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ORIGINAL INVESTIGATION

The role of dopaminergic transmission through D1-like and D2-like receptors in amphetamine-induced rat ultrasonic vocalizations

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Abstract
Rationale Systemic amphetamine (AMPH) administration increases the rate of 50-kHz ultrasonic vocalizations (USVs) in adult rats and preferentially enhances the 'trill' subtype; these effects of AMPH critically depend on noradrenergic transmission, but the possible contributions of dopamine are unclear.
Objective To assess the role of dopamine in 50-kHz USVs emitted drug-free and following systemic AMPH administration.
Methods Adult male Long–Evans rats pre-selected for high AMPH-induced calling rates were tested with AMPH (1 mg/kg, intraperitoneal (IP)) and saline following pretreatment with the following dopamine receptor antagonists: SCH 23390 (0.005–0.02 mg/kg, subcutaneous (SC)), SCH 39166 (0.03–0.3 mg/kg, SC), haloperidol (0.1, 0.2 mg/kg, IP), sulpiride (20–80 mg/kg, SC), raclopride (0.1–0.5 mg/kg, SC), clozapine (4 mg/kg, SC), risperidone (0.5 mg/kg, SC), and pimozide (1 mg/kg, IP). The dopamine and noradrenaline reuptake inhibitors (GBR 12909 and nisoxetine, respectively) were also tested, alone and in combination.
Results SCH 23390, SCH 39166, haloperidol, and raclopride dose-dependently inhibited vocalizations under AMPH and suppressed the proportion of trill calls. Sulpiride, however, had no discernable effect on call rate or profile, even at a high dose that reduced locomotor activity. Single doses of clozapine, risperidone, and pimozide all markedly decreased calling under saline and AMPH. Finally, GBR 12909 and nisoxetine failed to promote 50-kHz USVs detectably or alter the subtype profile, when tested alone or in combination.
Conclusions The rate of 50-kHz USVs and the call subtype profile following systemic AMPH administration depends on dopaminergic neurotransmission through D1-like and D2-like receptors. However, inhibiting dopamine and/or noradrenaline reuptake appears insufficient to induce calling.

Keywords Ultrasonic vocalization · Amphetamine · Dopamine · Noradrenaline · Atypical antipsychotic · Dose–response · D1 receptor · D2 receptor · Hedonia · Affect

Introduction

Higher-frequency ultrasonic vocalizations (USVs) emitted by adult laboratory rats, generally termed "50-kHz calls" (for review, see Brudzynski 2009; Wohr and Schwarting 2010), are frequently associated with appetitive stimuli (Burgdorf et al. 2010; Knutson et al. 2002) and have been proposed to reflect positive affect (Brudzynski 2007; Burgdorf and Moskal 2009; Burgdorf et al. 2010). However, 50-kHz USVs are acoustically diverse, with many identified subtypes including flat (i.e., constant frequency) calls and at least 12 types of frequency-modulated (FM) calls (Wright et al. 2010). The relative prevalence of the different call subtypes, which we have termed the "call profile" (Wright et al. 2010), can be experimentally modified independently of the

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overall rate of 50-kHz call emission (Ciucci et al. 2007, 2009; Wright et al. 2012b).

Dopaminergic (DAergic) neurotransmission appears to play a key role in USV emission. Notably, acute systemic injection of the dopamine (DA) agonist apomorphine promoted 50-kHz calls (Williams and Undieh 2010), and intra-accumbens administration of the D_2/D_3 agonist quinpirole modulated USV production in a dose-related triphasic fashion (Brudzynski et al. 2012). Conversely, DA receptor antagonists are reported to inhibit 50-kHz USVs elicited by several natural and artificial rewarding stimuli, namely systemic cocaine (Williams and Undieh 2010), intracerebral amphetamine (AMPH) and glutamate (Thompson et al. 2006; Wintink and Brudzynski 2001), tickling (Burgdorf et al. 2007), electrical brain stimulation (Burgdorf et al. 2007), and copulation-related contexts (Bialy et al. 2010; Ciucci et al. 2007, 2009).

The psychostimulant AMPH, which enhances both DAergic and noradrenergic transmission (McKittrick and Abercrombie 2007), exerts two principal effects on 50-kHz vocalizations: It increases the overall call rate (Ahrens et al. 2009; Simola et al. 2009; Wintink and Brudzynski 2001; Wright et al. 2010, 2012b), and in relative terms, it shifts the "call profile," thereby enhancing the trill subtype while suppressing flat calls (Wright et al. 2010, 2012b). These rate-enhancing and call profile-altering effects of AMPH are critically dependent on α_1 and β adrenergic receptor function, respectively (Wright et al. 2012b). To our knowledge, however, it has not been determined whether the effects of systemic AMPH administration on 50-kHz USV emission are also dependent on DAergic transmission.

The first main aim of the present study was therefore to test the hypothesis that DAergic neurotransmission is required for 50-kHz calls that are emitted when tested drug-free or following systemic AMPH administration. The second, related, aim was to determine whether either D1-like or D2-like DA receptors (Le Foll et al. 2009) play a role. These questions were addressed in Experiments 1–7, in which we tested the effects of acute pretreatment with several D1- or D2-like DA receptor antagonists in combination with systemic saline or AMPH challenge (see Table 1). During testing, it emerged that the atypical antipsychotic drug sulpiride (Rama Rao et al. 1981) did not inhibit AMPH-induced calling, in striking contrast to two classical D2 antagonists (i.e., haloperidol and raclopride). Therefore, as a third aim, we assessed whether sulpiride's lack of effect reflected its atypical antipsychotic profile, by testing two other atypical neuroleptic drugs (clozapine and risperidone) and one additional classical D2 antagonist (pimozide). We also recorded USVs and locomotor activity simultaneously (Experiment 7), in order to confirm that sulpiride was behaviorally active, despite its failure to influence 50-kHz calling.

A final aim was to address whether enhancing DA or noradrenaline (NA) transmission is *sufficient* to induce 50-kHz USVs or affect the call profile (Experiments 8–10—see Table 1). To this end, rats were acutely challenged with the selective DAT inhibitor GBR 12909 and the selective NET inhibitor nisoxetine, given alone and in combination.

Methods

Subjects

Subjects were 114 male Long–Evans rats (Charles River Laboratories, St Constant, Quebec, Canada), weighing 376 ±50 g (mean±SD) at the start of the experiment. They were housed two or three per cage ($25\times48\times20$ cm^3) in a temperature- and humidity-controlled colony room (19–20 °C, 50–60 %) at the McGill University Animal Research Center. Rats were maintained on a reverse 12:12 light/dark cycle, with lights off at 0700 h. All behavioral testing took place during the dark phase of the cycle. Food and water were available ad libitum, except during testing sessions. In all experiments, rats were initially drug- and experimentally naïve, with the following exceptions: In Experiments 3 and 4, rats had received four prior systemic injections of AMPH (0.25, 0.5, 1, and 2 mg/kg, IP), and in Experiment 7, rats had received four prior administrations of morphine (1 mg/kg, SC). All procedures were approved by the McGill Animal Care Committee in accordance with the guidelines of the Canadian Council on Animal Care.

Overview of experiments

Ten experiments were performed, as summarized in Table 1. Briefly, Experiments 1–7 tested the effects of antagonist pretreatment on the USV response (i.e., call rate and subtype profile) to systemic AMPH. Experiment 7 additionally examined locomotor activity during the USV recording. The acute USV responses to the DA and NA reuptake inhibitors (i.e., GBR 12909 and nisoxetine), given alone or in combination, were examined in Experiments 8–10.

