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Dopaminergic modulation of rat pup ultrasonic vocalizations

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Abstract

The dopamine D_1 receptor agonist, *R*(+)-6-chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrobromide (SKF 81297), the dopamine D_2/D_3 receptor agonist, *trans*-(−)-4*aR*-4,4*a*,5,6,7,8,8*a*,9-octahydro-5-propyl-1*H*-pyrazolo[3,4-*g*]quinoline hydrochloride (quinpirole), and the dopamine D_3 receptor agonist, (±)-7-hydroxy-dipropylaminotetralin hydrobromide (7-OH-DPAT) all reduced the frequency of isolation-induced infant rat ultrasonic vocalizations and lowered body temperature when compared to saline-injected controls. Ultrasonic vocalization rate was not affected by either the dopamine D_1 receptor antagonist, *R*(+)-2,3,4,5-tetrahydro-8-iodo-3-methyl-5-phenyl-1*H*-3-benzazepin-7-ol hydrochloride (SCH 23390) or the dopamine D_2/D_3 receptor antagonist, *S*(−)-raclopride-L-tartrate (raclopride) when given alone, nor did these antagonists block the ultrasonic vocalization reductions caused by the dopamine D_1 receptor agonist or the dopamine D_2/D_3 receptor agonist. The dopamine D_2/D_3 receptor antagonist but not the dopamine D_1 receptor antagonist blocked the dopamine D_3 receptor agonist's ultrasonic vocalization reduction. SKF 81297 reduced general activity while quinpirole and 7-OH-DPAT increased activity. Raclopride reversed quinpirole's reduction in body temperature, as well as 7-OH-DPAT's effects on body temperature, ultrasonic vocalizations, and activity. These results indicate that dopamine D_1, D_2/D_3, and D_3 receptor agonists all reduce ultrasonic vocalizations by as yet undetermined mechanisms.

Keywords: Dopamine; Ultrasonic vocalization; Activity, Infant rat

1. Introduction

Infant rats isolated from their dam and littermates emit 20–60 kHz ultrasonic vocalizations lasting 0.1–3.5 s at a sound pressure of 60–80 dB (Hofer and Shair, 1978; Miczek et al., 1995; Hofer, 1996). Isolation-induced ultrasonic vocalizations can be produced just hours after birth, peak between postnatal days 7–14, and become progressively harder to elicit with age (Noirot, 1972a,b). Infant rat ultrasonic vocalizations are under multifactorial regulation and can be stimulated by: (a) isolation from the dam and littermates (Hofer and Shair, 1978, 1980), (b) a decrease in ambient temperature from thermoneutrality (34–36°C) to about 2°C (Allin and Banks, 1971; Blumberg et al., 1992), (c) rough handling (Okon, 1970; Oswalt and Meier, 1975), (d) the abdominal compression reflex triggered by tilting the pup's head upwards (Blumberg et al., 1997), (e) recovery from deep hypothermia (Hofer and Shair, 1992), and (f) unfamiliar odors (Oswalt and Meier, 1975; Conley and Bell, 1978; D'Amato and Cabib, 1987). Factors suppressing ultrasonic vocalizations include: (a) hypoxia and milk deprivation (Blumberg and Alberts, 1991), (b) familiar nest-associated odors (Hofer and Shair, 1987), and (c) unfamiliar adult male odors (Takahashi, 1992). Brief exposure to maternal olfactory and tactile cues potentiates pup ultrasonic vocalizations (Hofer et al., 1994). Thus, although ultrasonic vocalization emission is considered a stress response, some stressors inhibit ultrasonic vocalization production.

1.1. Neurochemical modulation of ultrasonic vocalizations

Pharmacological studies have indicated that multiple neurochemical systems modulate ultrasonic vocalization

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emission. In general, anxiogenic drugs stimulate ultrasonic vocalization emission while anxiolytic drugs suppress ultrasonic vocalizations. However, not all drugs necessarily act through these two affective mechanisms. Drugs with positive reinforcing properties such as cocaine (Barr and Wang, 1993) and morphine (Carden and Hofer, 1990b) may reduce ultrasonic vocalizations because of their euphorogenic properties or indirectly via physiological effects on respiration or cardiovascular function. In addition, drugs that alter activity may affect ultrasonic vocalizations via respiratory mechanisms, and drugs that affect thermoregulation may affect the ultrasonic vocalization response to ambient temperature. Thus, activity levels and body temperature should be monitored during pharmacological studies of ultrasonic vocalization emission.

Benzodiazepine receptor agonists decrease the rate of isolation-induced ultrasonic vocalizations at doses that are nonsedating and do not alter locomotor activity (Gardner, 1985; Insel et al., 1986). The type A γ-aminobutyric acid ($GABA_A$) receptor agonists, muscimol and baclofen also decrease ultrasonic vocalizations (Nastiti et al., 1991). The nonspecific opiate receptor agonist, morphine decreases ultrasonic vocalizations while the opiate receptor antagonist naltrexone reverses this effect (Carden and Hofer, 1990a,b; Winslow and Insel, 1991a). The μ-opioid receptor agonist, [D-Ala^2, *N*-Me-Phe^4, Gly-ol^5]-enkephalin (DAMGO) and the δ-opioid receptor agonist, [D-Pen^2, D-Pen^5]-enkephalin (DPDPE) inhibit ultrasonic vocalizations while the κ-opioid receptor agonist (−)-*trans*-(1*S*,2*S*)-U-50488 hydrochloride (U50,488) increases ultrasonic vocalizations and activity (Carden et al., 1990, 1994; Kehoe and Shoemaker, 1991). Because DAMGO and DPDPE are thought to be reinforcing while U50,488 is thought to be aversive, these results suggest that ultrasonic vocalizations signal pup distress.

Serotonin's effect on ultrasonic vocalization emission depends on which serotonin receptor is activated. Serotonin 5-HT_{1A} receptor agonists reduce ultrasonic vocalizations in 10-day old pups at doses not affecting locomotion or thermoregulation (Winslow and Insel, 1990a,b; Kehne et al., 1991), while serotonin 5-HT_{1B} receptor agonists increase ultrasonic vocalizations (Winslow and Insel, 1991b). Serotonin 5-HT_{2A} receptor agonists and serotonin 5-HT reuptake inhibitors suppress ultrasonic vocalizations (Hard and Engel, 1988; Winslow and Insel, 1990a,b). Glutamatergic pathways also modulate infant rat ultrasonic vocalizations. Subconvulsant doses of *N*-methyl-D-aspartate (NMDA) increase ultrasonic vocalizations (Winslow et al., 1990), while NMDA antagonists decrease ultrasonic vocalizations at doses not affecting motor activity or thermoregulation (Winslow et al., 1990; Kehne et al., 1991). The competitive NMDA receptor antagonist, D,L-aminophosphonovaleric acid (AP-5); the noncompetitive NMDA receptor antagonist, (5*R*,10*S*)-(+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine hydrogen maleate (MK-801), and the strychnine-insensitive glycine receptor antagonist, 5,7-dichlorokynurenic acid (5,7-DCKA), also suppress ultrasonic vocalizations. However, these drugs also possess muscle relaxant effects (Kehne et al., 1991). The cannabinoid receptor agonist, (−)-*cis*-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-*trans*-4-(3-hydroxypropyl)cyclohexanol (CP 55,940), decreases both ultrasonic vocalizations and body temperature in 11–13 day old rat pups in a dose-dependent manner (McGregor et al., 1996). The cannabinoid receptor antagonist, *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride (SR 141716A), reverses this effect. When administered alone, SR 141716A increases ultrasonic vocalizations, suggesting that an endogenous cannabinoid may also regulate infant rat ultrasonic vocalizations.

