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Effects of acute and repeated methamphetamine treatment on the ultrasonic vocalizations of postnatal rats

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Abstract

Repeated exposure to cocaine (COC) has been reported to both increase ultrasonic vocalizations (USVs) of postnatal rats and enhance the crying of human infants. The purpose of the present study was to determine whether acute or repeated treatment with another commonly abused psychostimulant, methamphetamine (MAP), would affect the USV production of postnatal rats. In the first experiment, USVs were measured 30 min after rats were given an acute injection of saline or MAP (1, 2, 4, or 8 mg/kg ip) on postnatal day (PD) 10. In the second experiment, rats were exposed to MAP (0, 1, or 4 mg/kg/day ip) on PD 2–8 or PD 2–9. On PD 10, rats were given an acute injection of saline or MAP (1 or 4 mg/kg ip) 30 min prior to behavioral assessment. Results showed that acute treatment with MAP (4 or 8 mg/kg) decreased the USVs of rats on PD 10, while repeated exposure to MAP did not affect the USV emissions of rats subsequently treated with saline or MAP. The reason why acute MAP treatment decreased USV production is uncertain, but it is possible that MAP alleviates isolation distress by stimulating reward processes. Alternatively, MAP increases heart rate and blood pressure, so acute treatment with this drug may decrease USV emissions through peripheral physiological mechanisms (i.e., by reducing abdominal compression reactions).

Keywords: Methamphetamine; Ultrasonic vocalizations (USVs); Locomotor activity; Ontogeny

1. Introduction

Psychostimulant drugs like cocaine (COC) and (+)-methamphetamine hydrochloride (MAP) are increasingly being abused by adolescent and adult humans, including pregnant women (Baberg et al., 1996; Frank et al., 1988; Plessinger, 1998; Slutsker, 1992). In the latter situation, infants exposed to COC in utero often exhibit abnormal manifestations of crying and distress that persist for months after birth (Lester et al., 1991; Mayes et al., 1996). Although MAP can have pronounced teratogenic effects (Frost and Cadet, 2000), it has not yet been determined if prenatal MAP exposure is responsible for abnormal vocalizations in infants.

As with humans, rats are capable of emitting vocalizations. In young rats, a single vocalization may sweep across many frequencies (2–130 kHz), with the average peak frequency being beyond the range of human hearing (Brudzynski et al., 1999). Ultrasonic vocalizations (USVs) are frequently emitted when the young animal is under cold stress or is isolated from its dam and littermates (Blumberg and Stolba, 1996; Blumberg et al., 1999; Hofer and Shair, 1986, 1991; Kehoe and Blass, 1986). As is true with humans, psychostimulant drugs are capable of altering rat vocalizations, since acute treatment with COC has been shown to reduce USV production on postnatal day (PD) 7, PD 10, and PD 17 (Barr and Wang, 1993; Kehoe and Boylan, 1992; Meyer and Yacht, 1993; Nazarian et al., 1999). Whether prolonged COC exposure affects USV production is more uncertain, because there is conflicting evidence suggesting that repeated COC administration either increases USV emissions (Barr and Wang, 1993) or has no effect on USVs (Meyer and Yacht, 1993). At present, no studies have assessed whether acute or repeated

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treatment with MAP affects the USV production of postnatal rats.

To examine these issues, two separate experiments were conducted. In the first experiment, USVs were assessed after rats were given an acute injection of saline or MAP (1–8 mg/kg ip) on PD 10. In the second experiment, rats were repeatedly exposed to MAP on PD 2–8 or PD 2–9 and then challenged with saline or MAP on PD 10 (i.e., after either a 16- or 40-h drug abstinence period). Two abstinence periods were used so that we could better determine whether repeated MAP exposure had a prolonged effect on USV production. It was predicted that an acute injection of MAP would attenuate USVs of young rats, while repeated MAP exposure would stimulate USV production after both a 16-h and a 40-h drug abstinence period. The rationale for the latter prediction was twofold: First, there is evidence that repeated COC exposure causes a prolonged enhancement in USVs (Barr and Wang, 1993). Second, both MAP and COC act as indirect dopamine agonists (Kuczenski et al., 1991, 1995), suggesting that these two drugs might have similar effects on USV production. Alternative predictions were possible, however, because MAP and COC differ in some important respects. For example, these drugs differentially affect noradrenergic and serotonergic neurotransmitter systems (Florin et al., 1994, 1995; Munzar et al., 1999), and only MAP preexposure causes pronounced long-term reductions in dopamine and serotonin levels (Axt et al., 1994; Gibb et al., 1994; Kleven et al., 1988).