Experimental protocol

AMPH screen A significant minority of rats emit few calls in response to systemic AMPH (Wright et al. 2010). Therefore, subjects in most experiments were initially screened for AMPH-induced calling. Exceptionally, in order to reduce pre-experiment drug exposure, subjects in Experiments 3, 4, and 7 were not screened since they had already received prior AMPH or morphine administration (see above). The AMPH screening method was as described previously (see Wright et al. 2012b for further details). Briefly, rats

Table 1 Summary of experiments

Experiment	Pretreatment	Doses, mg/kg	Route	Time before saline/AMPH, min	*n*
1	SCH23390	0.005, 0.01, 0.02	SC	20	10
2	SCH39166	0.03, 0.1, 0.3	SC	30	12
3	Haloperidol	0.1, 0.2	IP	60	12
4	Sulpiride	20, 40	SC	60	12
5	Raclopride	0.1, 0.2, 0.5	SC	30	12
	Sulpiride	40, 80	SC	30	
6	Clozapine	4	SC	30	12
	Risperidone	0.5	SC	30	
	Pimozide	1	IP	30	
7	Sulpiride	80	SC	30	16
Experiment	Drug	Doses, mg/kg	Route	Time before testing, min	*n*
8	GBR 12909	5, 10, 20	IP	20	8
9	Nisoxetine	4, 8, 16	IP	15	8
10	GBR 12909	10	IP	20	12
	Nisoxetine	12	IP	15	

received three administrations of AMPH (1 mg/kg, IP) spaced 2 days apart; rats with the lowest rate of calling on the third AMPH test were excluded from subsequent testing. Only the third AMPH test session was analyzed because the first two sessions are not necessarily indicative of a rat's subsequent USV response to AMPH (unpublished observation). In total, 52 rats (out of 126 rats that underwent screening) were excluded on this basis.

Drug testing All experiments featured a fully parametric within-subject design, whereby each rat was tested once under each drug/dose condition (see Table 1 for details). Thus, in Experiments 1–7, rats received all combinations of pretreatment and treatment drugs including all vehicle controls. After the pretreatment time interval had elapsed, each rat was injected with saline or AMPH (1 mg/kg, IP) and immediately placed in a test chamber and recorded for 20 min. Similarly, in Experiments 8–10, every rat was tested under the following conditions: vehicle, AMPH (1 mg/kg—positive control), and each dose of the drug(s) being tested. Here, recording sessions were of 20-min duration except for the GBR 12909 dose–response study (Experiment 8), where rats were tested for 40 min. Within each experiment, the order of testing was counterbalanced as far as possible given the number of subjects. Test sessions were always spaced 2 days apart in order to minimize possible carry-over effects of the drugs.

Drugs

All test drugs, doses, routes of administration, and pretreatment/treatment time intervals are shown in Table 1. Drugs were: D-amphetamine sulfate (Sigma-Aldrich, Poole, UK); haloperidol and S(−)-sulpiride (both from Sigma-Aldrich, St. Louis, MO); pimozide, R(+)-SCH-23390 HCl, SCH 39166 HBr (i.e., Ecopipam), raclopride, and risperidone (all from Tocris Bioscience, Ellisville, MO); clozapine, GBR 12909 2HCl, and (±)-nisoxetine HCl (all from the NIMH Chemical Synthesis and Drug Supply Program). Doses of the different compounds refer to the form indicated above. GBR 12909 was administered in a volume of 2 ml/kg; all other drugs were administered in a volume of 1 ml/kg. Sulpiride was dissolved in a few drops of glacial acetic acid and diluted with sterile saline. Clozapine, GBR 12909, haloperidol, pimozide, and risperidone were dissolved in a 0.1 M tartaric acid solution. All other drugs were dissolved in sterile saline. Drug vehicles were used for control injections. The pH of GBR 12909 could not be raised beyond 4.5 (with NaOH) without precipitation. In case the lower pH affected call emission, each rat was tested twice with AMPH in Experiment 10, once with the standard drug solution and once with the same solution acidified with HCl to pH 4.5. Since there was no difference in call rate or profile between the two AMPH tests, data from these tests were pooled for the remainder of the analysis.

Behavioral recording

USV recordings were conducted as previously described (Wright et al. 2012b). With the exception of Experiment 7 (see below), recordings took place in four clear Plexiglas experimental chambers (ENV-007CT, Med Associates, St Albans, VT), each of which was enclosed in a melamine compartment lined with sound-attenuating acoustic foam (Primacoustic, Port Coquitlam, British Columbia). A condenser ultrasound microphone (CM16/CMPA, Avisoft Bioacoustics, Berlin, Germany) was securely inserted through a small (5-cm diameter) hole located centrally in the top panel

of each experimental chamber. Consequently, the microphones were 15–30 cm from rats during testing. Microphone signals were fed into an UltraSoundGate 416 H data acquisition device (Avisoft Bioacoustics) with a sampling rate of 250-kHz and 16-bit resolution.

For Experiment 7, USV recordings were made in rectangular, open-topped chambers (58 cm long×29 cm wide× 53 cm high) to allow simultaneous recording of USVs and locomotor activity, as previously described (Wright et al. 2012a). Two ultrasound microphones were secured inside each chamber at opposite corners, approximately 10 cm from the top (i.e., 40 cm above the floor). Sound-attenuating acoustic foam enveloped the walls and extended 20 cm above the top of each chamber. A video tracking system (EthoVision v 3.0, Noldus Information Technology, Leesburg, VA, USA) measured locomotor activity (expressed as the total horizontal distance moved) during the second half (i.e., min 11–20) of the session to allow AMPH to take effect.

All lights were off during behavioral testing, except for Experiment 7, where far-red (wavelength>650 nm) illumination using a Kodak GBX-2 safelight filter (Vistek, Toronto, Ontario, Canada) provided darkroom lighting.

Analysis and classification of ultrasonic vocalizations

Acoustical analysis was performed using Avisoft SASLab Pro (version 5.1, Avisoft Bioacoustics), as previously described (Wright et al. 2012b). Calls were selected manually from spectrograms by an individual who was masked to the treatment condition. Each identified 50-kHz call was classified into 1 of 14 distinct categories: complex, upward ramp, downward ramp, flat, short, split, step-up, step-down, multi-step, trill, flat–trill combination, trill with jumps, or composite (see Wright et al. (2010) for criteria for call identification and classification, several examples of each call type, as well as descriptive statistics relating to acoustic parameters). A few representative 50-kHz calls are shown in Fig. 1. This method of manual call selection has been validated by surgical devocalization, and classification is associated with high inter- and intra-rater reliability (Wright et al. 2010). The 22-kHz calls were not analyzed since they were rarely observed in this study (specifically, one rat made two calls under sulpiride 40 mg/kg plus AMPH 1 mg/kg and another rat made 20 calls under sulpiride 80 mg/kg plus AMPH 1 mg/kg).