The α_2-adrenoceptor agonist, clonidine, increases ultrasonic vocalizations, an effect reversed by the α_2-adrenoceptor antagonist yohimbine (Kehoe and Harris, 1989; Hansen, 1993). The β-adrenoceptor propranolol, the α_2-adrenoceptor antagonist yohimbine, and the α_1-adrenoceptor antagonist prazosin all decrease ultrasonic vocalizations in 8- and 12-day old rat pups (Ryan and Brown, 1990). The ultrasonic vocalization stimulating effects of the α_2-adrenoceptor agonist clonidine in 4–16 day old rat pups suggest that clonidine is anxiogenic in infant rats, however, a shift from anxiogenic to anxiolytic properties occurs after postnatal day 17 (Kehoe, 1988; Winslow and Insel, 1991b).

1.2. Dopamine modulation of ultrasonic vocalizations

The dopamine system modulates reward, cardiovascular and respiratory function, sexual behavior, and stereotypical behaviors (e.g., sniffing, licking, grooming, and yawning) (Bolme et al., 1977; Bozarth and Wise, 1981; Blackburn et al., 1992; McDougall, 1993; Nakajima et al., 1993; Kurashima et al., 1995). Some of these dopamine-mediated processes may regulate infant rat ultrasonic vocalizations; however, few studies have examined dopamine regulation of ultrasonic vocalizations, and these studies have used a limited number of dopamine receptor agonists and antagonists. Cocaine, a potent dopamine reuptake inhibitor, reduces ultrasonic vocalizations in 10-day old rat pups, an effect reversed by pretreatment with the dopamine D_2 receptor antagonist haloperidol (Kehoe and Boylan, 1992). Prolonged neonatal exposure to haloperidol, however, reduces ultrasonic vocalizations, possibly via disturbances in the functional maturation of dopamine receptors (Cagiano et al., 1986). Cuomo et al. (1987) found that the selective dopamine D_2 receptor antagonist (±)-5-(aminosulfonyl)-*N*-[ethyl-2-pyrolidinyl)methyl]-2-methoxybenzamide (sulpiride) decreased ultrasonic vocalization rate in 12–14 day old rat pups and decreased ultrasonic vocalization sound pressure levels at days 8–12, while the selective dopamine D_1 receptor antagonist *R*(+)-2,3,4,5-tetrahydro-8-iodo-3-methyl-5-phenyl-1*H*-3-benzazepin-7-ol hydrochloride

(SCH 23390) had no effect on ultrasonic vocalization rate. These results suggest that dopamine D_1 and D_2 receptors may differentially modulate ultrasonic vocalization emission. Long-term studies have found that 4-day old male rat pups exposed to haloperidol, in utero, produced fewer isolation-induced ultrasonic vocalizations than controls, and emitted longer duration 22 kHz postejaculatory ultrasonic vocalizations at 90 days of age (Cagiano et al., 1988). In adult male rats, the dopamine D_2 receptor agonist *trans*-(−)-4*aR*-4,4*a*,5,6,7,8,8*a*,9-octahydro-5-propyl-1*H*-pyrazolo[3,4-*g*]quinoline hydrochloride (quinpirole) reduced the duration of postejaculatory 22 kHz ultrasonic vocalizations, an effect antagonized by the dopamine D_2 antagonist *S*(−)-raclopride-L-tartrate (raclopride) but not by the dopamine D_1 antagonist SCH 23390 (Cagiano et al., 1989). Although infant ultrasonic vocalizations have different functions than adult ultrasonic vocalizations, this finding suggests that common neural substrates may underlie both types of ultrasonic vocalizations. The dopamine system also modulates thermoregulation (e.g., Sanchez, 1989; Nagashima et al., 1992; Salmi et al., 1993; Kurashima et al., 1995) and activity (Kelly et al., 1975; Le Moal and Simon, 1991; Eilam et al., 1992) both of which can influence ultrasonic vocalization emission (Thiessen and Upchurch, 1981; Blumberg et al., 1992).

The two experiments in this paper extended previous findings by examining a broader range of dopamine receptor agonists and antagonists, and measuring potentially confounding thermoregulatory and activity changes. The effects of the dopamine D_1 receptor agonist *R*(+)-6-chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrobromide (SKF 81297), the dopamine D_2/D_3 receptor agonist quinpirole, the dopamine D_3 receptor agonist (±)-7-hydroxy-dipropylaminotetralin hydrobromide (7-OH-DPAT) were measured alone and in combination with the dopamine D_1 receptor antagonist SCH 23390 and the dopamine D_2/D_3 antagonist raclopride on the emission of ultrasonic vocalizations in 11–13 day old rats.

2. Materials and methods

2.1. Subjects

Subjects were the offspring of Long–Evans rats purchased from Charles River Canada (St. Constant, Quebec) and mated at Dalhousie University. Animals were housed in male–female pairs in Plexiglas cages ($23 \times 45 \times 15$ cm^3) with wire mesh tops and wood chips as bedding in a colony room maintained at 22 ± 1°C on a 12:12 reversed light:dark cycle with lights off at 0930 h. Purina Rodent Laboratory Chow and water were available ad libitum. Shredded paper was added for nesting material just before the pups were born. Each litter was culled to 12–14 pups on postnatal day 1 (day 0 = parturition) and pups remained with their dams throughout the testing period (postnatal days 11–13). In Experiment 1, 12 litters totaling 108 pups (47 male and 61 female) were tested. These pups were tested in nine groups, with approximately equal numbers of males and females in each group. One pup from each litter was used for each condition to control for litter effects (Zorilla, 1997). In total, Experiments 2A, 2B and 2C used 144 Long–Evans rat pups (77 male and 66 female). One pup from each of 12 litters participated in each of the 12 conditions. Data from one pup in Experiment 2C was discarded due to experimenter error.

2.2. Drugs and dosages

2.2.1. Experiment 1

The following drugs (Research Biochemicals International, Natick, MA) were dissolved in saline (0.15 M sodium chloride): (a) the dopamine D_1 receptor agonist SKF 81297 at a low dose (0.25 mg/kg) and a high dose (2.5 mg/kg); (b) the dopamine D_2/D_3 receptor agonist quinpirole at a low dose (0.3 mg/kg) and a high dose (3.0 mg/kg); (c) the dopamine D_3 receptor agonist 7-OH-DPAT at a low dose (0.1 mg/kg) and a high dose (1.0 mg/kg); (d) the dopamine D_1 receptor antagonist SCH 23390 at 0.3 mg/kg; and (e) the dopamine D_2/D_3 receptor antagonist raclopride at 0.3 mg/kg. The control group received saline injections. These dosages have previously been used safely with rodents (Van den Buuse, 1993) and were selected following pilot work in our lab. All drugs and saline were given in a volume of 0.1 ml/10 g body weight.

2.2.2. Experiment 2

The following drugs, dissolved in 0.15 M saline, were administered: the dopamine D_1 receptor agonist SKF 81297 (2.5 mg/kg); the dopamine D_2/D_3 receptor agonist quinpirole (3.0 mg/kg); the dopamine D_3 receptor agonist 7-OH-DPAT (1.0 mg/kg); the dopamine D_1 receptor antagonist SCH 23390 (0.3 mg/kg); and the dopamine D_2 receptor antagonist raclopride (1.0 mg/kg).

2.3. Apparatus and procedure

2.3.1. Experiment 1

This study compared the effects of a single injection of dopamine D_1, D_2/D_3, and D_3 receptor agonists and antagonists on isolation-induced ultrasonic vocalizations in rat pups in a 5-min test given 30-min after injections. Axillary temperature was recorded before the drug injection and before and after the 5-min test. Animals were tested during the dark phase of their light:dark cycle. Pups were minimally handled, and surgical gloves were worn to minimize heat transfer and odor exposure between the experimenter and the pup.

To obtain the pup's preinjection temperature, a surface temperature probe (model SST-1 copper–constantan ther-

mocouple, Physitemp Instr., Clifton, NJ) was placed in the axillary region of the pup's right foreleg until the thermometer (Digi-Sense Model 8528-20; Cole-Parmer Instr., Chicago, IL) reading stabilized (approximately 30 s). Axillary temperature was used to measure body temperature because more direct but stressful methods such as rectal probes may stimulate ultrasonic vocalizations. Axillary temperature measurements correlate highly with rectal temperature measurements in rodent pups (Gebczynski, 1975).