2. Methods

2.1. Animals

Subjects were 158 rats of Sprague–Dawley descent (Harlan), born and raised at California State University, San Bernardino. Litters were culled to 10 pups at PD 4. One rat from each litter was randomly assigned to each treatment group. There were approximately an equal number of male and female rats per group. The colony room was maintained at 22–24 °C and kept under a 12-h light/dark cycle. Testing was done in a separate experimental room and was conducted during the light phase of the cycle. Subjects were treated according to the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985).

2.2. Apparatus

A clear Plexiglas holding cage (19 × 16 × 20 cm), maintained at 30 °C (±1 °C), was used to house rats prior to behavioral assessment. The testing apparatus was a clear Plexiglas chamber (20 × 20 × 20 cm) housed inside a heated incubator. A Mini-3 ultrasonic detector (Ultrasound Advice, London, UK) was tuned to 40 kHz and suspended 8 cm above the floor of the behavioral testing apparatus. USVs were measured using UltraVox data acquisition software (Noldus, Sterling, VA). Rectal temperatures were assessed using a microprobe thermometer (model: BAT-12; Physitemp Instruments, Piscataway, NJ).

2.3. Drugs

MAP was dissolved in saline and injected intraperitoneally (ip) at a volume of 5 ml/kg. Average volume per injection was 0.04 ml at PD 2 and 0.11 ml at PD 10. MAP was generously provided by the National Institute on Drug Abuse (Research Triangle Park, NC).

2.4. Procedure

2.4.1. Experiment 1—effects of acute MAP treatment

To determine whether acute administration of MAP affects USV production, rats from eight different litters were individually removed from their home cage on PD 10. Rats were weighed and then injected with saline or MAP (1, 2, 4, or 8 mg/kg ip). After being injected, rats were placed in a heated holding cage and allowed to huddle with same-aged controls (see Kehoe and Boylan, 1994). After 30 min, rats were taken to a separate experimental room and individually placed in the testing apparatus (28 °C, ±1 °C). USVs were measured during a 6-min testing session. This brief testing session was used because baseline rates of isolation-induced USVs decline rapidly over time (Carden et al., 1991; Kehoe and Boylan, 1994). Rectal temperatures were recorded immediately after behavioral testing. Rats were then removed to a separate room isolated from naive littermates.

2.4.2. Experiment 2—effects of repeated MAP treatment

The purpose of Experiment 2 was to determine whether repeated exposure to MAP on PD 2–8 or PD 2–9 would alter the USV production of rats challenged with saline or MAP on PD 10. To that end, 10 litters of rats were given twice daily injections (at approximately 9:00 a.m. and 5:00 p.m.) of 0, 0.5, or 2 mg/kg MAP (i.e., 0, 1, or 4 mg/kg/day ip) on PD 2–8. On PD 10 (i.e., 40 h after the last drug exposure), rats were weighed and injected with saline or MAP (1 or 4 mg/kg ip) prior to being placed in the heated holding cage (30 °C). After 30 min, rats were individually placed in the testing apparatus (28 °C, ±1 °C) and USVs were assessed. An additional seven litters were given twice daily injections of 0 or 2 mg/kg MAP on PD 2–9 and then challenged with saline or MAP (4 mg/kg ip) on PD 10 (i.e., 16 h after the last drug exposure). Rectal temperatures were recorded twice on the test day: before acute drug administration and immediately after behavioral testing.

2.5. Statistics

Analyses of variance (ANOVAs) were used for statistical analysis of behavioral and physiological data. Data from

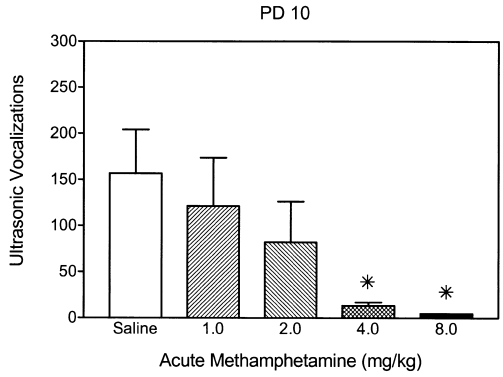

Fig. 1. Mean (±S.E.M.) number of USVs during the 6-min behavioral testing session. On PD 10, rats ($n=8$ per group) were injected with saline or MAP (1, 2, 4, or 8 mg/kg ip) 30 min prior to being placed in the testing apparatus. * Significantly different from rats acutely treated with saline ($P<.05$).