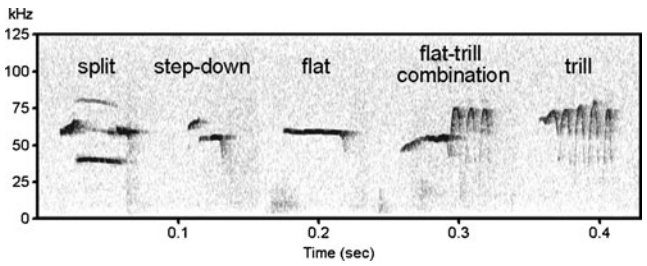

Fig. 1 Spectrogram containing individual 50-kHz calls representative of the following subtypes (*left to right*): split, step-down, flat, flat-trill combination, and trill. See Wright et al. (2010) for additional examples of all fourteen 50-kHz call subtypes

Data analysis and statistics

Data were analyzed using commercial software (Systat v11, SPSS, Chicago, IL; GraphPad Prism 4, GraphPad Software, La Jolla, CA). For Experiments 1–7, USVs that occurred during minutes 12, 14, and 16 of the 20-min session were counted and classified. These minutes were chosen since AMPH-induced calling becomes most pronounced within the 10–20 min time interval following AMPH administration (Wright et al. 2010). In Experiment 8, data throughout the entire 40 min session were analyzed. Finally, for Experiments 9 and 10, USV analysis was performed for minutes 3, 8, 13, and 18 of the 20-min session (i.e., we chose 4 min of time-sampling and spread it evenly across the session). One rat was removed for the call *subtype* analysis in Experiment 2 (SCH 39166) because it only emitted one call at the highest dose, making it an extreme outlier when evaluating the percentage data. Repeated-measures ANOVA was performed to determine the effect of the within-subjects factors "pretreatment" and "treatment," where appropriate. Pairwise comparisons were performed using paired *t*tests or Wilcoxon tests; the choice of test depended on the distribution of the raw data. ANOVA *p* values were subject to the Huynh–Feldt correction, where appropriate. Multiple comparisons relating to the call rate data were subject to Holm–Bonferroni corrections, except where stated. However, for the call subtype analysis, pairwise comparisons were performed using uncorrected tests, in order to maintain statistical power. For all analyses, a two-tailed p value<5 % (after any correction) was considered significant.

Results

Note that statistically significant results were found for certain of the less frequent call subtypes, but they were not consistently observed across doses or drugs of the same class and are likely to be false-positives; hence, these results are not reported here.

Experiments 1 and 2: effects of the D1 antagonists SCH 23390 and SCH 39166

As expected, AMPH given alone (i.e., with vehicle pretreatment) greatly increased the rate of 50-kHz calling (Wilcoxon Z=2.80 and 3.06, both p<0.01; Fig. 2a, b). The call rate under

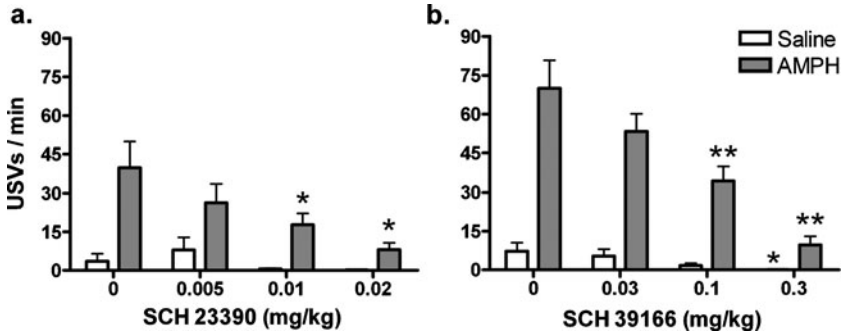

Fig. 2 Experiments 1 and 2: The D_1 antagonists SCH 23390 (**a**) and SCH 39166 (**b**) dose-dependently inhibited the call rate under AMPH. The *y* axes represent mean+SEM calls/min. Each rat was tested under all pretreatment/treatment conditions (SCH 23390 group $n=10$; SCH 39166 group $n=12$). SCH 39166 alone also decreased the call rate at the highest dose tested (i.e., 0.3 mg/kg). $^*p<0.05$, $^{**}p<0.01$ versus corresponding vehicle pretreatment condition

AMPH was dose-dependently reduced by both SCH 23390 and SCH 39166, with significant effects at the two higher doses (SCH 23390, Wilcoxon $Z=2.70$ and 2.70, $p<0.05$; SCH 39166, Wilcoxon $Z=2.90$ and 3.06, $p<0.01$; Fig. 2). Each antagonist, given alone, tended to suppress calling below the already-low baseline call rate, but a statistically significant inhibitory effect only occurred at the highest dose of SCH 39166 (Wilcoxon $Z=2.80$, $p<0.05$; Fig. 2b).

Higher doses of the D1-like antagonists also significantly affected the call profile. More specifically, the proportion of trill calls under AMPH was dose-dependently suppressed by both SCH 23390 (0.01 and 0.02 mg/kg versus vehicle, Wilcoxon $Z=2.29$ and 2.19, $p<0.05$; Fig. 3a) and SCH 39166 (0.3 mg/kg versus vehicle, Wilcoxon $Z=2.52$, $p<0.05$; Fig. 3c). In addition, SCH 39166 significantly enhanced the proportion of flat calls under AMPH at the highest dose tested (i.e., 0.3 mg/kg) (Wilcoxon $Z=2.38$, $p<0.05$; Fig. 3d). Although the proportion of flat calls appeared to be enhanced by SCH 23390, this failed to reach statistical significance (Fig. 3b). No other call subtype was significantly altered.

Experiments 3–5: effects of the D_2 antagonists haloperidol, sulpiride, and raclopride

Call rate under AMPH Haloperidol, at both doses tested (0.1 and 0.2 mg/kg), significantly inhibited calling following AMPH administration (respectively, Wilcoxon $Z=2.31$, $p<0.05$, and 3.06, $p<0.01$; Fig. 4a); sulpiride (20 and 40 mg/kg), in contrast, had no effect (Fig. 4b). Sulpiride was tested again at a higher dose (Experiment 5), this time in parallel with raclopride (Fig. 4c). Sulpiride again failed to affect the rate of calling after AMPH treatment, whereas raclopride behaved similarly to haloperidol, inhibiting 50-kHz calling at all doses tested (Wilcoxon $Z=3.06$, 2.98, and 3.06, $p<0.01$; Fig. 4c).

Call rate after antagonist alone Haloperidol did not alter the call rate after saline challenge (Fig. 4a); here, however, control call rates were very low (i.e., <3 calls/min). Sulpiride, tested alone, significantly reduced calling at only one dose (40 mg/kg Wilcoxon $Z=2.28$, $p<0.05$; Fig. 4c), and this apparent effect was not replicated across experiments