Pups were then sexed, marked with non-toxic ink for identification, weighed to the nearest 0.1 g on a Dial-o-Gram balance scale (Ohaus, Floram Park, NJ), and given a single interscapular subcutaneous injection. Each pup was then placed in a plastic chamber that was partially submerged in a water bath (34 ± 2°C) in the holding room for 30 min. Because the percentage of time spent vocalizing increases as ambient temperature deviates from thermoneutrality (Blumberg et al., 1992), this procedure minimized thermal loss by providing a consistent nest-like (34–36°C) ambient temperature (Conklin and Heggeness, 1971). The pretest body temperature was recorded and the pup was then carried to the test room in a plastic tub filled with home bedding. The pup was placed in the center of a Plexiglas testing chamber ($26 \times 15 \times 12$ cm^3) for 5 min at room temperature (22 ± 2°C).

Ultrasounds were detected with a microphone placed 10 cm above the center of the test chamber and connected to a ''bat detector'' (Model S-25; Ultra Sound Advice, London, UK). The broad-band output of the bat detector was sampled by a custom-built digitizer (adapted from Harrison and Holman, 1978) containing four variable band pass filters set at 28, 36, 44, and 52 kHz. The digitizer sampled output from the bat detector every 0.1 s, and sent this output via a terminal panel and interface card (Strawberry Tree) to a Macintosh 2CX computer where the number of ultrasounds at each frequency were recorded each minute. The dependent measure was the total number of ultrasounds summed across the four frequencies over the 5-min test.

General activity was measured using a passive infrared motion detector (''Safe House'', Radio Shack). The capacitor circuitry inside the motion detector was modified so that each movement of the pup triggered the detector for 0.5 s. The output of the motion detector was sent to a Macintosh 2CX computer on which an event-recording program written using Strawberry Tree Workbench Mac software (McGregor, 1996) recorded the number of seconds each pup spent moving during the 5-min test.

An observer blind to the pup's drug condition scored the following motor behaviors on a check sheet: (a) line crossing: the number of times the pup's body (excluding the tail) completely crossed any one of three lines (each separated by 6 cm) drawn on the bottom of the test chamber; (b) rotational activity: left or right body turns greater than 90° around an imaginary vertical axis going through the center of the pup's body; (c) forward locomotion: horizontally directed locomotion without rotational activity; (d) rolling: shifting from the prone position to the supine position and vice versa; and (e) head raising: upwards tilting of the head greater than 30° relative to the horizontal. Recording these behaviors allowed for a finer-grain analysis of movement than that obtained by the infrared activity monitor. After the test, the pup's posttest body temperature was taken and it was returned to the home cage. Between pups the test chamber was cleaned with 70% ethanol to remove any odors.

2.3.2. Experiment 2

Each pup was given two drug injections one min apart, and the pups were then placed in a holding cage for 30 min as in Experiment 1. Each part of Experiment 2 tested a different dopamine receptor agonist paired with saline, the dopamine D_1 receptor antagonist, SCH 23390, or the dopamine D_2/D_3 receptor antagonist, raclopride. Pups in Experiment 2A were given injections of (a) saline + saline, (b) the dopamine D_1 receptor agonist SKF 81297 + saline, (c) SKF 81297 + SCH 23390, and (d) SKF 81297 + raclopride. Pups in Experiment 2B were given injections of: (a) saline + saline, (b) the dopamine D_2/D_3 receptor agonist, quinpirole + saline, (c) quinpirole + SCH 23390, and (d) quinpirole + raclopride. Pups in Experiment 2C were given injections of: (a) saline + saline, (b) the dopamine D_3 receptor agonist 7-OH-DPAT + saline, (c) 7-OH-DPAT + SCH 23390, and (d) 7-OH-DPAT + raclopride.

2.4. Statistical analyses

2.4.1. Experiment 1

Data on 12 dependent measures were analyzed: (a) body weight, (b) preinjection body temperature, (c) pretest body temperature, (d) posttest body temperature, (e) the difference between posttest and preinjection body temperature, (f) total number of ultrasonic vocalizations after applying the $\log_{10}(x + 1)$ transformation to homogenize variances, (g) duration of general activity (s), (h) number of line crossings, (i) number of bouts of forward locomotion, (j) number of rotations, (k) number of body rollings, and (l) number of head raises.

Although one rat from each litter was tested in each of the nine drug groups, a completely randomized block design analysis of variance (ANOVA) would require 18 subjects per litter (i.e., one pup of each sex from each litter) if we were to use sex and drug condition as within variables. Therefore, we first conducted a completely randomized ANOVA ($\alpha = 0.05$) for each dependent measure to look for sex differences. The absence of significant differences in virtually all behaviors then justified pooling over sex and using a completely randomized block design ANOVA with litter as the blocking variable. ANOVAs and post hoc analyses using the Newman–Keuls test for pair-

wise comparisons ($\alpha = 0.05$) were performed using *SuperAnova* (Abacus Concepts, Berkeley, USA). For each drug condition, and pooled across drug conditions, Pearson correlation coefficients were computed between (a) posttest body temperature and $\log_{10}$(ultrasonic vocalizations), (b) posttest–preinjection body temperature and $\log_{10}$(ultrasonic vocalizations), and (c) activity and $\log_{10}$(ultrasonic vocalizations) using *Systat 5.2.1* (Systat, Evanston, USA).

2.4.2. Experiment 2

For each part of Experiment 2, data were analyzed by randomized blocks ANOVAs with litters used as the blocking variable. Newman–Keuls tests were used to make all pairwise comparisons between means at the $\alpha = 0.05$ level. Pearson correlation coefficients were computed for (a) posttest body temperature vs. $\log_{10}$(ultrasonic vocalizations), (b) posttest–preinjection body temperature vs. $\log_{10}$(ultrasonic vocalizations), and (c) activity vs. $\log_{10}$(ultrasonic vocalizations).

3. Results

3.1. Effects of dopamine D_1, D_2/D_3, and D_3 receptor agonists and antagonists given alone

There were no statistically significant main effects of sex for any of the dependent measures, but significant sex by drug interactions were found for posttest temperature ($F(8,90) = 2.62$, $P < 0.05$) and rotational activity ($F(8,90) = 2.05$, $P = 0.05$). The litter effects (blocks) were significant for all of the analyses except rotational activity and rolling (P-values ranging from $P < 0.05$ to $P < 0.001$), indicating that it is important to control for litter effects in studies of infant rat development.

The mean body weight of pups over all groups was 23.0 g and the mean preinjection body temperature was 36.0°C and there were no significant differences among the nine groups in either of these measures (Table 1).

3.1.1. Changes in body temperature

Thirty minutes after drug injection, there was a significant effect of drug treatment on pretest temperature (Table 1). Both doses of quinpirole (0.3 and 3.0 mg/kg) and both doses of 7-OH-DPAT (0.1 and 1.0 mg/kg) significantly reduced temperature compared with the saline controls. There was also a significant effect of drug treatment on posttest temperature (Table 1). Neither the SCH 23390 nor the raclopride groups differed from the saline group. Both of the SKF 81297 groups had significantly lower posttest temperature than the saline group, but higher posttest temperature than the two quinpirole and the two 7-OH-DPAT groups, which had lower temperatures than all other groups. Thus, although posttest temperatures dropped significantly in the dopamine D_1 receptor agonist group, this group still had a significantly higher temperature than the dopamine D_2/D_3 receptor agonist and the dopamine D_3 receptor agonist groups after the 5-min test.

3.1.2. Posttest–preinjection body temperature

There was a significant effect of drug treatment on the difference between posttest and preinjection temperature during the experiment (Table 1). Newman–Keuls tests indicated that both SKF 81297 groups, both quinpirole groups, and both 7-OH-DPAT groups showed a significantly greater drop in body temperature over the test period than the saline group. The SKF 81297 groups, however, showed less of a temperature drop than the quinpirole and the 7-OH-DPAT groups.

