** (4.7–143.9)	15.2** (3.2–80.9)	38.9** (0.4–87)	9.25** (0.8–184)
Defence/submission	T	0 (0–1.2)	2.7 (0–10.5)	0 (0–10.9)	0.25 (0–11.6)	0 (0–5.8)	1.5 (0–7.3)
	F	0 (0–2)	3 (0–8)	0 (0–5)	0.5 (0–7)	0 (0–6)	3 (0–5)
	L	600 (4.3–600)	295 (48.2–600)	600 (63.3–600)	499.5 (48.2–600)	600 (51.6–600)	344.3 (7.7–600)
Immobility	T[b]	0 (0–1.2)	0 (0–46.4)	0 (0–6.7)	14.6** (0–59.7)	30.1**## (0–89.3)	14.2**# (0–103.9)
	F[b]	0 (0–0)	0 (0–9)	0 (0–2)	4.5** (0 − 12)	5.5**## (0–13)	3**# (0–29)
	L[b]	600 (600–600)	600 (119–600)	600 (330.8–600)	348.3** (41.6–600)	353.9**# (48.3–600)	226.7**# (3–600)

Table 1 presents medians (with ranges) of accumulated times in seconds (T), frequency (F) and latency (L) found on agonistic behavior in male mice treated with an acute dosis of MDMA (8 mg/kg), PMA (2, 4, 8 y 12 mg/kg) or vehicle. Statistical differences among groups are indicated as follows:
Significant variance following the Kruskal-Wallis test: $^{a}p < 0.05$; $^{b}p < 0.01$.
Significant variance following paired comparisons using Mann-Whitney *U* test:
Differs from vehicle: $^{*}p < 0.05$; $^{**}p < 0.01$.
Differs from MDMA on Mann-Whitney U test: $^{\#}p < 0.05$; $^{\#\#}p < 0.01$.

Table 2
Summary table of the main effects of para-methoxyamphetamine PMA (2, 4, 8 and 12 mg/kg) administration in time spent in behavioral categories as compared to vehicle group (*) and to MDMA group (▲ increase ▼ decrease).

Augmentation of time spent in behavioral categories	MDMA 8	PMA 2	PMA 4	PMA 8	PMA 12
Body care	*	▲	▲	*	*
Digging	*	* ▲	*	*	*
Social investigation	*				
Threat	*	*	*	*	*
Attack	*	*	*	*	*
Disminution of time spent in behavioral categories	**MDMA 8**	**PMA 2**	**PMA 4**	**PMA 8**	**PMA 12**
Non-social exploration	*	* ▼	* ▼	* ▼	* ▼
Social investigation		* ▲	▲		
Avoidance/flee	*	* ▼	*	*	*
Immobility			*	* ▲	* ▲

1986). In contrast, avoidance/flee behaviors were increased, showing a very short onset latency, which could be suggestive of a conflict-ambivalence state between approximation and evitation of social contact with the opponent.

Distinct behavioral categories have been employed to analyze the anxiolytic/anxiogenic profile of compounds (Brain et al., 1991; Rodgers, 1997). Non- social exploration behaviors were increased after 2 mg/kg of PMA treatment, while a reduction in digging behavior was observed. Increases in digging behaviors have been reported after the administration of anxiolytic substances (Cutler et al., 1997), and reductions in digging have been related to anxiogenic actions of several compounds (Gómez et al., 2017; Navarro et al., 2004). Additionally, an increase in time spent in non-social exploration, taking into account the behavioral profile observed, could be indicative of an attempt to escape the test (Maldonado and Navarro, 2001).

The behavioral pattern observed could suggest that the lowest dose administered produces transitional effects from a state where both approach-contact behaviors and avoidance-flee behaviors coexist in a social interaction context to a state where only behaviors related to an anxiogenic effect of higher doses of the drug is shown. Thus, the evaluation of even lower doses than those used in the present study, would be interesting in order to report the first behavioral changes observed with lower doses of the drug.

The other doses of PMA used in the present study (4, 8, and 12 mg/kg) showed antiaggressive effects but this action was accompanied also by increases in immobility behavior. No effect on social investigation was observed, and just those behaviors related to anxiogenic actions of the drug remain (reductions in digging and increases in avoidance/flee and non-social exploration). Although immobility is significantly increased after 4, 8 and 12 mg/kg of PMA, this reduction in motor behavior is not uniquely responsible for the decrease in aggression since other behaviors such as social investigation do not differ between animals receiving vehicle (no immobility observed) and drug treatment, and also, the antiaggressive effect was appreciated in animals treated with 2 mg/kg of PMA, which did not show immobility. Moreover, behaviors that involve an extensive motor component such as non-social exploration were increased in animals receiving all doses of PMA when compared to vehicle treatment. Thus, the antiaggressive effect and the loss of the increment in social investigation previously observed with the lowest dose of PMA, should be due to other causes besides immobility.