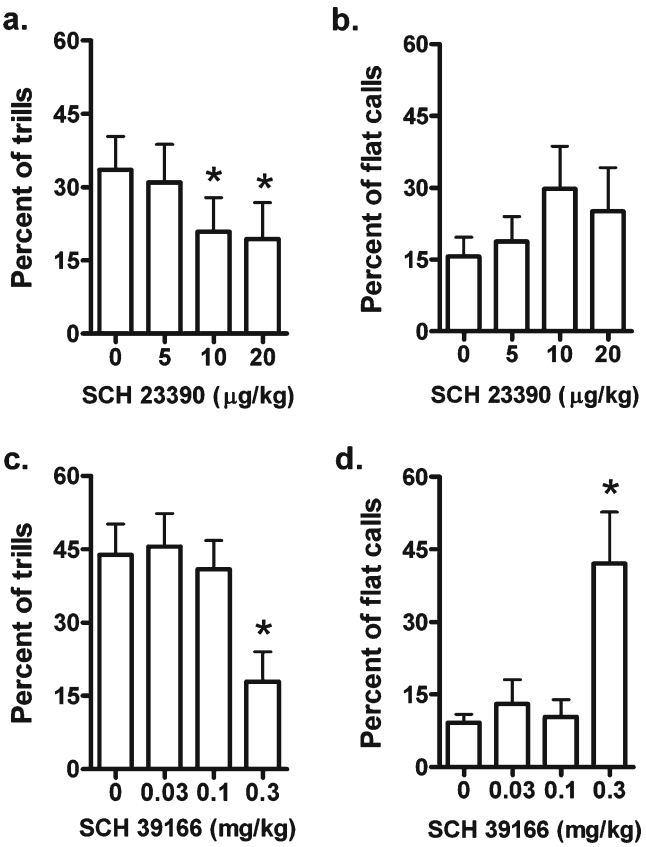

Fig. 3 Experiments 1 and 2: Pretreatment with the D_1 antagonists SCH 23390 (**a**) and SCH 39166 (**c**) before AMPH dose-dependently reduced the percent of trill calls. SCH 39166 also increased the percent of flat calls at the highest dose tested (0.3 mg/kg) (**d**). The apparent increase in the percent of flat calls with SCH 23390 was statistically non-significant (**b**). Each rat was tested under all pretreatment/treatment conditions (SCH 23390 group $n=10$; SCH 39166 group $n=12$). $^*p<0.05$ versus vehicle control

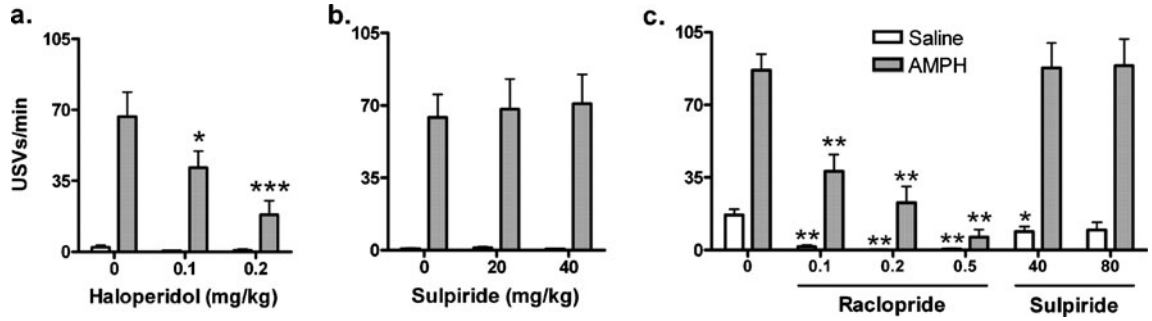

Fig. 4 Experiments 3–5: Haloperidol (**a**) and raclopride (**c**) dose-dependently inhibited USV emission under AMPH (*grey bars*) at all doses tested, while sulpiride (**b**, **c**) was ineffective. Raclopride (**c**) also reduced the call rate following saline treatment (*open bars*). Sulpiride only modestly reduced the drug-free call rate at 40 mg/kg in Experiment 5 (**c**). Each rat was tested under all pretreatment/treatment conditions (n=12 rats per experiment). *p<0.05, **p<0.01, ***p<0.001 versus corresponding vehicle pretreatment

(i.e., Experiment 4 versus 5; see Fig. 4b versus c). In contrast, raclopride tested alone significantly inhibited the call rate at all doses tested (0.1, 0.2, and 0.5 mg/kg versus vehicle, Wilcoxon Z=2.85, 3.06, and 3.06, p<0.01; Fig. 4c).

Call profile Haloperidol and raclopride dose-dependently suppressed the proportion of trill calls following AMPH challenge (haloperidol 0.2 mg/kg versus vehicle, Wilcoxon Z=2.51, p<0.05; raclopride 0.5 mg/kg versus vehicle, Wilcoxon Z=2.1, p<0.05; Fig. 5a, c). This effect appeared less potent than the rate-inhibiting effect (Fig. 4a, c). Raclopride (0.2 mg/kg) also increased the proportion of flat calls under AMPH (mean±SEM percent of flat calls following pretreatment with vehicle versus 0.2 mg/kg raclopride, 12.7±2.9 versus 32.8±4.5; Wilcoxon Z=2.5, p<0.05). In contrast, sulpiride marginally *increased* the proportion of trill calls at 40 mg/kg in Experiment 5 (Wilcoxon Z=2.19, p<0.05; Fig. 5c) but not in Experiment 4 (Fig. 5b).

Experiment 6: effects of pimozide and the atypical antipsychotics clozapine and risperidone

Pimozide, clozapine, and risperidone were all tested at a single, high dose. All three antagonists markedly inhibited both USV after saline treatment and AMPH-induced USV production (see Fig. 6). Despite low rates of calling, call subtype analysis revealed that pimozide significantly reduced the proportion of trill calls under AMPH (mean± SEM percent of trills: vehicle versus pimozide, 36.4±6.5 versus 13.3±11.4, respectively; Wilcoxon Z=2.37, p<0.05).

Experiment 7: effect of high-dose sulpiride on 50-kHz USVs and locomotor activity

Sulpiride (80 mg/kg) significantly decreased AMPH-induced locomotor activity (ANOVA pretreatment×treatment interaction, $F_{1,15}$=14.85, p<0.01; Fig. 7). Sulpiride also reduced locomotor activity when given alone (t_{15}= 3.39, p<0.01; Fig. 7a). In contrast, sulpiride exerted no detectable effect on either the call rate (Fig. 7b) or profile (not shown).

Experiments 8–10: effect of GBR 12909 and nisoxetine, alone and in combination

Unlike AMPH, neither GBR 12909 nor nisoxetine significantly promoted 50-kHz calling at any dose tested; all comparisons were statistically non-significant after Holm–

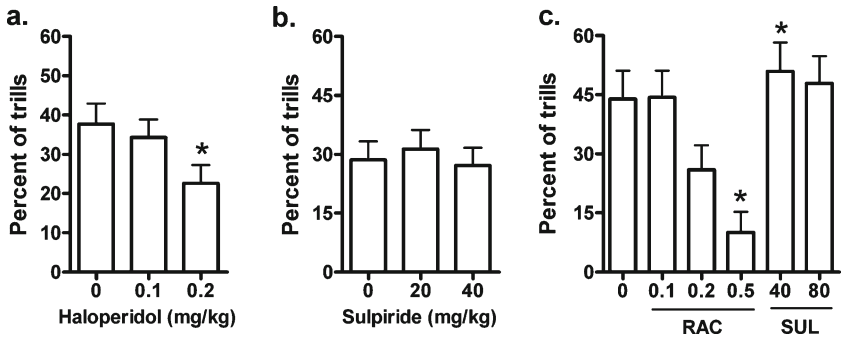

Fig. 5 Experiments 3 and 5: Haloperidol (**a**) and raclopride (*RAC*) (**c**) suppressed trills (as a proportion of all 50-kHz calls) following AMPH administration at the highest doses tested. Sulpiride (*SUL*), in contrast, was largely ineffective (**b**, **c**), except for an increase in the proportion of trills at 40 mg/kg in Experiment 5 (**c**). Each rat was tested under all pretreatment/treatment conditions (n=12 rats per experiment). *p< 0.05 versus vehicle control

