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ORIGINAL INVESTIGATION

The rewarding effect of aggression is reduced by nucleus accumbens dopamine receptor antagonism in mice

Maria H. Couppis · Craig H. Kennedy

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Abstract
Rationale Dopamine (DA) receptors within the nucleus accumbens (NAc) are implicated in the rewarding properties of stimuli. Aggressive behavior can be reinforcing but the involvement of NAc DA in the reinforcing effects of aggression has yet to be demonstrated.
Objective To microinject DA receptor antagonists into the NAc to dissociate their effects on reinforcement from their effects on aggressive behavior and general movement.
Materials and methods Male Swiss Webster mice were implanted with guide cannulae aimed for the NAc and tested for aggressive behavior in a resident–intruder procedure. Aggressive mice were then conditioned on a variable-ratio 5 (VR-5) schedule with presentation of the intruder as the reinforcing event. The D1- and D2-like receptor antagonists SCH-23390 and sulpiride were microinfused (12–50 ng) before the mice responded on the VR-5 schedule and attacked the intruder. Open-field activity was also determined following the highest doses of these drugs.
Results SCH-23390 and sulpiride dose-dependently reduced VR responding but did not affect open-field activity. The 50-ng SCH-23390 dose suppressed response rates by 40% and biting behaviors by 10%; other aggressive behaviors were not affected. The 25 and 50 ng sulpiride doses almost completely inhibited VR responding; the 50-ng dose suppressed biting by 50%.
Conclusions These results suggest that both D1- and D2-like receptors in the ventral striatum are involved in the rewarding properties of aggression, but that D1-like receptors may be related to the motivation to earn reinforcement as opposed to aggressive behavior.

Keywords Aggression · Dopamine · Nucleus accumbens · Reward · Operant behavior · Positive reinforcement · Resident–intruder · Mice

M. H. Couppis · C. H. Kennedy
Vanderbilt Kennedy Center, Vanderbilt University,
Nashville, TN 37204, USA

M. H. Couppis · C. H. Kennedy
Center for Integrative and Cognitive Neuroscience,
Vanderbilt University,
Nashville, TN 37204, USA

C. H. Kennedy (✉)
Department of Special Education, Vanderbilt University,
P.O. Box 328, Nashville, TN 37204, USA
e-mail: craig.kennedy@vanderbilt.edu

C. H. Kennedy
Department of Pediatrics, Vanderbilt University Medical Center,
Nashville, TN 37204, USA

Introduction

Aggression occurs among virtually all vertebrates and many invertebrate species, and is necessary for obtaining and maintaining important resources such as mates, territory, and food (Nelson 2006; Scott 1958). In humans, it also figures prominently as a positive symptom in many neuropsychiatric disorders (Chaplin 2006; Steiner et al. 2003). One characteristic of aggression is that animals will emit arbitrary responses to earn access to agonistic encounters, indicating that access to aggression can function as positive reinforcement (Cherek et al. 1973; De Almeida and Miczek 2002; Fish et al. 2002; Thompson 1963). For other events functioning as positive reinforcers, such as food, drugs, or sex, mesocorticolimbic dopamine (DA) is associated with the incentive salience of rewarding stimuli (Berridge 2007). Within the mesocorticolimbic circuit, DA neurons from the

ventral tegmental area (VTA) synapse on neurons in the nucleus accumbens (NAc). After access to or administration of stimuli serving as positive reinforcers, DA levels increase in the NAc (Wise 2004). If DA receptors in the NAc are genetically or pharmacologically disrupted, the rewarding effects of stimuli are diminished with receptor agonism having a correspondingly facilitative effect for positively reinforcing stimuli (Nestler 2004).

Dopamine has also been implicated in the rewarding properties of aggression. Experiments increasing extracellular levels of DA result in increased aggression, while the administration of DA antagonists decrease aggression (Kudryavtseva et al. 1999; Sokolov and Cadet 2006). DA receptor knockout systems have also shown a reduced aggressive phenotype (Drago et al. 1998; Miczek et al. 2001). Evidence further supporting a role for mesocorticolimbic DA in agonistic encounters comes from microdialysis experiments showing increased extracellular DA levels in the NAc after aggressive episodes (van Erp and Miczek 2000, 2007). However, further characterization of the mesocorticolimbic pathway in relation to aggression has been confounded by the lack of behavioral specificity of systemically administered DA antagonists (Miczek et al. 2002). This lack of behavioral specificity of DA receptor antagonism has been a significant barrier to determining the role of mesocorticolimbic DA in aggression.