The administration of 8 and 12 mg/kg of PMA provokes the same effects than those observed after 4 mg/kg but another behavioral change appears, since there is a reduction in body care behaviors. In this sense, Bustamante et al. (2004) observed a decrease in body care in rats treated with 8 mg/kg of PMA when evaluating spontaneous motor responses. In rodents, body care is an ethological response that can be modulated by anxiety (Kalueff et al., 2016) and a decrease in time spent in body care has been considered a reliable index of the anxiogenic effects of the drugs (Navarro et al., 2004). It could then be suggested that and anxiogenic profile of PMA, showed by distinct behavioral categories after the administration of the lowest dose of PMA, is been consolidated after the administration of higher doses of the drug.

In this study, a group of animals received MDMA in order to compare the behavioral effects of PMA with those observed after the administration of MDMA (8 mg/kg). The behavioral profile of PMA is similar to that produced by MDMA, similarities are observed after 4 mg/kg of PMA but are clearer for the doses of 8 and 12 mg/kg. The main differences between PMA and MDMA are the increase in immobility observed after PMA (4–12 mg/kg).

The present study is the first one that analyzes the effect of the PMA administration in agonistic encounters in male mice, therefore there is no similar study to compare the results reported. However, the reduction in aggressive behaviors (threat and attack) observed are in accordance with the effects showed by MDMA in this study and also with those observed by MDMA in previous studies using the same animal model (Maldonado and Navarro, 2001; Navarro and Maldonado, 1999, 2004) and the social interaction model (Machalova et al., 2012), in mice and rats (Andó et al., 2006; Kirilly et al., 2006; Kirilly, 2010; Morley and McGregor, 2000). The antiaggressive effect of PMA is observed after the administration of all doses used in this work. Other behavioral categories are affected differently by distinct doses of the drug, but the antiaggressive effect is consistently shown with each dose used.

Neurochemical studies analyzing the mechanisms of action of PMA reflect that it acts primary increasing the release and inhibiting the reuptake of 5HT in frontal cortex, but also reducing dopamine and noradrenaline reuptake and increasing its release, although its actions are between 1.5 and 2 times less potent than those of MDMA (Golembiowska et al., 2016). The prefrontal cortex is a brain region rich in 5-HT_{1A} and 5-HT_{1B} receptors, and it has been identified as particularly important in the inhibitory control of the subcortical circuit mediating aggressive and impulsive behavior (de Almeida et al., 2005; de Boer et al., 2015). Activation of 5-HT_{1B} and 5-HT_{1A} receptors in prefrontal cortex decreases different types of aggression (de Almeida et al., 2006; Faccidomo et al., 2012; Stein et al., 2013; Takahashi et al., 2014; Veiga et al., 2007, 2011), being medial prefrontal cortex specifically involved in the inhibition of male aggressive behavior (Wang et al., 2011). The agonism of 5-HT_{1A} or 5-HT_{1B} receptors in the ventral or-