3.1.3. Ultrasonic vocalizations

Drug treatment had a significant effect on the number of ultrasonic vocalizations emitted by rat pups. The high doses of SKF 81297, quinpirole, and 7-OH-DPAT significantly reduced ultrasonic vocalizations compared to the saline group, but the low doses of these drugs did not. Neither of the two antagonists, SCH 23390 nor raclopride, reduced ultrasonic vocalizations.

3.1.4. General activity

The high dose of SKF 81297 and the two antagonists, SCH 23390 and raclopride, all reduced general activity, while both doses of quinpirole and 7-OH-DPAT increased general activity (Table 1). Both the low and high doses of quinpirole and 7-OH-DPAT increased the number of line crossings. The low dose of quinpirole and both doses of 7-OH-DPAT increased forward locomotion, while both the dopamine D_1 and D_2 receptor antagonists decreased forward locomotion. Overall, quinpirole and 7-OH-DPAT increased activity. SKF 81297 reduced activity, but the results were not always significant, especially when the scores of the saline group were low. The two dopamine antagonists reduced the duration of general activity and the amount of forward locomotion, but not the number of lines crossed.

3.1.5. Stereotyped movements

Both doses of both quinpirole and 7-OH-DPAT increased rotational activity compared to the saline group (Table 1). Although rolling did not occur very often, the two quinpirole groups showed more rolling than the saline group or any of the other drug groups. Both of the dopamine antagonists, SCH 23390 and raclopride, reduced the number of head raises, as did the high dose of SKF 81297. Thus, with respect to the stereotyped movements, quinpirole increased rotational activity and rolling and 7-OH-DPAT increased rotational activity, while the high dose of SKF 81297 reduced head raising. SCH 23390 and raclopride reduced bouts of head raising.

Table 1
Mean (±S.E.M.s) scores on each dependent measure for each drug group in Experiment 1 and results of the randomized block ANOVAs and significance levels for each measure
Note: Abbreviations and dosages for drugs: SAL = saline; SKF = 0.25 (low) or 2.5 mg/kg (high) SKF 81297; SCH = 0.3 mg/kg SCH 23390; QUIN = 0.3 (low) or 3.0 mg/kg (high) quinpirole; 7-OH = 0.1 (low) or 1.0 mg/kg (high) 7-OH-DPAT; RAC = 0.3 mg/kg raclopride.

Dependent measure	SAL	SKF low	SKF high	SCH	QUIN low	QUIN high	RAC	7-OH low	7-OH high	*F*-values ($df = 8,88$)
Body weight (g)	23.10 (0.70)	23.61 (0.94)	22.24 (0.98)	23.23 (0.94)	23.26 (0.92)	23.97 (0.70)	23.07 (0.84)	22.13 (0.64)	23.28 (0.95)	1.36, $P = 0.22$
Preinjection temperature (°C)	35.88 (0.10)	36.02 (0.11)	35.82 (0.11)	36.13 (0.07)	36.23 (0.15)	36.03 (0.07)	36.10 (0.10)	35.92 (0.12)	36.02 (0.12)	1.70, $P = 0.11$
Pretest temperature (°C)	36.46 (0.13)	36.22 (0.11)	36.47 (0.13)	36.23 (0.15)	35.66[a] (0.17)	35.65[a] (0.15)	36.43 (0.11)	35.67[a] (0.19)	35.65[a] (0.16)	12.53, $P < 0.001$
Posttest temperature (°C)	35.70 (0.17)	35.08[a] (0.21)	34.80[a] (0.21)	35.68 (0.19)	34.12[a] (0.20)	34.11[a] (0.10)	35.43 (0.16)	34.57[a] (0.24)	34.31[a] (0.13)	20.83, $P < 0.001$
Posttest–preinjection temperature (°C)	−0.18 (0.17)	−0.94[a] (0.26)	−1.02[a] (0.25)	−0.45 (0.18)	−2.12[a] (0.22)	−1.92[a] (0.12)	−0.67 (0.16)	−1.35[a] (0.24)	−1.71[a] (0.17)	17.34, $P < 0.001$
Ultrasounds log ($x+1$)	2.20 (0.11)	1.81 (0.27)	1.02[a] (0.17)	2.01 (0.15)	1.65 (0.15)	1.39[a] (0.20)	2.10 (0.13)	2.39 (0.12)	1.46[a] (0.26)	8.06, $P < 0.001$
General activity (s)	205.58 (14.00)	196.05 (21.61)	118.78[a] (17.76)	132.29[a] (20.19)	282.32[a] (3.27)	268.08[a] (8.68)	149.83[a] (19.30)	273.42[a] (4.52)	262.66[a] (10.10)	21.80, $P < 0.001$
Line crossings	5.83 (1.09)	4.83 (1.03)	3.50 (0.68)	1.00 (0.41)	17.75[a] (2.94)	14.50[a] (1.41)	3.83 (0.88)	17.00[a] (2.61)	17.17[a] (2.42)	21.46, $P < 0.001$
Forward locomotion	4.50 (0.75)	4.50 (1.00)	1.67 (0.56)	0.83 (0.35)	8.75[a] (1.30)	6.92 (1.21)	1.83 (0.42)	10.25[a] (1.46)	8.17[a] (1.16)	16.64, $P < 0.001$
Rotation	16.58 (1.95)	18.58 (1.95)	10.75 (1.39)	9.00 (1.36)	41.42[a] (2.87)	43.58[a] (3.43)	11.92 (1.71)	33.42[a] (2.55)	37.67[a] (2.06)	43.15, $P < 0.001$
Rolling	0.00 (0.00)	0.08 (0.08)	0.00 (0.00)	0.00 (0.00)	2.08[a] (0.80)	2.58[a] (0.58)	0.00 (0.00)	0.33 (0.14)	1.17 (0.32)	8.78, $P < 0.001$
Head raises	7.08 (0.91)	5.58 (0.85)	3.75[a] (0.58)	3.50[a] (0.63)	6.58 (0.82)	4.92 (0.48)	4.08[a] (0.54)	6.42 (0.93)	7.00 (0.98)	4.53, $P < 0.001$

[a] $P < 0.05$ compared to saline control group.

3.1.6. Correlations between body temperature and ultrasonic vocalizations

Even though the dopamine receptor agonists influenced body temperature, there were no significant correlations between posttest temperature and ultrasonic vocalizations for any of the conditions or when collapsed across all nine conditions. Nor were there any significant correlations between posttest minus preinjection body temperature and ultrasonic vocalizations for any of the conditions or when collapsed across all nine conditions.

3.1.7. Correlations between activity and ultrasonic vocalizations

A significant positive correlation between general activity and ultrasonic vocalizations was found for the low dose of SKF 81297 ($r(10) = 0.65$, $P < 0.05$); while negative correlations were found for the low dose of quinpirole ($r(10) = -0.65$, $P < 0.05$) and the low dose of 7-OH-DPAT ($r(10) = -0.63$, $P < 0.05$). No significant correlation was found when data were collapsed across all nine conditions ($r(106) = 0.125$, ns).

3.2. Effects of the dopamine D_1 receptor agonist SKF 81297 administered in combination with the dopamine D_1 receptor antagonist SCH 23390 or the dopamine D_2 receptor antagonist raclopride

The mean body weight of pups from all four groups in Experiment 2A was 21.6 g and their mean preinjection temperature was 35.8°C. There were no significant differences among the four drug groups in these two measures (Table 2). There were no significant sex differences or drug by sex interactions for any of the dependent measures, but the litter effects (blocks) were significant for seven of the 12 analyses: body weight, all four temperature measures, rotational activity, and head raises (*P*-values ranged from $P < 0.05$ to $P < 0.001$).