In the experiments reported in this study, we used an operant contingency paradigm to (1) functionally establish access to aggression as a positive reinforcer and (2) separate the eliciting effects of introducing a conspecific from the motivation to earn access to aggression as a reward (Fish et al. 2002; Fish et al. 2005; Michael 1982). This motivational component was then manipulated by locally infusing DA-receptor-specific antagonists directly into the NAc. These experimental tactics allowed for the elimination of general motor disruptions produced by systemic administration of DA antagonists while showing that DA-receptor-specific antagonists reduced the rewarding properties of agonistic encounters. In addition, we used open-field tests to further show the absence of motoric impairment at levels of drug administration reducing the motivation to earn aggression as a reward.

Materials and methods

Subjects

Male Swiss Webster albino mice (Charles River Labs) were maintained on a 12:12-h light/dark cycle (lights on at 6:00 A.M.) with experimental sessions occurring during the lights-on cycle. At 28 days postpartum, each "resident male" was housed with a same-strain female. The sire and dam were housed together for the duration of the experiment. Following a similar timeline, "intruder males" were group-housed (five males per cage) throughout the experiment. Cages were clear polycarbonate plastic (29×17×53 cm) with standard stainless-steel wire lids and CareFresh paper bedding. All mice had ad libitum access to rodent chow (Purina, St. Louis, MO, USA) and water. The protocol was approved by the Vanderbilt Institutional Animal Care and Use Committee and followed the National Institutes of Health guidelines.

Surgical procedures

At 60 to 75 days postpartum, resident males were unilaterally implanted with guide cannula (CMA7, CMA Microdialysis, Solna, Sweden) positioned directly above the nucleus accumbens (AP, 1.6 mm; ML, 0.75 mm; DV, 4.5 mm) (Paxinos and Franklin 2001). Before surgery, subjects were anesthetized with 125 mg/kg ketamine and 10 mg/kg xylazine. Cannulae were adhered to the skull using Geristore (resin-based fluoro alumina silica glass) dental adhesive (Denmat Corporation, Santa Maria, CA, USA). The skin was replaced over the base of the guide cannula and sutured closed. After surgery, 7 days of isolated recovery occurred. Mice were then paired with the original female mate and left to acclimate for 7 to 14 days. After the acclimation period, mice were screened for aggression.

Aggression screening

Aggression was assessed by introducing an intruder mouse into the home cage of the male resident mouse with female removed (Miczek and O'Donnell 1978). Aggression screening involved three separate 10 min resident–intruder encounters each separated by 3 days. If a resident emitted aggression (biting or boxing) in two or more test sessions, it was included in a subsequent pharmacological analysis (87% of mice were aggressive).

Aggression as positive reinforcement apparatus

The operant conditioning panel (29×17×0.6 cm) was comprised of two nose-poke sensors (only the right sensor was operative during the experiment) and a house light (see Fish et al. 2002). The instrument panel, which was inserted into the resident vivarium cage, was controlled by software developed by the Vanderbilt Kennedy Center and run on a MSDOS-based personal computer through a Med Associates interface.

Behavioral contingency

During all behavioral contingency tests, the dam and pups were removed from the resident cage and the operant conditioning panel was inserted. All behavioral contingency

sessions were run once daily. Mice meeting the criteria in the aggression screening were taught to nose poke via shaping successive approximations with the manual introduction of an intruder mouse into the resident cage for 6 s as a consequent stimulus. Resident mice were trained (2 to 3 weeks) to nose poke on a variable-ratio 5 (VR-5) reinforcement schedule to earn access to the intruder mouse. All sessions began with house light illumination and lasted for 15 min. Each time the VR-5 contingency requirement was met, the house light turned off for 0.5 s and the stimulus mouse was introduced for 6 s. Along with the automatically recorded nose pokes, sessions were videotaped and scored for aggression/locomotion as described below.

Dopamine antagonist tests

After subjects demonstrated steady nose-poking rates in baseline, drug microinjections were conducted. Double determinations were made at each dosage in an ascending dose–effect function with baseline sessions occurring in between each drug test. A minimum of two baseline sessions were conducted between injections to reestablish behavioral levels before the next injection. Determinations were established for mock-infusions (cannula without liquid were inserted into guides of subjects for 3 min), vehicle (artificial cerebral spinal fluid), the D1-like receptor antagonist SCH-23390 (12, 25, and 50 ng), and the D2-like receptor antagonist sulpiride (12, 25, and 50 ng). All drugs were obtained from Sigma-Aldrich (St. Louis, MO, USA). Each microinjection was 150 nl in volume and manually infused over 3 min using a microsyringe (0.2 ml micrometer syringe; Gilmont Instruments, Morgantown, PA, USA). Microinjections were administered 15 min before behavioral testing based on previous microinjection studies of these drugs.