bitofrontal cortex reduces aggressive behaviors in male mice in the social instigation model, suggesting that enhanced 5-HT signaling in this region, most likely due to activation of postsynaptic sites, shows antiaggressive effects (Centenaro et al., 2008). Agonists of the 5-HT_{1A} subtype receptors strongly suppress the initiation and execution of offensive conducts displayed in various vertebrate species ranging from fish, rodents, guinea pigs, canines to primates, including man (see de Boer and Koolhaas, 2005; Takahashi et al., 2012; Manchia et al., 2017, for a review). However, full 5-HT_{1A} agonists indiscriminately activate 5-HT_{1A} receptors subpopulations in brain regions that mediate a host of other behavioral, neuroendocrine and autonomic physiological responses (de Boer and Newman-Tancredi, 2016) and most of these compounds show sedation in the dose range that produce effective reduction of aggressive behaviors (Miczek et al., 1998; de Boer and Koolhaas, 2005). Recent studies indicate that selective agonists that act primarily at somatodendritic 5-HT_{1A} autorreceptors of the raphe nuclei reduce aggressive behavior in a more potent manner than compounds that stimulate 5-HT_{1A} postsinaptic receptors in frontal cortex. In both cases, the antiaggressive effect was observed using lower doses than those causing immobility or motor inactivity (de Boer and Newman-Tancredi, 2016). In the present study, PMA exhibits reductions in aggressive behaviors with lower doses than those affecting motor activity, while MDMA does not show any sign of motor alteration at the dose used, and increases in 5HT levels in the frontal cortex have been reported for both drugs, thus, this increase in 5HT neurotransmission could be responsible for the antiaggressive effects observed. 5-HT_{1B} receptors agonists seem to be more specific than 5-HT_{1A} receptors ones in order to reduce aggressive behaviors, thus, systemic injection of 5-HT_{1B} agonists reduced aggressive behavior without sedation or motor impairment in rats and mice (de Almeida et al., 2001; de Almeida and Miczek, 2002; de Boer and Koolhaas, 2005; Fish et al., 1999) and microinjection of these agonist in prefrontal cortex reduces territorial aggression in male mice (Faccidomo et al., 2012). It seems reasonable to suggest that the antiaggressive actions observed in the present study after the administration of all doses of PMA may be mediated by the activation of serotonin neurotransmission in the medial prefrontal cortex. However, both PMA and MDMA are active releasers of dopamine and noradrenaline, and these transmitter systems are related to different behavioral effects of the drug. In this sense, recent studies have shown that serotoninergic neurons containing D1 (Drd1a/Pet1) and or D2 (Drd2/Pet1) receptors participate in the regulation of aggression, since silencing this neurons in transgenic mice increases specific aggressive behaviors, modifying some of its main elements, but not all. Nevertheless, the silencing of other subsets of serotonin neurons did not affect aggressive behavior (Niederkofler et al., 2016). Therefore, both increases in 5HT and dopamine neurotransmission produced by PMA and MDMA, which are area and dose-dependent, could be modulating the effects observed in this study.

On the other hand, the effects of PMA administration upon behaviors related to anxiety are dose-dependent. Animals receiving the dose 2 mg/kg of PMA, show a mixed behavioral pattern, where behaviors suggesting anxiolytic and behaviors suggesting anxiogenic effects of the drug coexist. As the doses increase, anxiolytic and prosocial or entactogenic actions disappear. These results are in part in concordance with those reported by Ponzoni et al. (2016b) who observed a biphasic prosocial action of PMA in the shoaling preference test. Thus, while low doses increase approach behaviors, higher doses were ineffective. Moreover, in the present study, as PMA doses increase, the animals display more behaviors that suggest the anxiogenic effect of the drug, closer to the behavioral profile exhibited by the animals treated with MDMA in our study and in previous report (Maldonado and Navarro, 2001). The dual role played by serotonin in anxiety is well documented, and often explained by the neuroanatomical localization of its actions. Thus, while the stimulation of 5-HT_{1A} or 5-HT_2 receptors localized in midbrain periacueductal grey often reduce anxiety-like behaviors in rodents, the activation of these receptors in the limbic forebrain (amygdala, hippocampus) increases anxiety-like behaviors (Cornélio and Nunes-de-Souza, 2007; de Paula Soares and Zangrossi, 2009; Nunes-de-Souza et al., 2008). Although there is no data regarding the effects of PMA on anxiety, it has been reported that the anxiogenic profile shown by animals in the social interaction test after MDMA treatment is accompanied by an increase in c-fos protein expression in central and basolateral amygdala, suggesting that these brain areas might be involved in the anxiogenic-like action of MDMA (Navarro et al., 2004). This anxiogenic profile of MDMA has been described using various animal models of anxiety such as the elevated plus-maze test (Navarro and Maldonado, 2002) and the light-dark box (Maldonado and Navarro, 2000). It is reasonable to suggest that PMA could act similarly.

Furthermore, besides the facilitation of serotonin neurotransmission, increases in dopamine and noradrenaline have been reported as part of the mechanism of action of both MDMA and PMA (Golembiowska et al., 2016), therefore, it is reasonable to consider whether these three neurotransmitters play a role or interact with each other in mediating anxiogenic-like and anxiolytic-like effects of these drugs. Transgenic mice which serotoninergic Drd1a/Pet1 neurons were silenced showed increased prosocial behavior while animals which serotonin Drd2/Pet1 neurons were silenced increased hyperactivity and impulsivity in novel environments (Niederkofler et al., 2016). These results suggest that, although the silence of raphe serotoninergic neurons that contain dopaminergic (D1 or D2) receptors produces the same behavioral effect upon aggressive behavior, increasing it, the effects upon anxiety behaviors seems to depend on the relation between dopamine and serotonin. Further studies are needed to clarify the neurobiological mechanisms involved in this biphasic action on anxiety.