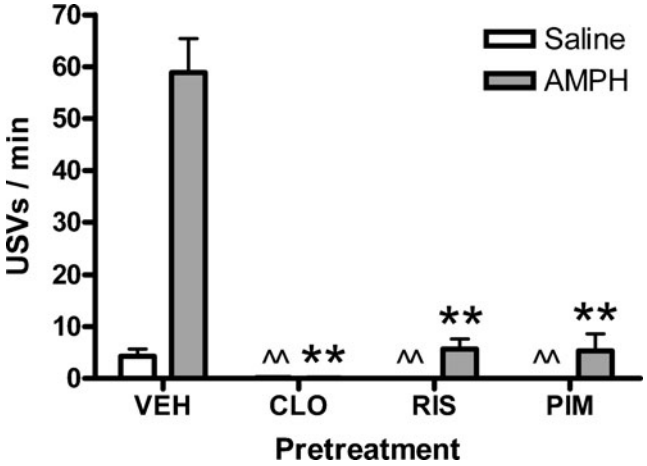

Fig. 6 Experiment 6: Single doses of clozapine (4 mg/kg, SC; *CLO*), risperidone (0.5 mg/kg, SC; *RIS*), and pimozide (1 mg/kg, IP; *PIM*), all markedly reduced the 50-kHz call rate under saline (*open bars*) and AMPH 1 mg/kg IP (*grey bars*). Each rat was tested under all pretreatment/treatment conditions (n=12 rats). ^^p<0.01 versus vehicle/saline control, **p<0.01 versus vehicle/AMPH control

Bonferroni correction (Experiments 8 and 9, respectively; Fig. 8a, b). In Experiment 8, GBR 12909 tended to increase the call rate at 10 mg/kg, especially in the first half of the 40-min session, i.e., time 20–40 min post-injection (Supplemental Fig. S1). Accordingly, this shorter post-injection interval was used when this drug was retested in Experiment 10. Here, selected doses of GBR 12909 (i.e., 10 mg/kg) and nisoxetine (i.e., 12 mg/kg) were administered, not only alone but also in combination; there was still no significant enhancement (or suppression) of call rate (Fig. 8c). Notably, the 10 mg/kg dose of GBR 12909 which appeared to increase calling in Experiment 8 no longer showed such a trend (Fig. 8c).

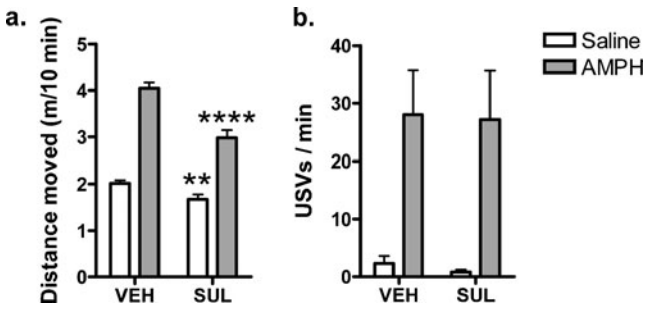

Fig. 7 Experiment 7: Sulpiride (*SUL*; 80 mg/kg, SC) significantly inhibited AMPH-induced locomotor activity (panel **a**) (ANOVA pretreatment×treatment interaction—$F_{1,15}$=14.85, p<0.01) but produced no detectable effect on the rate of USV emission (panel **b**). The y axes represent mean+SEM total horizontal distance (meters) travelled (panel **a**) or the 50-kHz call rate (panel **b**), following administration of saline (*open bars*) or AMPH (*grey bars*). **p<0.01, ****p<0.0001 versus corresponding vehicle (*VEH*) control

The reuptake inhibitors, given alone or in combination, failed to mimic the effect of AMPH on the call profile. For example, in Experiment 10, AMPH significantly increased the relative prevalence of trill calls, but neither GBR 12909, nor nisoxetine, or their combination showed this effect (mean±SEM percent trills: vehicle versus AMPH, 22.9± 5.2 versus 46.3±6.7, respectively; Wilcoxon Z=2.58, p< 0.01). Conversely, a significant reduction in the proportion of flat calls was observed following the co-administration of GBR 12909 and nisoxetine, yet AMPH unexpectedly did not reduce the proportion of flat calls in this particular experiment (mean±SEM percent flat calls: vehicle versus GBR 12909+nisoxetine, 21.9± 6.3 versus 10.3±6.0, respectively; Wilcoxon Z=2.67, p<0.01).

Discussion

The present study provides the first evidence that D1-like and D2-like receptor antagonists modulate the effects of systemic AMPH administration on the 50-kHz call rate and profile. Exceptionally, sulpiride, which is a D2-like antagonist with atypical antipsychotic features, consistently failed to affect USV emission. In addition, neither GBR 12909 (DAT inhibitor) nor nisoxetine (NET inhibitor), or their combination, mimicked the effects of AMPH on USV production. Below, we argue that both D1-like and D2-like DA receptors play a critical role in 50-kHz USV emission, and we suggest mechanisms contributing to sulpiride's lack of effect. We subsequently review antagonist-induced USVs suppression in the context of other behavioral and clinical effects of the same drugs. Finally, we discuss whether enhanced DA or NA transmission is sufficient to promote USV emission.

D1 dopaminergic receptor antagonism

The D1-like antagonists SCH 23390 and SCH 39166 dose-dependently inhibited the 50-kHz call rate and the percentage of trill calls following AMPH challenge; both antagonists also tended to reduce the call rate below control (i.e., drug-free) levels, although a significant reduction was only seen at the highest dose of SCH 39166. SCH 23390 and SCH 39166 both bind with high affinity to D1 and D5 receptors, with negligible affinity for D2-like receptors (i.e., D2, D3, and D4) (Tice et al. 1994). While SCH 23390 also has considerable affinity for serotonin receptors, namely $5HT_2$ and $5HT_{1C}$ (Bischoff et al. 1986; Nicklaus et al. 1988), SCH 39166 does not (Alburges et al. 1992; McQuade et al. 1991a, b; Wamsley et al. 1991). To our knowledge, these drugs do not have any other significant off-target effects. Thus, DA D1-like receptors appear critical to the USV-altering effects of systemic AMPH and may also regulate USV emission in the absence of this drug.

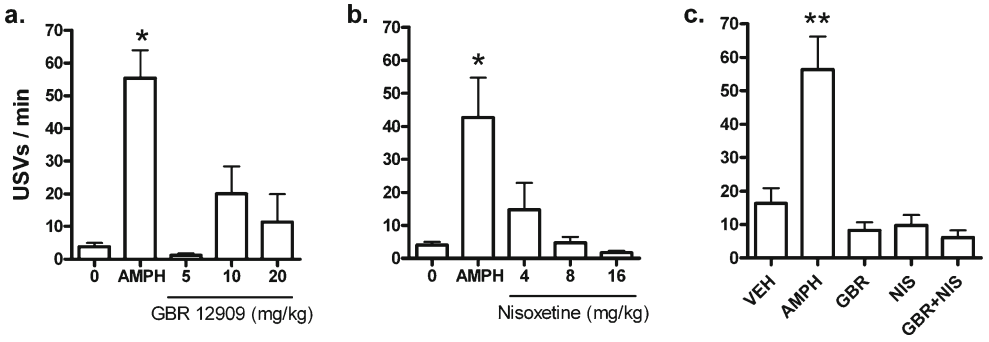

Fig. 8 Experiments 8–10: GBR 12909 (**a**) and nisoxetine (**b**) failed to significantly promote 50-kHz calling at any dose tested. Panel **c** shows that single doses of GBR 12909 (*GBR*, 10 mg/kg IP) and nisoxetine (*NIS*, 12 mg/kg IP), given either alone or even in combination (*GBR+NIS*), still failed to modify the call rate detectably (**c**). *$p<0.05$, **$p<0.01$ versus vehicle control (*VEH*)