3.2.1. Body temperature

The mean pretest body temperature of pups (36.4°C) did not differ between groups, but there was a significant difference in posttest body temperature between groups (Table 2). The SKF 81297 + saline and the SKF 81297 + raclopride groups had lower body temperatures than the saline + saline and the SKF 81297 + SCH 23390 groups. Thus, the dopamine D_1 receptor antagonist was more effective than the dopamine D_2 receptor antagonist in reversing the body temperature reduction caused by the dopamine D_1 receptor agonist SKF 81297, but did not reverse body temperature to saline + saline levels. The change in body temperature (posttest–preinjection) over the experiment was also affected by drug treatment. The SKF 81297 + raclopride group showed the greatest thermal loss over the test, followed by the SKF 81297 + saline and the SKF 81297 + SCH 23390 groups, all of which lost

Table 2
Mean (±S.E.M.s) scores on each dependent measure for each drug group in Experiment 2A, with results of ANOVAs and significance levels for each measure
Note: Drug abbreviations and dosages: SAL = saline; SKF = 2.5 mg/kg SKF 81297; SCH = 0.3 mg/kg SCH 23390; RAC = 0.3 mg/kg raclopride.

Dependent measure	Drug group				*F*-values (*df* = 3,33)
	SAL + SAL	SKF + SAL	SKF + SCH	SKF + RAC	
Body weight (g)	20.99 (1.18)	22.05 (0.79)	21.43 (0.80)	21.87 (0.81)	0.97, ns
Preinjection temperature (°C)	35.53 (0.31)	35.82 (0.13)	35.82 (0.15)	36.03 (0.15)	1.58, ns
Pretest temperature (°C)	36.56 (0.19)	36.35 (0.21)	36.33 (0.16)	36.33 (0.20)	1.14, ns
Posttest temperature (°C)	35.30 (0.27)	34.27[a] (0.33)	34.84 (0.33)	34.31[a] (0.30)	25.80, $P < 0.001$
Posttest–preinjection temperature (°C)	−0.23 (0.28)	−1.55[a] (0.27)	−0.98[a] (0.31)	−1.72[a] (0.35)	15.97, $P < 0.001$
Ultrasounds log ($x + 1$)	2.15 (0.07)	1.29[a] (0.22)	1.00[a] (0.21)	1.26[a] (0.16)	7.52, $P < 0.001$
General activity (s)	198.43 (26.08)	131.78[a] (22.18)	71.10[a] (15.05)	96.28[a] (20.89)	7.93, $P < 0.001$
Line crossings	6.58 (2.49)	2.50[a] (0.56)	1.33[a] (0.31)	1.58[a] (0.45)	4.20, $P < 0.05$
Forward locomotion	2.67 (0.76)	0.92[a] (0.23)	0.50[a] (0.15)	0.92[a] (0.26)	6.35, $P < 0.01$
Rotation	16.17 (3.39)	10.00[a] (2.48)	6.83[a] (1.18)	6.75[a] (1.46)	4.89, $P < 0.01$
Rolling	0.33 (0.23)	0.17 (0.11)	0.00 (0.00)	0.00 (0.00)	1.53, ns
Head raises	4.25 (0.70)	2.75[a] (0.55)	1.42[a] (0.29)	1.58[a] (0.26)	10.30, $P < 0.001$

[a] $P < 0.05$ compared to saline + saline group.

more temperature than the saline + saline group. Thus, the dopamine D_1 receptor antagonist partially blocked thermal loss caused by the dopamine D_1 receptor agonist while the dopamine D_2 receptor antagonist did not.

3.2.2. Ultrasonic vocalizations

All three drug groups had significantly fewer ultrasonic vocalizations than the saline + saline group, thus the dopamine D_1 receptor agonist SKF 81297 reduced ultrasonic vocalizations and neither the dopamine D_1 receptor antagonist nor the dopamine D_2 receptor antagonist reversed this effect (Table 2).

3.2.3. Activity

The SKF 81297 + saline group showed a significant reduction in general activity, in number of lines crossed, and in bouts of forward locomotion (Table 2). Neither the dopamine D_1 receptor antagonist SCH 23390 nor the dopamine D_2 receptor antagonist raclopride were effective in reversing the effects of SKF 81297 on activity.

3.2.4. Stereotyped movements

The SKF 81297 + saline group showed significantly fewer bouts of rotational activity and head raising than the saline + saline group (Table 2). Neither the dopamine D_1 receptor antagonist nor the dopamine D_2 receptor antagonist reversed these effects. There were no significant differences among groups in bouts of rolling (Table 2). Thus, the dopamine D_1 receptor agonist SKF 81297 reduced stereotyped movements, and neither antagonist reversed these effects.

3.2.5. Correlations between body temperature and ultrasonic vocalizations

There were no significant correlations between posttest body temperature and ultrasonic vocalizations for any group or when pooled over all drug conditions. Nor were there significant correlations for the change in body temperature (posttest–preinjection) over the experiment and ultrasonic vocalizations for any group or when pooled over all conditions.

3.2.6. Correlations between activity and ultrasonic vocalizations

There were no significant correlations between the duration of general activity and ultrasonic vocalizations for any condition or when pooled over all conditions.

3.3. Effects of the dopamine D_2/D_3 receptor agonist quinpirole administered in combination with the dopamine D_1 receptor antagonist SCH 23390 or the dopamine D_2 receptor antagonist raclopride

There were no differences among the four drug groups in the mean body weight of pups (20.0 g) or the mean preinjection body temperature (35.3°C) (Table 3). There were no significant sex differences for any of the measures. Significant litter effects were seen for body weight, preinjection temperature, line crossing, and forward locomotion (*P*-values from $P < 0.01$ to 0.001).

3.3.1. Body temperature

The quinpirole + saline group had lower pretest and posttest body temperature than the saline + saline group (Table 3). Raclopride partially reversed these effects but SCH 23390 did not. Over the experiment, the quinpirole + saline group showed a greater decrease in body temperature (posttest–preinjection) than the saline + saline group, and this was blocked by the dopamine D_2 receptor antagonist raclopride but not the dopamine D_1 receptor antagonist SCH 23390.

Table 3
Means (±S.E.M.s) scores on each dependent measure for each drug group in Experiment 2A, with results of ANOVAs and significance levels for each measure
Note: Abbreviations and dosages for drugs: SAL = saline; QUIN = 3.0 mg/kg quinpirole; SCH = 0.3 mg/kg SCH 23390; RAC = 1.0 mg/kg raclopride.

Dependent measure	Drug group				*F*-values (*df* = 3,41)
	SAL + SAL	QUIN + SAL	QUIN + SCH	QUIN + RAC	
Body weight (g)	20.00 (0.69)	19.50 (0.52)	20.25 (0.64)	20.08 (0.92)	0.52, ns
Preinjection temperature (°C)	35.30 (0.17)	35.18 (0.15)	35.26 (0.21)	35.43 (0.24)	0.35, ns
Pretest temperature (°C)	35.67 (0.11)	33.53[a] (0.19)	33.33 (0.12)	34.89 (0.22)	44.07, $P < 0.001$
Posttest temperature (°C)	34.75 (0.20)	32.65[a] (0.18)	33.18 (0.28)	34.20 (0.16)	20.51, $P < 0.001$
Change in temperature (°C)	−0.92 (0.18)	−0.88[a] (0.09)	−0.14[a] (0.32)	−0.69 (0.14)	3.49, $P < 0.05$
Ultrasounds log ($x + 1$)	2.03 (0.15)	1.07[a] (0.21)	0.95[a] (0.20)	1.39[a] (0.22)	6.44, $P < 0.01$
General activity (s)	138.77 (19.80)	209.10 (19.48)	154.04 (23.43)	188.85 (18.53)	2.61, ns
Line crossings	0.92 (0.31)	5.75 (1.90)	2.42 (1.32)	6.33 (3.00)	2.72, ns
Forward locomotion	0.75 (0.25)	3.08[a] (0.94)	1.17 (0.51)	3.42[a] (1.52)	2.85, $P < 0.05$
Rotation	10.17 (2.49)	31.58[a] (3.52)	24.08[a] (3.38)	30.00[a] (4.53)	7.63, $P < 0.001$
Head raises	5.75 (1.02)	8.58[a] (0.96)	6.42 (1.57)	10.83[a] (1.34)	3.41, $P = 0.05$

[a] $P < 0.05$ compared to saline + saline group.

3.3.2. Ultrasonic vocalizations

The quinpirole + saline group emitted significantly fewer ultrasonic vocalizations than the saline + saline group (Table 3), and neither the dopamine D_1 receptor antagonist SCH 23390 nor the dopamine D_2 receptor antagonist raclopride blocked this effect.