Administration of PMA at 4, 8, and 12 mg/kg produced immobility behaviors in animals in the present study. However, this behavior represents the 3.5% of the behavioral pattern exhibited by these animals, and is not accompanied by the reduction of other behaviors that require motor activity such as non-social exploration, social investigation or avoidance/flee behaviors. Previous studies have shown inconsistent motor effects of PMA. Thus, an increase in locomotor activity has been reported, although this effect was lower than that shown by rats treated with MDMA (Daws et al., 2000; Jaehne et al., 2005; Romero et al., 2006) and no effect upon motor activity has been observed in rats (Bustamante et al., 2004; Hegadoren et al., 1995; Martin-Iverson et al., 1991) or mice (Glennon et al., 1988; Hitzemann et al., 1971). However, a decrease in motor activity has also been reported after administration of 3 mg/kg (Hitzemann et al., 1971) and 10 mg/kg (Hatoum and Davis, 1978) of PMA. Although the causes of this increase in immobility are still unknown, recently, the effects of acute doses of PMA (5 and 10 mg/kg) have been proved to cause a release of DA and 5-HT in rat striatum. PMA promoted the release of 5-HT (being 3.5 times more potent than MDMA in this action) and DA (1.5 less potent than MDMA) (Golembiowska et al., 2016). The possible dysregulation of the 5-HT/DA equilibrium in this brain area may contribute to the motor effects of PMA. Further studies are needed to address the effects of PMA on locomotor activity.

5. Conclusion

The results observed in the present study show that acute administration of PMA (2–12 mg/kg) elicits a significant antiaggressive action. However, this action cannot be described as a selective action, since the lowest dose of the drug administered (2 mg/kg) produces also a complex behavioral profile, exhibiting an ambivalent behavior where the animals both approach and avoid the opponent. Higher doses of

PMA (4–12 mg/kg) maintain the antiaggressive effects, but are accompanied by immobility and behaviors that suggest a dose-dependent anxiogenic effect of the drug. MDMA (8 mg/kg) shows an unespecific antiaggressive action, no motor affectation and behaviors suggesting an anxiogenic action of this substance.

PMA actions on serotonin, but also on dopamine and noradrenaline, may be responsible for the results observed in the present study. Further studies could analyze the effects of specific antagonists of the different 5HT receptors subtypes, specifically 5-HT_{1A}, 5-HT_{1B}, 5-$HT_{2A,}$ and 5-HT_{2C}, in order to elucidate the mechanism responsible for dose-dependent effects of PMA, together with the brain regions involved in the effects observed.

Some limitations of our study should be considered. Thus, in order to compare the effects of PMA to those observed after MDMA administration, only a standard dose of MDMA has been used. A wide range of doses of MDMA could allow direct comparisons between the effects of PMA administration and that of MDMA. Similarly, in order to better understand the effects of PMA on aggressive behavior, a drug with a selective agonist action on 5-HT1B receptors could have been included to analyze possible antiaggressive effects and to compare directly the effects of this kind of drugs to those induced by PMA.

On the other hand, regarding the results observed on anxiety related behaviors, the standard procedure in the isolation-induced aggression model includes a short period of habituation (1 min) to the neutral area before the agonistic encounters begins. This short period might affect anxiety related behaviors, and although equal for all the animals, both receiving the drug and vehicle, might induce an initial high level of anxiety. Further research could study the effects of PMA on anxiety behaviors using specific anxiety measures.

In the present study, a behavioral analysis is conducted. The use of other behavioral tests and techniques allowing the study of brain tissue and functionality after PMA administration would be of interest to better understand the effects of this illegal drug. Additionally, illegal substances are often consumed repeatedly. Future studies could analyze the effects of repeated administration of PMA. The results in the present research may be useful for selecting doses for this kind of study. Furthermore, the coadministration of both PMA and MDMA would also be interesting to explore, since both drugs are occasionally consumed together. Finally, as it happens in humans, just a proportion of the animals used in behavioral experiments, show excessive or pathological aggression (de Boer, 2018), thus, also further work could analyze the effects of PMA in animal models of increased aggression.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgements

This research was supported by grants from the Junta de Andalucía, Spain (CTS-195).