D2 dopaminergic receptor antagonism

All six D2-like antagonists, with the notable exception of sulpiride, markedly inhibited or abolished the stimulatory effect of AMPH on call rate. Additionally, haloperidol and raclopride dose-dependently decreased the proportion of trill calls under AMPH. The latter finding is in line with previous studies showing a reduction in the proportion of FM calls in response to sexual odors following systemic haloperidol pretreatment (Ciucci et al. 2007, 2009). It appears likely that DA transmission through D2-like receptors is critical for both the call rate and profile following AMPH, since several possibilities exist as to why sulpiride is anomalous:

1. Sulpiride may exert an additional (as yet unidentified) action which functionally counteracts D2 receptor blockade. Indeed, studies with muscarinic cholinergic and adenosine A2A receptor antagonists have provided such a precedent, in that these drugs can reverse the behavioral effects of DA receptor blockade (Collins et al. 2012; Morpurgo and Theobald 1964).
2. The phenomenon of D2-like receptor heteromerization (Maggio et al. 2009) suggests another plausible mechanism by which sulpiride might exert functional effects that are distinct from those of other D2-like antagonists.
3. It is unlikely that our doses of sulpiride were insufficient to antagonize USV emission, since comparable or even lower doses have proven effective in a number of DA-dependent behavioral assays, i.e., apomorphine hyperactivity and stereotypy (de Paulis et al. 1985), the AMPH cue (Nielsen and Andersen 1992; Nielsen and Jepsen 1985), conditioned place preference (CPP) induced by food or testosterone (Guyon et al. 1993; Schroeder and Packard 2000), and intravenous self-administration of nicotine or cocaine (Sorge and Clarke 2009). Importantly, a high dose of sulpiride that failed to affect the call rate did, at the same time, reduce AMPH-induced hyperactivity (present study—Experiment 7); the latter effect is consistent with previous findings (Ljungberg and Ungerstedt 1985; Moore and Kenyon 1994; Sharp et al. 1986; White et al. 1992).
4. Sulpiride, in contrast to many D2-like antagonists, possesses considerably lower affinity at D4 compared with D2 and D3 receptors (Rondou et al. 2010; Seeman et al. 1997; Seeman and Van Tol 1994). However, it is unlikely that D4 receptors are critical to USV emission since raclopride (Experiment 5) markedly reduced USVs despite also having very low affinity at D4 receptors (Seeman and Van Tol 1994).
5. The "atypical" antipsychotic properties of sulpiride do not appear related to its lack of effect on USV emission, since the atypical drugs clozapine and risperidone clearly inhibited calling.
6. Since D2-like antagonists tend to be pharmacologically non-selective (Jafari et al. 2012), it is conceivable that all the D2-like antagonists tested, except for sulpiride, fortuitously suppressed calling through some shared non-DAergic mechanism. However, this possibility seems remote since the compounds were drawn from multiple, structurally heterogeneous chemical classes (Jafari et al. 2012), and we are unaware of any such shared receptor candidate. Notably, α1 adrenergic receptor blockade abolishes AMPH-induced calling (Wright et al. 2012b), but some DA antagonists (e.g., raclopride) lack significant affinity for this receptor (Hall et al. 1986; Ishiwata et al. 2001; Ogren et al. 1986).

Behavioral mechanisms

The USV-related effects produced by the DA-like antagonists in the present study are summarized in Table 2, together with several other behavioral effects of the same drugs reported in the literature. Antagonist doses that inhibited saline- or AMPH-induced USVs frequently overlapped with those affecting other behavioral measures. However, as discussed below, no particular behavioral measure matched our USV findings completely.

Table 2 Effects of antagonists on USVs and other behavioral measures

Pretreatment		USV results (present study)			Other behavioral effects					
Drug	Dose	USV rate under saline[a]	USV rate under AMPH	Trills under AMPH	Spontaneous LMA	Catalepsy	AMPH[b]-induced LMA	CPA/CPP	AMPH[c] CPP	AMPH[d] cue
SCH 23390	0.005	–	–	–	– (Cervo and Samanin 1996; Hoffman and Beninger 1985; Menzaghi et al. 1997; Sacaan et al. 1996; Salmi et al. 1998)	– (Christensen et al. 1984; Morelli and Di 1985; Ouagazzal et al. 1993)	?	– (Acquas et al. 1989; Leone and Di Chiara 1987)	– (Hiroi and White 1991)	– (Callahan et al. 1991; Nielsen and Andersen 1992; Nielsen and Jepsen 1985)
	0.01	–	↓	↓	– (Cervo and Samanin 1996; Hoffman and Beninger 1985; Sacaan et al. 1996),↑ (Meyer et al. 1993), ↓ (Menzaghi et al. 1997; Salmi et al. 1998)	– (Christensen et al. 1984; Morelli and Di 1985; Ouagazzal et al. 1993)	↓ (Ouagazzal et al. 1993)	– (Acquas et al. 1989; Leone and Di Chiara 1987), CPA (Shippenberg and Herz 1987; Shippenberg and Herz 1988)	– (Hiroi and White 1991)	– (Callahan et al. 1991; Nielsen and Andersen 1992; Nielsen and Jepsen 1985; Nielsen et al. 1989), ↓ (Arnt 1988)
	0.02	–	↓	↓	– (Cervo and Samanin 1996; Shen et al. 2010),↓ (Menzaghi et al. 1997; Salmi et al. 1998)	– (Christensen et al. 1984; Morelli and Di 1985; Ouagazzal et al. 1993)	↓ (Ouagazzal et al. 1993)	– (Acquas et al. 1989; Leone and Di Chiara 1987), CPA (Shippenberg and Herz 1987; Shippenberg and Herz 1988)	– (Hiroi and White 1991), ↓ (Acquas and Di Chiara 1994)	↓ (Arnt 1988; Exner et al. 1989; Nielsen and Andersen 1992; Nielsen and Jepsen 1985; Smith et al. 1989)
SCH 39166	0.03	–	–	–	– (Batsche et al. 1994)	– (Hietala et al. 1992), yes (Prinssen et al. 1993)	?	?	↓ (Acquas and Di Chiara 1994)	?
	0.1	–	↓	–	– (Batsche et al. 1994)	– (Hietala et al. 1992), yes (Prinssen et al. 1993)	?	?	↓ (Acquas and Di Chiara 1994)	↓ (West et al. 1995)
	0.3	↓	↓	↓	– (Batsche et al. 1994),↓ (Collins et al. 2010)	– (Hietala et al. 1992), yes (Prinssen et al. 1993)	?	?	↓ (Acquas and Di Chiara 1994)	↓ (West et al. 1995)
Haloperidol	0.1	–	↓	–	– (Sanchez et al. 1991)	– (Christensen et al. 1984; Liao et al. 1999), yes (Hoffman and Donovan 1995b; Morelli and Di 1985)	↓ (Arnt 1995; Hoffman and Donovan 1995a; Hoffman and Donovan 1995b; Poncelet et al. 1987)	– (Hoffman and Donovan 1995a; Spyraki et al. 1982)	↓ (Hoffman and Donovan 1995a)	↓ (Exner et al. 1989; Nielsen and Jepsen 1985; Nielsen et al. 1989)
	0.2	–	↓	↓	↓ (Sanchez et al. 1991)	– (Christensen et al. 1984; Liao et al. 1999), yes (Hoffman and Donovan 1995b; Morelli and Di 1985; Sanchez et al. 1991)	↓ (Arnt 1995; Hoffman and Donovan 1995a; Hoffman and Donovan 1995b; Mithani et al. 1986; Poncelet et al. 1987)	– (Spyraki et al. 1982)	↓ (Hoffman and Donovan 1995a; Mithani et al. 1986; Spyraki et al. 1982)	↓ (Arnt 1996; Exner et al. 1989; Nielsen and Jepsen 1985; Nielsen et al. 1989)
(-)Sulpiride	20	–	–	–	– (Ferrari and Giuliani 1995; Morgenstern et al. 1983)	– (Imperato and Di Chiara 1985; Tagliamonte et al. 1975)	↓ (Ljungberg and Ungerstedt 1985; Moore and Kenyon 1994; Poncelet et al. 1987; White et al. 1992)	– (Shippenberg and Herz 1988)	– (Hiroi and White 1991)	– (Nielsen and Andersen 1992; Nielsen and Jepsen 1985)
	40	– or ↓	–	– or ↑	– (Ferrari and Giuliani 1995; Morgenstern et al. 1983)	– (Imperato and Di Chiara 1985; Tagliamonte et al. 1975)	↓ (Ljungberg and Ungerstedt 1985; Moore and Kenyon 1994; Poncelet et al. 1987; White et al. 1992)	– (Shippenberg and Herz 1988)	↓ (Hiroi and White 1991)	– (Nielsen and Jepsen 1985), ↓ (Nielsen and Andersen 1992)