3.3.3. Activity

There were no significant differences in general activity or line crossing between the four groups (Table 3). Quinpirole increased forward locomotion and this was reversed by SCH 23390 but not by raclopride.

3.3.4. Stereotyped movements

The quinpirole + saline group showed increased rotational activity relative to the saline + saline group, and neither antagonist reversed this effect (Table 3). The quinpirole + raclopride group had more bouts of head raising than the saline + saline group, with the quinpirole + saline group falling between these two. The quinpirole + SCH 23390 group did not differ from the saline + saline group (Table 3). Thus, quinpirole increased bouts of rotational activity and head raising. The increase in rotation was not reversed by the dopamine D_1 receptor antagonist SCH 23390 or the dopamine D_2 receptor antagonist raclopride, while the increase in head raising was reversed by the dopamine D_1 receptor antagonist SCH 23390. Rolling was not measured in this experiment.

3.3.5. Correlations between body temperature and ultrasonic vocalizations

There were no significant correlations between posttest body temperature and ultrasonic vocalizations for any group; however, there was a significant positive correlation when pooled over all drug conditions ($r(46) = 0.53$, $P < 0.001$). Significant positive correlations between posttest–preinjection body temperature and ultrasonic vocalizations were found for the quinpirole + SCH 23390 condition ($r(10) = 0.73$, $P < 0.01$) and for all conditions when pooled ($r(46) = 0.51$, $P < 0.001$), suggesting that the warmer pups produced more ultrasonic vocalizations than the cooler pups.

3.3.6. Correlations between activity and ultrasonic vocalizations

No significant correlations between activity and ultrasonic vocalizations were found for any of the groups or when pooled over all conditions.

3.4. Effects of the dopamine D_3 receptor agonist 7-OH-DPAT administered in combination with the dopamine D_1 receptor antagonist SCH 23390 or the dopamine D_2 receptor antagonist raclopride

There were no significant body weight differences between the four groups (mean = 22.0 g), and no significant preinjection body temperature differences (mean = 35.8°C; Table 4). There were no significant sex differences or sex by drug interactions for any of the dependent measures, but the litter effects were significant for eight of the 12 dependent measures: body weight, all four temperature measures, ultrasonic vocalizations, line crossings, and forward locomotion (all *P*-values < 0.001).

3.4.1. Body temperature

The 7-OH-DPAT + saline group had lower pretest and posttest body temperatures than the saline + saline group (Table 4). Raclopride reversed these effects but SCH 23390 did not. The 7-OH-DPAT + saline group showed a greater decline in temperature over the experiment than the saline + saline group, and raclopride blocked this effect while SCH 23390 did not.

Table 4
Mean (±S.E.M.s) scores on each dependent measure for each drug group in Experiment 2C, with results of ANOVAs and significance levels for each measure
Note: Abbreviations and drug dosages: SAL = saline; 7-OH = 1.0 mg/kg 7-OH-DPAT; SCH = 0.3 mg/kg SCH 23390; RAC = 0.3 mg/kg raclopride.

Dependent measure	Drug group				*F*-values (*df* = 3,33)
	SAL + SAL	7-OH + SAL	7-OH + SCH	7-OH + RAC	
Body weight (g)	22.20 (0.69)	21.87 (1.20)	22.08 (1.07)	21.65 (0.94)	1.60, ns
Preinjection temperature (°C)	35.87 (0.15)	35.92 (0.19)	35.67 (0.34)	35.79 (0.17)	0.71, ns
Pretest temperature (°C)	36.51 (0.14)	35.78[a] (0.26)	35.58[a] (0.39)	36.51 (0.08)	9.16, $P < 0.001$
Posttest temperature (°C)	35.16 (0.22)	34.23[a] (0.33)	34.37[a] (0.43)	35.35 (0.18)	9.45, $P < 0.001$
Posttest–preinjection temperature (°C)	−0.71 (0.17)	−1.69[a] (0.20)	−1.30[a] (0.25)	−0.44 (0.10)	11.19, $P < 0.001$
Ultrasounds log ($x + 1$)	2.25 (0.06)	1.39[a] (0.21)	1.40[a] (0.19)	2.04 (0.14)	10.42, $P < 0.001$
General activity (s)	177.13 (17.53)	275.68[a] (7.00)	225.54[a] (22.50)	176.79 (30.36)	5.15, $P < 0.01$
Line crossings	6.08 (1.77)	13.33[a] (2.93)	8.75[a] (1.84)	5.09 (1.37)	5.13, $P < 0.01$
Forward locomotion	1.75 (0.39)	3.75 (1.06)	2.75 (0.54)	2.00 (0.51)	2.71, ns
Rotation	14.92 (2.42)	37.58[a] (3.83)	26.50[a] (3.90)	15.55 (3.38)	10.22, $P < 0.001$
Rolling	0.17 (0.11)	0.83 (0.61)	0.67 (0.36)	0.18 (0.18)	1.02, ns
Head raises	4.00 (0.65)	4.33 (0.41)	3.92 (0.50)	3.46 (0.47)	0.41, ns

[a] $P < 0.05$ compared to saline + saline group.

3.4.2. Ultrasonic vocalizations

The 7-OH-DPAT + saline group emitted fewer ultrasonic vocalizations than the saline + saline group. Raclopride blocked this reduction while SCH 23390 did not (Table 4).

3.4.3. Activity

7-OH-DPAT increased general activity and line crossings relative to the saline + saline group (Table 4). Raclopride blocked these effects but SCH 23390 did not. There were no significant differences in forward locomotion between groups (Table 4). Thus, the dopamine D_3 receptor agonist 7-OH-DPAT increased the general activity and line crossing measures of locomotor activity and the dopamine D_2 receptor antagonist raclopride but not the dopamine D_1 receptor antagonist SCH 23390 blocked these effects.

3.4.4. Stereotyped movements

7-OH-DPAT increased rotational activity and raclopride blocked this increase while SCH 23390 did not (Table 4). There were no significant differences in the number of bouts of rolling or head raising between groups.

3.4.5. Correlations between body temperature and ultrasonic vocalizations

There were no significant correlations between posttest body temperature and ultrasonic vocalizations for any group; however, there was a significant positive correlation between posttest body temperature and ultrasonic vocalizations when collapsed across conditions ($r(45) = 0.37$, $P < 0.05$). There were no significant correlations between posttest–preinjection body temperature and ultrasonic vocalizations for any group; however, a significant negative correlation was found after collapsing across conditions ($r(45) = -0.38$, $P < 0.01$).

3.4.6. Correlations between activity and ultrasonic vocalizations

There were no significant correlations between the duration of general activity and ultrasonic vocalizations for any condition or when pooled over all conditions.

4. Discussion

The high doses of all three dopamine receptor agonists (SKF 81297, quinpirole, and 7-OH-DPAT) reduced ultrasonic vocalizations, but neither the dopamine D_1 receptor antagonist SCH 23390 nor the dopamine D_2 receptor antagonist raclopride affected ultrasonic vocalizations when given alone; nor did these antagonists reverse the effects of the agonists on ultrasonic vocalizations. Cuomo et al. (1987) also found no effect SCH 23390 on ultrasonic vocalizations. The ultrasonic vocalization reductions were accompanied by decreases in body temperature by all three receptor agonists. The body temperature results for the dopamine D_2/D_3 receptor agonist quinpirole and the dopamine D_3 receptor agonist 7-OH-DPAT are consistent with the findings in adult rats and mice, however, the body temperature decrease following the dopamine D_1 receptor agonist SKF 81297 contradicted the hyperthermic effect seen in adults. Thermal losses over the experiment (posttest–preinjection temperature) were larger for all three receptor agonists than for controls or the two antagonists; however, these drops in body temperature did not correlate with ultrasonic vocalizations. SCH 23390 partially blocked the reduction in body temperature caused by SKF 81297, and raclopride partially blocked the temperature reduction caused by quinpirole and completely blocked the temperature reduction caused by 7-OH-DPAT. SCH 23390 unexpectedly blocked the decrease in body temperature caused by 7-OH-DPAT.