References

de Almeida, R.M., Miczek, K.A., 2002. Aggression escalated by social instigation or by discontinuation of reinforcement ("frustration") in mice: inhibition by anpirtoline: a 5-HT1B receptor agonist. Neuropsychopharmacology 27, 171–181.

de Almeida, R.M., Nikulina, E.M., Faccidomo, S., Fish, E.W., Miczek, K.A., 2001. Zolmitriptan a 5-HT1B/D agonist, alcohol, and aggression in mice. Psychopharmacology 157, 131–141.

de Almeida, R.M., Ferrari, P.F., Parmigiani, S., Miczek, K.A., 2005. Escalated aggressive behavior: dopamine, serotonin and GABA. Eur. J. Pharmacol. 526, 51–64.

de Almeida, R.M.M., Rosa, M.M., Santos, D.M., Saft, D.M., Benini, Q., et al., 2006. 5-HT1B receptors, ventral orbitofrontal cortex, and aggressive behavior in mice. Psychopharmacology 185, 441–450.

Andó, R.D., Benko, A., Ferrington, L., Kirilly, E., Kelly, P.A.T., Bagdy, G., 2006. Partial lesion of the serotonergic system by a single dose of MDMA results in behavioural disinhibition and enhances acute MDMA-induced social behaviour on the social interaction test. Neuropharmacology 50, 884–896.

Bedi, G., Hyman, D., de Wit, H., 2010. Is ecstasy an "empathogen"? Effects of ±3, 4-methylenedioxymethamphetamine on prosocial feelings and identification of emotional states in others. Biol. Psychiatry 68, 1134–1140.

de Boer, S.F., 2018. Animal models of excessive aggression: implications for human aggression and violence. Curr. Opin. Psychol. 19, 81–87.

de Boer, S.F., Koolhaas, J.M., 2005. 5-HT1A and 5-HT1B receptor agonists and aggression: a pharmacological challenge of the serotonin deficiency hypothesis. Eur. J. Pharmacol. 526, 125 − 139.

de Boer, S.F., Newman-Tancredi, A., 2016. Anti-aggressive effects of the selective high-efficacy 'biased'5-HT1A receptor agonists F15599 and F13714 in male WTG rats. Psychopharmacology 233, 937–947.

de Boer, S.F., Olivier, B., Veening, J., Koolhaas, J.M., 2015. The neurobiology of offensive aggression: revealing a modular view. Physiol. Behav. 146, 111–127.

Brain, P.F., Benton, D., Childs, G., Parmigiani, S., 1981. The effect of the opponent in tests of murine aggression. Behav. Process. 6, 319–328.

Brain, P.F., McAllister, K.H., Walmsey, S., 1989. Drug effects on social behaviour: methods in ethopharmacology. In: Boulton, A.A., Baker, G.B., Greenshaws, A.J. (Eds.), Neuromethods. Humana Press, New Jersey, pp. 687–739.

Brain, P.F., Kusumorini, N., Benton, D., 1991. 'Anxiety' in laboratory rodents: a brief review of some recent behavioural developments. Behav. Process. 25, 70–80.

Bustamante, D., Díaz-Véliz, G., Paeile, C., Zapata-Torres, G., Cassels, B.K., 2004. Analgesic and behavioral effects of amphetamine enantiomers, p-methoxyamphetamine and n-alkyl-p-methoxyamphetamine derivatives. Pharmacol. Biochem. Behav. 79, 199–212.

Caldicott, D.G., Edwards, N.A., Kruys, A., Kirkbride, K.P., Sims, D.N., Byard, R.W., et al., 2003. Dancing with "death": p-methoxyamphetamine overdose and its acute management. J. Toxicol. Clin. Toxicol. 41, 143–154.

Callaghan, P.D., Irvine, R.J., Daws, L.C., 2005. Differences in the in vivo dynamics of neurotransmitter release and serotonin uptake after acute para-methoxyamphetamine and 3,4-methylenedioxymethamphetamine revealed by chronoamperometry. Neurochem. Int. 47, 350–361.

Centenaro, L.A., Vieira, K., Zimmermann, N., Miczek, K.A., Lucion, A.B., de Almeida, R.M., 2008. Social instigation and aggressive behavior in mice: role of 5-HT1A and 5-HT1B receptors in the prefrontal cortex. Psychopharmacology 201, 237–248.

Cheng, H.C., Long, J.P., Nichols, D.E., Barfknecht, C.F., 1974. Effects of para methoxyamphetamine (PMA) on the cardiovascular system of the dog. Arch. Int. Pharmacodyn. Ther. 212, 83–88.

Coccaro, E.F., Fanning, J.R., Phan, K.L., Lee, R., 2015. Serotonin and impulsive aggression. CNS Spectr. 20, 295–302.