Table 2 (continued)

Pretreatment		USV results (present study)			Other behavioral effects					
Drug	Dose	USV rate under saline[a]	USV rate under AMPH	Trills under AMPH	Spontaneous LMA	Catalepsy	AMPH[b]-induced LMA	CPA/CPP	AMPH[c] CPP	AMPH[d] cue
	80	–	–	–	↓ (Cervo and Samanin 1996; present study)	– (Imperato and Di Chiara 1985; Tagliamonte et al. 1975)	↓ (present study; Ljungberg and Ungerstedt 1985; Moore and Kenyon 1994; Poncelet et al. 1987; Sharp et al. 1986; White et al. 1992)	?	↓ (Hiroi and White 1991)	↓ (Nielsen and Andersen 1992; Nielsen and Jepsen 1985)
Raclopride	0.1	↓	↓	–	– (Garcia Horsman and Paredes 2004; Hillegaart and Ahlenius 1987; Salmi et al. 1998; Shen et al. 2010), ↓ (Millan et al. 2004)	– (Hillegaart and Ahlenius 1987; Hoffman and Donovan 1995b; Ouagazzal et al. 1993; Wadenberg et al. 2000a; Wadenberg et al. 2000b)	– (Ouagazzal et al. 1993), ↓ (Hoffman and Donovan 1995a; Hoffman and Donovan 1995b)	– (Garcia Horsman and Paredes 2004; Hoffman and Donovan 1995a)	?	– (Furmidge et al. 1991; Nielsen and Andersen 1992), ↓ (Varty and Higgins 1997)
	0.2	↓	↓	–	– (Hillegaart and Ahlenius 1987; Salmi et al. 1998), ↓ (Millan et al. 2004; Shen et al. 2010)	– (Hillegaart and Ahlenius 1987; Hoffman and Donovan 1995b; Wadenberg et al. 2000b), yes (Ouagazzal et al. 1993)	↓ (Hoffman and Donovan 1995a; Hoffman and Donovan 1995b; Ouagazzal et al. 1993)	– (Hoffman and Donovan 1995a)	↓ (Garcia Horsman and Paredes 2004)	– (Furmidge et al. 1991; Nielsen and Andersen 1992),↓ (Nielsen et al. 1989)
	0.5	↓	↓	↓	↓ (Garcia Horsman and Paredes 2004; Hillegaart and Ahlenius 1987; Millan et al. 2004; Salmi et al. 1998; Shen et al. 2010)	– (Hillegaart and Ahlenius 1987), yes (Hoffman and Donovan 1995b; Ouagazzal et al. 1993; Wadenberg et al. 2000b)	↓ (Hoffman and Donovan 1995a; Hoffman and Donovan 1995b; Ouagazzal et al. 1993)	– (Hoffman and Donovan 1995a)	↓ (Garcia Horsman and Paredes 2004; Hoffman and Donovan 1995a)	↓ (Furmidge et al. 1991; Nielsen and Andersen 1992; Nielsen et al. 1989)
Clozapine	4	↓	↓	–	↓ (Arnt 1995; Sanchez et al. 1991)	– (Hoffman and Donovan 1995b; Liao et al. 1999; Sanchez et al. 1991)	↓ (Arnt and Skarsfeldt 1998; Hoffman and Donovan 1995a; Hoffman and Donovan 1995b)	– (Hoffman and Donovan 1995a)	– (Hoffman and Donovan 1995a)	↓ (Arnt 1996; Nielsen and Andersen 1992; Nielsen and Jepsen 1985)
Risperidone	0.5	↓	↓	–	– (Arnt 1995)	– (Arnt and Skarsfeldt 1998), yes (Hoffman and Donovan 1995b)	↓ (Arnt 1995; Hoffman and Donovan 1995a; Hoffman and Donovan 1995b)	– (Hoffman and Donovan 1995a)	↓ (Hoffman and Donovan 1995a)	↓ (Arnt 1996)
Pimozide	1	↓	↓	–	↓ (Agmo and Soria 1999; Horvitz and Ettenberg 1991; Schaefer and Michael 1984; Spivak and Amit 1986)	– (McMillen et al. 1980), yes (Christensen et al. 1984)	↓ (Poncelet et al. 1987; Schaefer and Michael 1984)	?	?	↓ (Ho and Huang 1975)

Minus sign no significant change, *question mark* currently no published data (to our knowledge), *arrow up* or *arrow down* significant increase or decrease, respectively

[a] Particularly for SCH 23390, haloperidol, and sulpiride, inhibitory effects might have been masked by the low rate of drug-free calling

[b] 0.5–3.5 mg/kg AMPH

[c] 1–2 mg/kg AMPH

[d] 0.3–1 mg/kg AMPH

USVs versus motor function Several DA antagonists (i.e., haloperidol, clozapine, risperidone, pimozide) inhibited USV emission at doses expected to markedly suppress drug-free or AMPH-associated locomotion (Table 2). In general, however, there was no consistent relationship between motor impairment and USV emission. In particular, raclopride inhibited drug-free USV production even at low doses which tend not to inhibit locomotion, and conversely, sulpiride inhibited drug-free and AMPH-induced locomotion without detectably affecting USV production (Table 2).

AMPH cue The discriminative stimulus effects of AMPH are of particular interest since they serve to model the drug's subjective effects in humans (Brauer et al. 1997). The USV-stimulatory and cue effects of AMPH appear similarly affected by our D1 and D2 antagonists, but only the latter is attenuated by sulpiride (see Table 2 for references).