Videotaped scoring of locomotion

Each behavioral contingency test session was videotaped and scored for movement and aggression. Movement included time spent running/walking, grooming, and rearing during mock-infusion, vehicle, and DA antagonist test conditions. Aggression included tail rattle, sideways threat, boxing, and biting during mock-infusion, vehicle, and DA antagonist after the intruder mouse was introduced. Trained graduate students blinded to the conditions scored videotaped sessions with 5% of sessions scored for intraobserver and interobserver agreement, which was greater than 90% (see Miczek and O'Donnell 1978).

Open-field tests

Naïve cannulated mice were treated one time in each condition (mock-infusion, vehicle, and 25 and 50 ng of SCH-23390 or sulpiride using a Latin square randomization design) 15 min before open-field test. Animals were then placed in a 43×43 cm open field chamber (ENV-515 test environment; MED Associates, St. Albans, VT, USA) for 15 min in a lit room. Total distance traveled was recorded and analyzed as the measure of locomotion using MED Associates SOF-811 Open-field Activity Software.

Histology

After completing the behavioral contingency tests, mice were deeply anesthetized with 800 mg/kg pentobarbital (Abbot Laboratories, Chicago, IL, USA) and transcardially perfused with 4% paraformaldehyde (Sigma-Aldrich, St. Louis, MO, USA). Brains were removed and cryoprotected by overnight submersion in 30% sucrose:70% paraformaldehyde fixative. Tissue was frozen on dry ice and sliced at 50 μm using a microtome. Mounted tissue was then Nissel stained to verify cannula placement. To verify the size and spread of infusions, a spread analysis was conducted. In this analysis, 15 min before perfusion, animals (n=4) were infused with 150 nl of microruby (Sigma-Aldrich, St. Louis, MO, USA) mixed in vehicle. Fifteen minutes after the microruby infusion, animals were perfused and tissue was treated as described above.

Statistical analysis

Within-subject, repeated-measures analysis of variance (ANOVA) with Tukey–Kramer post hoc analyses were used to analyze the differences in behavioral response to drug doses in each test (i.e., behavioral contingency test, videotaped aggression/movement, open-field test). Homogeneity was assessed pre-ANOVA using Levene's test of homogeneity. All datasets were determined to be adequately homogeneous before the repeated-measures ANOVA tests. All comparisons of drug effects were in reference to vehicle.

Results

Histological verification of cannula placement

After perfusion of each cannulated animal, tissue was sliced and stained to verify placement. Twenty-five animals had cannula placed within the boundaries of the NAc. Nine animals had cannula placed outside of the boundaries of the NAc. Figure 1 shows a diagram depicting the coronal mouse brain sections through the NAc indicating individual cannula placements. Figure 2a shows a photomicrograph of cannulated tissue.

Infusion of microruby before perfusion was conducted to quantify the spread of infusions (see Fig. 2b). The infusions