Cornélio, A.M., Nunes-de-Souza, R.L., 2007. Anxiogenic-like effects of mCPP microinfusions into the amygdala (but not dorsal or ventral hippocampus) in mice exposed to elevated plus-maze. Behav. Brain Res. 178, 82–89.

Cutler, M.G., Rodgers, R.J., Jackson, J.E., 1997. Behavioural effects in mice of subchronic buspirone, ondansetron and tianeptine. I. Social interactions. Pharmacol. Biochem. Behav. 56, 287–293.

Daws, L.C., Irvine, R.J., Callaghan, P.D., Toop, N.P., White, J.M., Bochner, F., 2000. Differential behavioural and neurochemical effects of para-methoxyamphetamine and 3,4-methylenedioxymethamphetamine in the rat. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 24, 955–977.

Dukat, M., Young, R., Glennon, R.A., 2002. Effect of PMA optical isomers and 4-MTA in PMMA-trained rats. Pharmacol. Biochem. Behav. 72, 379–387.

European Monitoring Centre for Drugs Drug Addiction (EMCDDA), 2003. Report on the Risk Assessment of PMMA in the Framework of the Joint Action on New Synthetic Drugs. Publications Office of the European Union, Luxembourg.

Faccidomo, S., Quadros, I.M., Takahashi, A., Fish, E.W., Miczek, K.A., 2012. Infralimbic and dorsal raphe microinjection of the 5-HT(1B) receptor agonist CP-93,129: attenuation of aggressive behavior in CFW male mice. Psychopharmacology 222, 117–128.

File, S.E., Seth, P., 2003. A review of 25 years of the social interaction test. Eur. J. Pharmacol. 463, 35–53.

Fish, E.W., Faccidomo, S., Miczek, K.A., 1999. Aggression heightened by alcohol or social instigation in mice: reduction by the 5-HT1B receptor agonist CP-94,253. Psychopharmacology 146, 391–399.

Glennon, R.A., Ismaiel, A.E.M., Martin, B., Poff, D., Sutton, M., 1988. A preliminary behavioral investigation of PMMA, the 4-methoxy analog of methamphetamine. Pharmacol. Biochem. Behav. 31, 9–13.

Golembiowska, K., Jurczak, A., Kaminska, K., Noworyta-Sokolowska, K., Górska, A., 2016. Effect of some psychoactive drugs used as "legal highs" on brain neurotransmitters. Neurotox. Res. 29, 394–407.

Gómez, C., Redolat, R., Carrasco, C., 2017. Bupropion induces social anxiety in adolescent mice: influence of housing conditions. Pharmacol. Rep. 69, 806–812.

Green, A.R., Cross, A.J., Goodwin, G.M., 1995. Review of the pharmacology and clinicalpharmacology of 34-methylenedioxymethamphetamine (MDMA or ecstasy). Psychopharmacology 119, 247–260.

Hale, M.W., Shekhar, A., Lowry, C.A., 2012. Stress-related serotonergic systems: implications for symptomatology of anxiety and affective disorders. Cell. Mol. Neurobiol. 32, 695–708.

Hatoum, H.T., Davis, W.M., 1978. Motility effects of amphetamine and 4-methoxyamphetamine (PMA): interaction with agents altering central neuromediators. Res. Commun. Psych. Psy. Behav. 3, 325–334.