USVs versus reward/aversion Since 50-kHz USVs have been proposed as a measure of drug reward, it is potentially informative to compare our results with published work using the conventional reward measure of CPP, while acknowledging that the latter reflects conditioned rather than unconditioned drug effects. Both D1 antagonists appeared to inhibit 50-kHz calling under saline treatment, allowing for the low rate of drug-free calling. However, it is unclear whether D1 receptor blockade reliably produces a conditioned place aversion (CPA) in rats (Table 2), since D1 antagonist effects are either mixed (SCH 23390) or unreported (SCH 39166). In contrast, D2-like antagonists consistently fail to produce a CPP or CPA in adult rats (Tzschentke 1998). The lack of D2 antagonist-induced CPP or CPA does not appear to reflect a learning or memory deficit, since D2 receptor blockers do not inhibit the acquisition of all types of CPP or CPA (Tzschentke 1998). Thus, D2 receptor antagonists appear neutral in the CPP/CPA test, yet all our D2 receptor antagonists (with the exception of sulpiride) tended to inhibit calling under saline treatment.

The acquisition of AMPH CPP is inhibited by D1 and D2 receptor antagonists, according to most reports (Table 2). However, our USV findings reveal two striking differences: (1) sulpiride did not inhibit AMPH-induced calling (present study), whereas it inhibited AMPH CPP (Hiroi and White 1991), and (2) clozapine abolished AMPH-induced calling, yet failed to inhibit AMPH CPP (Hoffman and Donovan 1995a). Importantly, these studies employed comparable doses of antagonist and AMPH.

USVs versus affect Although classic antipsychotics (e.g., haloperidol) do not produce a CPA in rats (see above), they often produce dysphoria in human subjects (Emerich and Sanberg 1991; Voruganti and Awad 2004). Atypical antipsychotics, in contrast, appear far less commonly associated with dysphoria, as evidenced by sulpiride, clozapine, and risperidone (Mehta et al. 1999; Potvin et al. 2003; Voruganti et al. 2000). Although the latter two drugs produced profound alterations in USV emission in the present study, circulating levels of these three DA antagonists probably far exceeded the clinical range.

USVs versus AMPH euphoria The dose of AMPH employed in the present study (i.e., 1 mg/kg) appears comparable to euphorigenic doses in human studies (Grilly and Loveland 2001). FM 50-kHz ultrasonic vocalizations (USVs) have been proposed to reflect hedonia (Burgdorf and Moskal 2009), and the trill subtype in particular appears most closely associated with rewarding doses of AMPH and cocaine (Wright et al. 2010, 2012b). Although trill calls following AMPH were preferentially inhibited by both D1-like and some D2-like (i.e., haloperidol, raclopride, and pimozide) antagonists in the present study, it is important to note that animal and human studies do not strongly support a role for DA in hedonia but rather in incentive salience or "wanting" (Brauer and de Wit 1997; Leyton et al. 2005, 2007; Smith et al. 2011). Therefore, in view of the present findings, we speculate that emission of FM 50-kHz calls, and trills in particular, may relate to incentive salience rather than hedonia. Flat calls, in contrast to trill calls, were significantly increased in relative terms by certain doses of SCH 39166 and raclopride, possibly as a consequence of trill call suppression. Flat calls have been proposed to have a social-coordinating function unrelated to positive affect (Wohr et al. 2008).

Dopamine and noradrenaline reuptake inhibitors

AMPH and cocaine, which increase both DA and NA transmission (McKittrick and Abercrombie 2007), enhance USV production and modulate the call profile (Wright et al. 2010, 2012b). The results of the present study together with previous findings (Wright et al. 2012b) suggested that both DA and NA transmission are *necessary* for the observed effects of AMPH on USV emission. The question of *sufficiency* was addressed by subsequently examining whether the selective DAT and NET inhibitors GBR 12909 (Andersen 1989) and nisoxetine (Wong et al. 1982; Wong and Bymaster 1976), respectively, could mimic the USV effects of AMPH or cocaine. Neither GBR 12909 nor nisoxetine, alone or in combination, mimicked the effect of AMPH on the call rate or profile in the present study. At doses tested here, GBR 12909 would be expected to elevate extracellular DA, and co-administration of a NET blocker would likely potentiate this increase (Carboni et al. 2006). To our knowledge, there are no studies directly examining extracellular NA following nisoxetine administration in rats. Instead, the doses of nisoxetine were chosen based on their ability to generalize to the cues produced by the non-selective β-adrenergic

agonist isoproterenol (Crissman and O'Donnell 2002) and the NET blocker reboxetine (Millan and Dekeyne 2007); the latter drug produces a marked increase in extracellular levels of NA (Dekeyne et al. 2001).

GBR 12909 and nisoxetine, unlike AMPH, appear to exert their behavioral effects solely through transmitter reuptake inhibition. We have previously found that the DA/NA reuptake blocker cocaine moderately stimulated 50-kHz calling, while mimicking AMPH's ability to promote trill calls preferentially (Wright et al. 2012b). It is unclear why GBR 12909 and nisoxetine failed to exert either of these effects; here, cocaine's ability to inhibit the 5-HT reuptake transporter (Wall et al. 1995) or enhance exocytotic DA release (Ramsson et al. 2011) may be relevant.

Limitations

Adult rats exhibit large variability in their USV response to systemic AMPH (Taracha et al. 2012; Wright et al. 2010). In order to examine drug effects on AMPH-induced calling, we identified low responders using an initial AMPH screen in most experiments. A substantial number of subjects were then excluded, resulting in a selected population that may differ in other behavioral or neurochemical respects (Burgdorf et al. 2008). Notably, the failure of sulpiride to modify the call rate or profile was independent of whether rats were screened or not (compare Experiment 5 with Experiments 4 and 7). The present method of selecting adult rats based on their acute response to AMPH helps to address the issue of low baseline call rates and high individual differences. Other approaches include selective breeding (Burgdorf et al. 2008) and possibly through prior social manipulations (Vivian and Miczek 1991).

Due to the labor-intensive nature of this type of USV analysis, only a small fraction of the entire session (i.e., 3 or 4 min) was time-sampled for most experiments. It is possible that USV effects outside our chosen time intervals were missed. This method of time-sampling therefore limits interpretation of the present findings.

Finally, certain drugs, namely sulpiride, GBR 12909, and nisoxetine, exerted no discernable effects on USV emission. In the case of sulpiride, we performed an additional experiment (Experiment 7) where USVs and locomotion were assessed simultaneously. However, the negative findings with GBR 12909 and nisoxetine (or their combination) were not followed up with additional behavioral testing. While GBR 12909 would be expected to stimulate locomotor activity at all the doses tested (Hooks et al. 1994; Powell et al. 2001), nisoxetine does not appear to affect this measure in adult rats (Davids et al. 2002; Powell et al. 2001). The lack of positive controls in Experiments 8–10 is a limiting factor when interpreting these results.

Conclusion

USVs are a potentially rich source of information about the rat's subjective state. The present study furthers our understanding of the neurochemical substrates regulating USV production in adult rats. DA transmission appears critical for the 50-kHz USV response to systemic AMPH, since antagonism of either D1-like or D2-like receptors (with the notable exception of sulpiride) reversed the effects of AMPH on the call rate and profile. DA transmission also appears to modulate drug-free call emission. It appears that, although both DA and NA are required, inhibition of DA and NA reuptake per se is not sufficient to elicit an AMPH-like USV response.

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