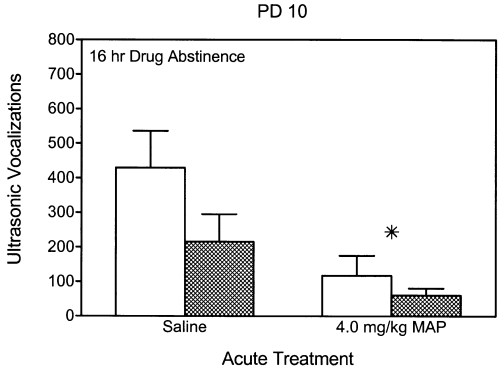

Fig. 3. Mean (±S.E.M.) number of USVs during the 6-min behavioral testing session. Rats were previously exposed to 0 mg/kg/day (open bars) or 4 mg/kg/day (cross-hatched bars) MAP on PD 2–9. On PD 10 (after a 16-h drug abstinence period), rats ($n=7$ per group) were injected with saline or 4 mg/kg MAP 30 min prior to being placed in the testing apparatus. * Significantly different from rats acutely treated with saline ($P<.05$).

Experiment 1 were analyzed using one-way ANOVAs, whereas two-way ANOVAs (Repeated exposure × Acute treatment) were used to analyze USV data from Experiment 2. In each of these analyses, litter effects were controlled by using within-litter statistical procedures (i.e., a within analysis using one value/condition/litter) (Zorrilla, 1997). Separate between-subjects statistical analyses showed the lack of significant sex effects, so these analyses are not presented. Post hoc analysis of the behavioral data was made using Tukey tests ($P<.05$).

3. Results

3.1. Experiment 1

Acute MAP treatment caused a dose-dependent decrease in the USV production of the young rats, acute treatment effect [$F(4,28)=2.76$, $P<.05$] (Fig. 1). More specifically, rats injected with 4 or 8 mg/kg MAP on PD 10 emitted significantly fewer USVs than saline controls. Rectal temperatures ($M=33.9–34.1$ °C) taken immediately after testing were not affected by acute MAP treatment (data not shown).

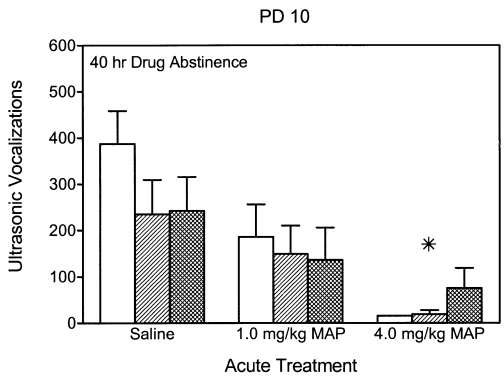

Fig. 2. Mean (±S.E.M.) number of USVs during the 6-min behavioral testing session. Rats were previously exposed to 0 mg/kg/day (open bars), 1 mg/kg/day (hatched bars), or 4 mg/kg/day (cross-hatched bars) MAP on PD 2–8. On PD 10 (after a 40-h drug abstinence period), rats ($n=10$ per group) were injected with saline or MAP (1 or 4 mg/kg ip) 30 min prior to being placed in the testing apparatus. * Significantly different from rats acutely treated with saline ($P<.05$).

3.2. Experiment 2

Repeated exposure to MAP on PD 2–8 did not significantly alter the USV production of rats acutely treated with saline or MAP on PD 10 (i.e., 40 h after the last drug exposure), Repeated exposure × Acute treatment interaction [$F(4,36)=1.85$, $P>.05$] (Fig. 2). As in Experiment 1, rats given an acute injection of 4 mg/kg MAP on the test day emitted fewer USVs than saline controls, acute treatment main effect [$F(2,18)=10.37$, $P<.001$]. The same pattern of results was obtained when repeated drug exposure occurred on PD 2–9 and testing occurred 16 h later on PD 10. More specifically, repeated exposure to MAP (4 mg/kg/day) on PD 2–9 did not alter the USV emissions of rats when tested on PD 10, Repeated exposure × Acute treatment interaction [$F(1,6)=1.93$, $P>.05$] (Fig. 3). Once again, acute administration of 4 mg/kg MAP depressed the USV production of rats on the test day, acute treatment main effect [$F(1,6)=11.21$, $P<.05$].