Hegadoren, K.M., Martin-Iverson, M.T., Baker, G.B., 1995. Comparative behavioural and neurochemical studies with a psychomotor stimulant, an hallucinogen and 3,4-methylenedioxy analogues of amphetamine. Psychopharmacology 118, 295–304.
Hitzemann, R.J., Loh, H.H., Domino, E.F., 1971. Effect of para-methoxyamphetamine on catecholamine metabolism in the mouse brain. Life Sci. 10, 1087–1095.
Jaehne, E.J., Salem, A., Irvine, R.J., 2005. Effects of 3,4-methylenedioxy-methamphetamine and related amphetamines on autonomic and behavioral thermoregulation. Pharmacol. Biochem. Behav. 81, 485–496.
Kalueff, A.V., Stewart, A.M., Song, C., Berridge, K.C., Graybiel, A.M., Fentress, J.C., 2016. Neurobiology of rodent self-grooming and its value for translational neuroscience. Nat. Rev. Neurosci. 17, 45–59.
Kirilly, E., 2010. Long-term neuronal damage and recovery after a single dose of MDMA: expression and distribution of serotonin transporter in the rat brain. Neuropsychopharmacol. Hung. 12, 413–423.
Kirilly, E., Benko, A., Ferrington, L., Andó, R.D., Kelly, P.A.T., Bagdy, G., 2006. Acute and long-term effects of a single dose of MDMA on aggression in dark agouti rats. Int. J. Neuropsychopharmacol. 9, 63–76.
Krsiak, M., Sulcova, A., Donat, P., Tomasikova, Z., Dlohozkova, N., Kosar, E., et al., 1984. Can social and agonistic interactions be used to detect anxiolytic activity of drugs?. Prog. Clin. Biol. Res. 167, 93–114.
Lurie, Y., Gopher, A., Lavon, O., Almog, S., Sulimani, L., Bentur, Y., 2012. Severe paramethoxymethamphetamine (PMMA) and paramethoxyamphetamine (PMA) outbreak in Israel. Clin. Toxicol. 50, 39–43.
Machalova, A., Slais, K., Vrskova, D., Sulcova, A., 2012. Differential effects of modafinil, methamphetamine, and MDMA on agonistic behavior in male mice. Pharmacol. Biochem. Behav. 102, 215–223.
Maldonado, E., Navarro, J.F., 2000. Effects of 3, 4-methylenedioxy-methamphetamine (MDMA) on anxiety in mice tested in the light-dark box. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 24, 463–472.
Maldonado, E., Navarro, J.F., 2001. MDMA ('ecstasy') exhibits an anxiogenic-like activity in social encounters between male mice. Pharmacol. Res. 44, 27–31.
Manchia, M., Carpiniello, B., Valtorta, F., Comai, S., 2017. Serotonin dysfunction, aggressive behavior, and mental illness: exploring the link using a dimensional approach. ACS Chem. Neurosci. 8, 961–972.
Manzaneque, J.M., Navarro, J.F., 1999. Behavioral profile of amisulpride in agonistic encounters between male mice. Aggress. Behav. 25, 225–232.
Martin-Iverson, M.T., Yamada, N., By, A.W., Lodge, B.A., 1991. "Designer" amphetamines: effects on behavior and monoamines with or without reserpine and/or alpha-methyl-para-tyrosine pretreatment. J. Psychiatry Neurosci. 16, 253–261.
Matsumoto, T., Maeno, Y., Kato, H., Seko-Nakamura, Y., Monma-Ohtaki, J., Ishiba, A., 2014. 5-hydroxytryptamine-and dopamine-releasing effects of ring-substituted amphetamines on rat brain: a comparative study using in vivo microdialysis. Eur. Neuropsychopharmacol. 24 (8), 1362–1370.
Miczek, K.A., Haney, M., 1994. Psychomotor stimulant effects of d-amphetamine, MDMA and PCP: aggressive and schedule-controlled behavior in mice. Psychopharmacology 115, 358–365.
Miczek, K.A., Hussain, S., Faccidomo, S., 1998. Alcohol-heightened aggression in mice: attenuation by 5-HT1A receptor agonists. Psychopharmacology 139, 160–168.
Morley, K.C., McGregor, I.S., 2000. (±)-3,4-Methylenedioxymethamphetamine (MDMA,'ecstasy') increases social interaction in rats. Eur. J. Pharmacol. 408, 41–49.
Navarro, J.F., Maldonado, E., 1999. Behavioral profile of 3,4-methylenedioxy-methamphetamine (MDMA) in agonistic encounters between male mice. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 23, 327–334.
Navarro, J.F., Maldonado, E., 2002. Acute and subchronic effects of MDMA ("ecstasy") on anxiety in male mice tested in the elevated plus-maze. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 26, 1151–1154.
Navarro, J.F., Maldonado, E., 2004. Effects of acute, subchronic and intermittent MDMA ("ecstasy") administration on agonistic interations between male mice. Aggress. Behav. 30, 84–91.