The dopamine D_1 receptor agonist SKF 81297 decreased general activity and stereotyped movements (head raises) in Experiments 1 and 2, and neither antagonist blocked these effects. The dopamine D_2/D_3 receptor agonist quinpirole and the dopamine D_3 receptor agonist 7-OH-DPAT increased general activity, line crossings, forward locomotion, and rotational activity, but only quinpirole increased rolling. SCH 23390 partially blocked the increased forward locomotion and rotation caused by quinpirole, and raclopride blocked the increase in general activity, line crossing, and rotation caused by 7-OH-DPAT. Correlations between ultrasonic vocalizations and the activity measures in Experiment 1 revealed differential receptor agonist effects: a positive correlation with the dopamine D_1 receptor agonist SKF 81297 and negative correlations with the dopamine D_2/D_3 and D_3 receptor agonists.

The antagonists used in this study did not consistently block the effects of the receptor agonists. Several reasons may explain this. The dopamine D_1 receptor agonist SKF 81297 and the dopamine D_2/D_3 receptor agonist quinpirole may reduce ultrasonic vocalizations via nonspecific drug effects making them less susceptible to antagonism. Alternatively, the dopamine D_1 receptor antagonist SCH 23390 and the dopamine D_2 receptor antagonist raclopride may not have been administered at sufficiently high doses, although this is unlikely given the relatively high doses used in this study. Another possibility is that SKF 81297 and quinpirole lowered ultrasonic vocalizations by activating other dopamine receptor types with low affinities for the dopamine D_1 receptor antagonist SCH 23390 and the dopamine D_2 receptor antagonist raclopride.

In general, these results support and extend previous findings examining dopamine modulation of ultrasonic vocalizations. Kehoe and Boylan (1992) found that the dopamine reuptake inhibitor cocaine suppressed ultrasonic vocalizations in 10-day old Sprague–Dawley rat pups, and, like the dopamine D_2/D_3 receptor agonist quinpirole and the dopamine D_3 receptor agonist 7-OH-DPAT in our study, cocaine increased overall activity compared to saline-treated controls. The dopamine D_2 receptor antagonist haloperidol when given with cocaine returned ultrasonic vocalizations to control levels. In our study, only the dopamine D_2 receptor antagonist raclopride co-administered with the dopamine D_3 receptor agonist 7-OH-DPAT showed any convincing antagonistic effect on ultrasonic vocalizations. The studies of Cagiano et al. (1986, 1988) on prenatally and neonatally administered haloperidol demonstrated that exposure to this dopamine D_2 receptor antagonist suppresses ultrasonic vocalizations. In our study, we found no evidence that raclopride or SCH 23390 suppressed ultrasonic vocalizations. This discrepancy may be a result of ontogenetic differences (Cagiano tested 4-day old pups; we tested 11–13 day old pups) and/or pharmacological differences in the efficacy of haloperidol vs. the dopamine D_2 receptor antagonist raclopride. Cuomo et al. (1987) found that the dopamine D_1 receptor antagonist SCH 23390 did not affect ultrasonic vocalization calling rate, which is consistent with our findings, however, they found increases in ultrasonic vocalization sound pressure level and duration. Sound pressure and duration are seldom measured ultrasonic vocalization acoustic parameters so the relevance of this difference is not clear. The dopamine D_2 receptor antagonist raclopride's inability to reverse quinpirole's suppression of ultrasonic vocalizations in this study contrasts with the finding of Cagiano et al. (1989) that raclopride reversed the quinpirole-induced reduction of the adult male rat 22 kHz ultrasonic vocalizations. Finally, Thiessen and Upchurch (1981) reported that the dopamine D_1/D_2 receptor agonist apomorphine decreased ultrasonic vocalizations in adult gerbils, and that haloperidol reversed this effect. Taken together, these results suggest that a common age-independent, dopamine-mediated neurobiological mechanism may underlie ultrasonic vocalization regulation. However, the absence of antagonism in our experiments also suggests that the specific mechanisms may differ in infants and adults.

We found no evidence that body temperature changes influenced ultrasonic vocalizations. Most body temperature and ultrasonic vocalization correlations were not significant. As the greatest mean drop in body temperature was 2.12°C, it is possible that the range of body temperatures was too restrictive to give significant correlations. Also, because testing occurred at room temperature, it is possible that a limit was placed on the ability of the pups to exhibit hyperthermia. Studies using other drugs have also failed to find a relationship between ultrasonic vocalization emission and body temperature. Studies of the κ-receptor agonist U50,488 found no correlations between the infant rats that lost the most heat and those that produced the most ultrasonic vocalizations (Kehoe and Boylan, 1992). Blake (1992) found that ultrasonic vocalizations did not vary with body temperature among three species of infant voles. As these voles began vocalizing before their body temperature dropped, Blake proposed that ultrasonic vocalizations are a thermoreceptive response that signal cooling.

Similar to previous findings, the dopamine D_1 receptor agonist SKF 81297 reduced locomotor activity and small movements while the dopamine D_2/D_3 and D_3 receptor agonists elevated locomotor activity and small movements. The reduction of ultrasonic vocalizations by SKF 81297 may be an incidental consequence of motor inhibition, which suggests that the failure of SCH 23390 to block the ultrasonic vocalization reduction may be a consequence of its failure to block motor inhibition. Quinpirole and 7-OH-DPAT both increased activity; however, previous studies have shown that these receptor agonists can have dose-dependent, biphasic effects on activity (Mogenson and Wu, 1991; Daly and Waddington, 1993; Van Hartesveldt et al., 1994). Because there were no significant correlations between activity levels and ultrasonic vocalizations, the ultrasonic vocalization reduction found with

these two receptor agonists cannot be attributed to motor inhibition. Thus, the dopamine D_1 and D_2/D_3 receptor agonists had differential effects on activity, but not body temperature or ultrasonic vocalization emission, both of which were reduced by all three dopamine receptor agonists.

The pup's physiological response to decreasing ambient temperature helps regulate ultrasonic vocalizations (Okon, 1970, 1971; Blumberg and Alberts, 1990; Blumberg and Stolba, 1996; Blumberg et al. 1992; Blake, 1992). However, the precise role that thermal factors play in the elicitation and modulation of infant rat ultrasonic vocalizations is controversial. Blumberg and Alberts (1990) have suggested that ultrasonic vocalizations are downstream acoustical by-products of laryngeal braking, a respiratory maneuver that enhances pulmonary oxygen transport during brown adipose tissue-activated nonshivering thermogenesis. This hypothesis views ultrasonic vocalizations as a physiological response within a thermoregulatory adaptation. Hofer and Shair (1993) have challenged this acoustic by-product view, suggesting that falling ambient temperature elicits ultrasonic vocalizations because it reliably signals separation from conspecifics and exposure to survival hazards outside the nest. They view ultrasonic vocalizations as a behavioral response within a social adaptation. Direct tests of these two hypotheses (Hofer and Shair, 1992, 1993) found that brown adipose tissue thermogenesis is neither necessary nor sufficient to elicit ultrasonic vocalizations. Blumberg and Alberts' hypothesis thus appears to be correct during extreme hypothermia when edema disrupts pulmonary gas exchange, but not under the more typical ambient temperature conditions accompanying isolation.

In our protocol, all three dopamine agonists suppressed isolation-induced ultrasonic vocalizations in 11–13 day old rat pups. There may be a number of explanations for these results. Dopamine circuits regulate a variety of motivated behaviors and mediate rewards in the brain (Barr and Lithgow, 1986; Bozarth and Wise, 1981; Le Moal and Simon, 1991; Blackburn et al., 1992; Moody et al., 1993; Salamone, 1994). Dopamine neurons are activated in association with rewarding stimuli, and electrical self-stimulation of dopamine neurons in the ventral tegmental area, medial forebrain bundle, and nucleus accumbens has rewarding effects (Routtenberg and Malsbury, 1969; Wise and Rompre, 1989). The ability of dopamine antagonists to attenuate instrumental (Wise, 1982), consummatory (Wise and Colle, 1984), and preparatory (Blackburn et al., 1987) behaviors correlates with dopamine D_2 receptor affinity (Gallistel and Davis, 1983), although dopamine D_1 receptor blockade (e.g., SCH 23390) can also be effective (Nakajima and McKenzie, 1986). Thus, our dopamine agonists may have reduced ultrasonic ''distress'' vocalizations due to their rewarding properties.