Repeated exposure to MAP did not significantly affect the body weights of rats when measured on PD 10 (Table 1). Rectal temperatures taken before acute drug administration and after behavioral testing showed that neither repeated nor

Table 1
Mean (±S.E.M.) body weights (g) of rats tested on PD 10

Repeated MAP exposure		
0 mg/kg/day	1 mg/kg/day	4 mg/kg/day
22.4±0.37 g	21.0±0.49 g	21.8±0.72 g

Rats were previously exposed to MAP (0, 1, or 4 mg/kg/day) on PD 2–8 or PD 2–9 (data from these two injection schedules were combined).

acute MAP treatment affected rectal temperatures of rats tested on PD 10 (data not shown).

4. Discussion

As predicted, rats given an acute administration of MAP on PD 10 showed a dose-dependent reduction in USV emissions. The acute effects of MAP were not modulated by MAP preexposure. More specifically, repeated exposure to MAP on PD 2–8 or PD 2–9 did not significantly affect the USV production of rats tested on PD 10. This was true regardless of whether rats were challenged with saline or MAP on the test day (i.e., PD 10).

The finding that acute MAP treatment reduced the USVs of preweanling rats has not been reported before, and is consistent with studies showing that psychostimulants (e.g., COC) decrease USV emissions (Barr and Wang, 1993; Kehoe and Boylan, 1992; Meyer and Yacht, 1993; Nazarian et al., 1999). The neural basis for this MAP-induced reduction in USVs is uncertain, but a number of explanations are available. First, both MAP and COC activate reward mechanisms by modulating transmission in the mesolimbic dopamine pathway (Wise and Bozarth, 1987). Thus, MAP may indirectly depress USVs by inducing reward and, consequently, alleviating isolation distress (Kehoe and Boylan, 1992). Second, MAP may directly alter the functioning of brain areas (e.g., the periaqueductal gray) implicated in USV production (for a more detailed discussion, see Nazarian et al., 1999). Third, MAP is known to increase the heart rate and blood pressure of rats and humans (Johnson et al., 2000; Yoshida et al., 1993). This is of potential relevance because Blumberg and colleagues have postulated that USVs are an ''acoustic by-product'' of an adaptive physiological response, called the abdominal compression reaction, that is triggered by decreased venous blood flow (Blumberg et al., 1999, 2000a,b). According to these researchers, cold stress decreases venous return and, in this way, causes both abdominal compression reactions and a concomitant increase in USVs (Blumberg et al., 1999). Thus, MAP may reduce cold-induced USV emissions by increasing blood pressure and obviating the need for abdominal compression reactions.

Although acute treatment with MAP caused a dose-dependent reduction in USV emissions, repeated exposure to MAP on PD 2–8 or PD 2–9 did not enhance the USVs of rats tested on PD 10. When this evidence is considered along with past data, it is possible to provide a more complete explanation regarding the effects of repeated psychostimulant exposure on USV production. More specifically, Barr and Wang (1993) reported that USV production was substantially enhanced 6 h, and minimally enhanced 30 h, after the last COC preexposure; whereas Meyer and Yacht (1993) reported that USV emissions were not altered 24 h after cessation of daily COC pretreatments. In the present study, USV production was not enhanced either 16 or 40 h after the last MAP injection. Therefore, despite the many procedural differences (e.g., age at testing, length of drug abstinence, dose and type of psychostimulant used, etc.), the most parsimonious explanation is that repeated psychostimulant exposure produces a transient enhancement in USV production that is apparent after 6 h, but dissipates soon thereafter. A 6 h drug abstinence period was not utilized in the present study, so it is not known whether repeated MAP exposure, like COC exposure, produces a transient increase in USV production.