Navarro, J.F., Rivera, A., Maldonado, E., Cavas, M., de la Calle, A., 2004. Anxiogenic-like activity of 3,4-methylenedioxy-methamphetamine ("ecstasy") in the social interaction test is accompanied by an increase of c-fos expression in mice amygdala. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 28, 249–254.
Navarro, J.F., De Castro, V., Martín-López, M., 2008. JNJ16259685, a selective mGlu1 antagonist, suppresses isolation-induced aggression in male mice. Eur. J. Pharmacol. 586, 217–220.
Nichols, D.E., 1986. Differences between the mechanism of action of MDMA, MBDB, and the classic hallucinogens. Identification of a new therapeutic class: Entactogens. J. Psychoactive Drugs 18, 305–313.
Niederkofler, V., Asher, T.E., Okaty, B.W., Rood, B.D., Narayan, A., Hwa, L.S., et al., 2016. Identification of serotonergic neuronal modules that affect aggressive behavior. Cell Rep. 17, 1934–1949.
Nunes-de-Souza, V., Nunes-de-Souza, R.L., Rodgers, R.J., Canto-de-Souza, A., 2008. 5-HT 2 receptor activation in the midbrain periaqueductal grey (PAG) reduces anxiety-like behaviour in mice. Behav. Brain Res. 187, 72–79.
de Paula Soares, V., Zangrossi, H., 2009. Stimulation of 5-HT1A or 5-HT2A receptors in the ventrolateral periaqueductal gray causes anxiolytic,-but not panicolytic-like effect in rats. Behav. Brain Res. 197, 178–185.
Ponzoni, L., Braida, D., Sala, M., 2016. Abuse potential of methylenedioxy-methamphetamine (MDMA) and its derivatives in zebrafish: role of serotonin 5HT2-type receptors. Psychopharmacology 233, 3031–3039.
Ponzoni, L., Sala, M., Braida, D., 2016. Ritanserin-sensitive receptors modulate the prosocial and the anxiolytic effect of MDMA derivatives, DOB and PMA, in zebrafish. Behav. Brain Res. 314, 181–189.
Raj, Y.P., 2004. Psychopharmacology of borderline personality disorder. Curr. Psychiatry Rep. 6, 225–231.
Rodgers, R.J., 1997. Animals models of 'anxiety': where next?. Behav. Pharmacol. 8, 477–496.
Rojek, S., Bolechala, F., Kula, K., Maciów-Glab, M., Klys, M., 2016. Medicolegal aspects of PMA-related deaths. Legal Med. 21, 64–72.
Romero, C.A., Bustamante, D.A., Zapata-Torres, G., Goiny, M., Cassels, B., Herrera-Marschitz, M., 2006. Neurochemical and behavioural characterisation of alkoxyamphetamine derivatives in rats. Neurotox. Res. 10, 11–22.
Smythies, J.R., Johnston, V.S., Bradley, R.J., Benington, F., Morin, R.D., Clark Jr., L.C., 1967. Some new behaviour-disrupting amphetamines and their significance. Nature 216, 128–129.
Stanley, N., Salem, A., Irvine, R.J., 2007. The effects of co-administration of 3,4-methylenedioxymethamphetamine ("ecstasy") or para-methoxyamphetamine and moclobemide at elevated ambient temperatures on striatal 5-HT, body temperature and behavior in rats. Neuroscience 146, 321–329.
Stein, D.J., Miczek, K.A., Lucion, A.B., de Almeida, R.M., 2013. Aggression reducing effects of F15599, a novel selective 5-HT1A receptor agonist, after microinjection into the ventral orbital prefrontal cortex, but not in infralimbic cortex in male mice. Psychopharmacology 230, 375–387.
Takahashi, A., Quadros, I.M., de Almeida, R.M., Miczek, K.A., 2012. Behavioral and pharmacogenetics of aggressive behavior. Curr. Top. Behav. Neurosci. 12, 73–138.
Takahashi, A., Nagayasu, K., Nishitani, N., Kaneko, S., Koide, T., 2014. Control of intermale aggression by medial prefrontal cortex activation in the mouse. PLoS One 9, e94657.
Tseng, L.F., Menon, M.K., Loh, H.H., 1976. Comparative actions of monomethoxy amphetamines on the release and uptake of biogenic amines in brain tissue. J. Pharmacol. Exp. Ther. 197, 263–271.
Veiga, C.P.D., Miczek, K.A., Lucion, A.B., de Almeida, R.M., 2007. Effect of 5-HT1B receptor agonists injected into the prefrontal cortex on maternal aggression in rats. Braz. J. Med. Biol. Res. 40, 825–830.
Veiga, C.P.D., Miczek, K.A., Lucion, A.B., de Almeida, R.M.M., 2011. Social instigation and aggression in postpartum female rats: role of 5-HT1A and 5-HT1B receptors in the dorsal raphe nucleus and prefrontal cortex. Psychopharmacology 213, 475–487.
Wang, F., Zhu, J., Zhu, H., Zhang, Q., Lin, Z., Hu, H., 2011. Bidirectional control of social hierarchy by synaptic efficacy in medial prefrontal cortex. Science 334, 693–697.
Winter, J.C., 1994. The stimulus effects of serotonergic hallucinogens in animals. NIDA Res. Monogr. 146, 157–182.