A different model of the effects of dopamine on ultrasonic vocalizations integrates dopamine's rewarding effects with social attachment in pups. This is analogous to the model of Panksepp et al. (1978) of opiate-mediated social attachment in puppies which proposed that isolation produces a state of distress similar to withdrawal from an addictive drug. Similarly, endogenous dopamine may be released while the pup is in contact with the dam and littermates. Isolated pups would then vocalize because isolation inhibits dopamine release, thus initiating a sequence of neural and physiological mechanisms that activate ultrasonic vocalization emission. Dopamine receptor agonists may mimic endogenous dopamine release and thus quiet the pup.

Another explanation for our results involves dopamine's effects on activity (Le Moal and Simon, 1991; Eilam et al., 1992; McDougall et al., 1990). Activity levels have been positively correlated with ultrasonic vocalization emission (Pontet et al., 1989). In adult gerbils, motor movements that compress the lungs and force air through the larynx such as ventral scent marking, hopping, and foot-thumping also tend to produce ultrasonic vocalizations (Thiessen et al., 1980). The drugs AP-5, MK-801, and the strychnine-insensitive glycine receptor antagonist, 5,7-dichlorokynurenic acid all reduce ultrasonic vocalizations, but they also possess muscle relaxant effects (Kehne et al., 1991). Thus, dopamine receptor agonists may nonspecifically modulate ultrasonic vocalizations by affecting activity levels. Experiments 1 and 2A showed that the dopamine D_1 receptor agonist SKF 81297 decreased activity. Thus, inhibition of activity may explain the low number of ultrasonic vocalizations produced by these pups. However, the dopamine D_2/D_3 receptor agonist quinpirole and the dopamine D_3 receptor agonist 7-OH-DPAT increased activity but decreased ultrasonic vocalization emission in Experiments 1, 2B, and 2C, ruling out increased activity as a confound in the effects of these two drugs.

The behavioral effects of dopamine receptor agonists change with development, with different dopamine receptor populations maturing at different rates (Spear and Brake, 1983; Van Hartesveldt et al., 1994). For example, dopamine D_1 receptor binding sites are more prominent than dopamine D_2 sites around weaning (Murrin, 1986; Gelbard et al., 1989). The type of behavioral stereotypies induced by co-administration of dopamine D_1 and D_2 receptor agonists also changes across ontogeny: older rats show intense licking and biting, while 10-day old rats show increased wall climbing, roll curling, and forward locomotion (Braun and Chase, 1986). Studies on the behavioral effects of selective and nonselective dopamine receptor agonists revealed that dopamine receptors show dramatic ontogenetic differences but that the synergism between dopamine D_1 and D_2 receptors is qualitatively similar in young (17-day old) and adult rats (McDougall et al., 1993).

The ontogeny of mesolimbic dopamine D_2 receptors parallels ontogenetic increases in locomotor activity (Hartley and Seeman, 1983). Dopamine D_2 receptors are pre-

sent in newborn rats, and rapidly increase until adult mesolimbic and striatal levels are reached around postnatal day 21 (Hartley and Seeman, 1983; Murrin and Zeng, 1986). More specifically, quinpirole increases locomotor activity and rotational activity (also called turning or pivoting) in 8–14 day old rat pups (Eilam et al., 1992). Low doses of the mixed dopamine D_1/D_2 receptor agonist, apomorphine, decreased locomotor activity in rats older than 21 days, probably via preferential stimulation of dopamine D_2 autoreceptors; however, high doses of apomorphine increased activity, likely via stimulation of postsynaptic dopamine D_2 receptors (Lin and Walters, 1994).

The importance of dopamine autoreceptors in modulating dopamine activity is well-recognized (Elsworth and Roth, 1997). Studies on *S*(−)-3-(3-hydroxyphenyl)-*N*-propylpiperidine hydrochloride ((±)-3-PPP) and apomorphine-induced stereotypies (Lin and Walters, 1994) and quinpirole-induced locomotor suppression (Van Hartesveldt et al., 1994) indicate that dopamine D_2 autoreceptor-mediated behaviors do not appear until after postnatal day 20, and that the autoreceptors are not functional at postnatal day 10. However, studies with 7-OH-DPAT indicate that dopamine D_3 synthesis-modulating autoreceptors exist in the rat brain at postnatal day 10 (Andersen and Teicher, 1995). These results suggest that quinpirole in our study was most likely acting at postsynaptic receptor sites but that 7-OH-DPAT could have been acting at postsynaptic receptor sites, autoreceptors, or both.

Central and peripheral dopamine systems regulate cardiovascular and respiratory activity in rats (Bolme et al., 1977; Chen et al., 1988; Moss and Inman, 1989), and both of these processes influence ultrasonic vocalization emission (Hofer and Shair, 1993; Blumberg et al., 1997; Kirby and Blumberg, 1998). Hofer and Shair (1992, 1993) showed that the respiratory dynamics (i.e., increased tracheal pressure) involved in an infant rat's recovery from deep hypothermia lead to ultrasonic vocalization emission along the lines suggested by Blumberg and Alberts (1990). Kirby and Blumberg (1998) recently suggested that ultrasonic vocalizations may be an epiphenomenon of abdominal muscle compression during expiration which increases cardiac venous return by inducing peripheral vasodilation. Apomorphine decreases cardiac venous return and has been shown to suppress ultrasonic vocalizations in adult gerbils (Thiessen and Upchurch, 1981). It remains to be seen if rat pups would respond similarly. The dopamine receptor agonists used in this study may thus have decreased ultrasonic vocalization emission by decreasing venous return to the heart and indicating that cardiac and respiratory variables should be measured.

Dopamine drugs also interact with many other neurochemical systems: 7-OH-DPAT has agonistic effects at α_2-adrenoreceptors and serotonin 5-HT_{1A} receptors (Van den Buuse, 1993), SCH 23390 blocks the motivational properties of μ-opioid and κ-opioid receptor agonists (Shippenberg and Herz, 1987), and quinpirole has agonistic effects at α_2-adrenoreceptors and histamine H_2-receptors (Armstrong et al., 1983; Cohen et al., 1984). Thus, the interaction of dopamine drugs with these other neurochemical systems may also modulate ultrasonic vocalizations.

Although the proposal that isolation-induced ultrasonic vocalizations in infant rats are a valid model of anxiety has been questioned (e.g., Blumberg and Alberts, 1990), Hofer (1996) has argued that many studies show that drugs which are anxiolytic in adult rats and humans inhibit rat pup ultrasonic vocalizations, while those that are anxiogenic stimulate ultrasonic vocalizations. However, this pattern is not universal: clonidine is anxiolytic in adult humans but stimulates ultrasonic vocalizations in infant rats. We have suggested several ways in which dopamine might influence ultrasonic vocalizations. The hypothesis that dopamine receptor agonists are anxiolytic as measured by suppression of isolation-induced ultrasonic vocalizations requires further direct experimentation. In particular, cardiovascular and respiratory effects need to be monitored; more selective dopamine receptor agonists and antagonists for postsynaptic receptors and autoreceptors need to be tested; dopamine D_1:D_2 receptor interactions require examination; and the developmental state of the pup need to be addressed. Interactions between monoamines and neuropeptides should be addressed given the findings that neurotensin is colocalized in mesocortical dopamine neurons while cholecystokinin is colocalized in some ventral tegmental dopamine neurons, and that both peptides modulate dopamine function (Hommer et al., 1986; Deutch and Zahm, 1992). Such studies will increase our understanding of how external stimuli produce neurochemical changes that integrate ultrasonic vocalization emission into a functional and socially-adaptive behavior.

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