The only other study to examine the effects of an amphetamine-like drug on USV production used the ring-substituted amphetamine derivative, 3,4-methylenedioxymethamphetamine (MDMA). Interestingly, repeated treatment with MDMA caused a long-term reduction in USV production that was detectable for at least 11 days after the last drug preexposure (Winslow and Insel, 1990). The persistent decline in USVs was apparently the result of MDMA's neurotoxic actions, as there was a pronounced reduction of serotonergic markers in various brain regions (Winslow and Insel, 1990). In the present study, there was a nonsignificant trend ($P < .1$) towards decreased USV emissions after repeated MAP treatment (see Figs. 2 and 3). Although not having the same neurotoxic properties as MDMA, repeated treatment with high doses of MAP causes dopaminergic and serotonergic neurotoxicity in young and adult rats (Axt et al., 1994; Frost and Cadet, 2000; Gibb et al., 1994). Thus, the nonsignificant decline in USV production after MAP preexposure (4 mg/kg/day) may have resulted from the neurotoxic actions of the drug. This possibility is less than certain, however, because very high doses of MAP (25–100 mg/kg/day) are typically needed to produce measurable levels of neurotoxicity in young rats (Cappon et al., 1997; Lucot et al., 1982; Vorhees and Pu, 1995; Wagner et al., 1981).

In the present study, MAP was administered on PD 2–9 because rat brain development during the early postnatal period is approximately analogous to human brain development during later fetal stages (Bayer et al., 1993). As such, it is not surprising that dopamine systems in rat brain undergo substantial changes across the postnatal period. Although expression of D_{1A} and D_2 messenger RNA reaches adult levels by birth (Schambra et al., 1994), D_1-like and D_2-like binding sites, as well as dopamine transporters, increase steadily in number across the postnatal period (Demotes-Mainard et al., 1996; Jung and Bennett, 1996; Murrin and Zeng, 1986, 1990; Rao et al., 1991; Schambra et al., 1994). Dopamine receptors appear to be functional at an early age because D_2-like receptors are coupled to G proteins prior to birth (Sales et al., 1991) and to adenylyl cyclase by PD 7 (Broaddus and Bennett, 1990; DeVries et al., 1992); whereas, D_1-like receptors are coupled to G proteins by at least PD 5 (Jung and Bennett, 1996) and to adenylyl cyclase by PD 1 (Broaddus and Bennett, 1990; DeVries et al., 1992). Importantly, behavioral studies indicate that dopamine systems are capable of

mediating behavior in an adult-typical manner early in ontogeny. For example, direct dopamine receptor agonists (e.g., apomorphine and quinpirole) increase the locomotor activity of rat pups by PD 4 (Camp and Rudy, 1987; Moody and Spear, 1992; Shalaby and Spear, 1980), while DA receptor antagonists (e.g., haloperidol, SCH 23390, and sulpiride) reduce behavioral activity in young rats as well as adults (Camp and Rudy, 1987; Fitzgerald and Hannigan, 1989; McDougall et al., 1990). The present findings are generally consistent with these past studies, as acute treatment with MAP did have behavioral impact (i.e., it depressed USVs) when assessed on PD 10. Unexpectedly, repeated exposure to MAP on PD 2–9 did not cause a prolonged increase in USVs. While it could be interpreted that early MAP treatment (i.e., before PD 10) was ineffective at stimulating dopamine systems (i.e., perhaps because dopamine systems were not sufficiently mature), this possibility seems unlikely since amphetamine-like compounds stimulate locomotion by PD 1 (Lal and Sourkes, 1973; Sobrian et al., 1975) and activate reward processes by at least PD 3 (Barr and Lithgow, 1986).

In conclusion, the young of many mammalian and non-mammalian species are capable of crying or emitting vocalizations (Christensson et al., 1995; Kalin et al., 1988; Panksepp et al., 1997). For example, postnatal rats and neonatal humans vocalize when under cold stress or when separated from their mother (Blumberg and Stolba, 1996; Blumberg et al., 1999; Christensson et al., 1995; Hofer and Shair, 1986, 1991; Kehoe and Blass, 1986). Because of these and other similarities, a number of researchers have speculated that rodent USVs and human crying are potentially analogous (Christensson et al., 1995; Fish et al., 2000). In the present study, we showed that repeated exposure to MAP did not enhance the USV production of preweanling rats after a short (16 or 40 h) drug abstinence period. Whether these results can be extended to human crying is uncertain, since relevant studies involving human infants have not been reported. However, if rat USV production were a useful model of psychostimulant-induced changes in human crying, then we would predict that prenatal exposure to MAP would, at most, only transiently impact the crying of human neonates.

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