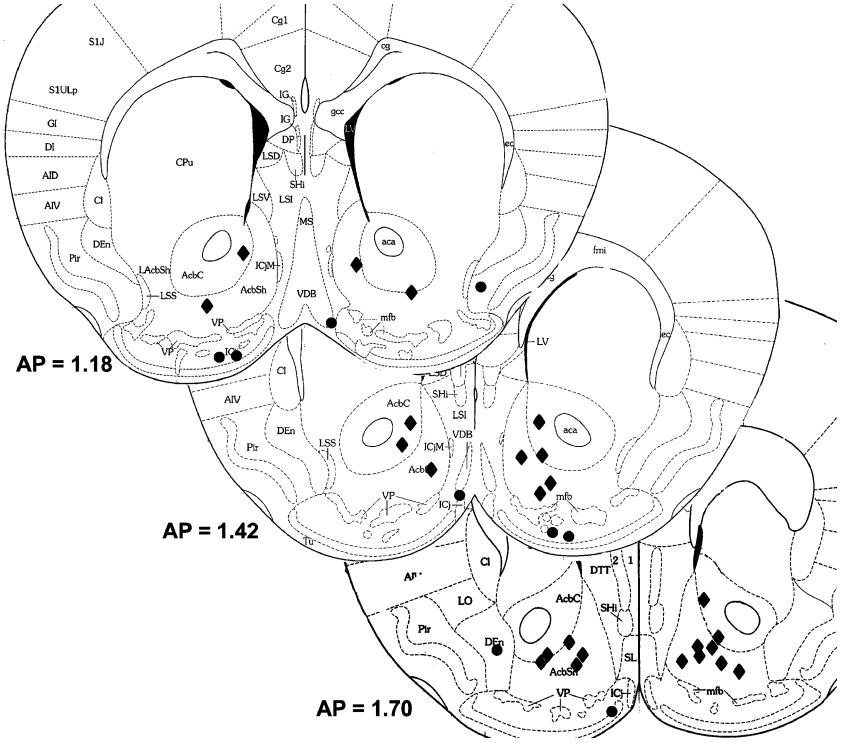

Fig. 1 Diagram showing coronal mouse brain sections at three different levels through the NAc (adapted from Paxinos and Franklin 2001). Each *diamond* represents the centermost medial–lateral point of an indwelling cannula within the boundaries of the NAc (N=25). Each *circle* represents the centermost medial–lateral point of an indwelling cannula outside the boundaries of the NAc (N=9). *AP* measurements are in millimeters from the bregma

were teardrop-shaped with the mean length (dorsal to ventral) at the largest point being 475 μm (±120) and the mean width (medial to lateral) being 400 μm (±37).

Dopamine antagonist effects on the rewarding properties of aggression

For cannula placements within the NAc, infusing SCH-23390 significantly reduced nose poking for aggression at the 50-ng dosage compared to vehicle ($F_{(3,49)}$=6.26, p<.001; see Fig. 3a). Infusing sulpiride into the NAc resulted in reduced nose poking for aggression at the 25- and 50-ng dosages of sulpiride compared to vehicle ($F_{(3,55)}$=6.26, p<.001; see Fig. 3b). Table 1 shows high levels of agonistic behaviors during vehicle injections when intruder mice were present. Reductions in aggression occurred at the 50-ng dosage of SCH-23390 for biting ($F_{(3,56)}$=5.06, p<.01). Aggression was reduced at the 25-ng dosage of sulpiride for tail rattle ($F_{(3,56)}$=11.04, p<.01) and biting ($F_{(3,56)}$=70.66, p<.01) and for all aggressive behaviors at the 50-ng dosage of sulpiride (p<.01). For cannula placements outside the NAc, no dosage of SCH-23390 (Fig. 3c) or sulpiride (Fig. 3d) affected nose poking for aggression.

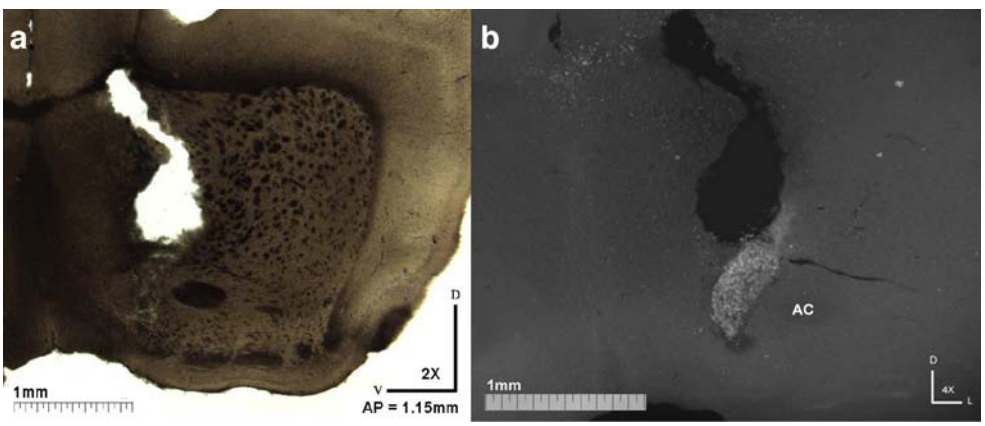

Fig. 2 A high-resolution photomicrograph of a coronal section at approximately 1.15 mm anterior to the bregma, photographed at ×2 magnification (**a**). The same section photographed at ×4 magnification and under green fluorescence to visualize and measure typical infusion spread (**b**). Each scale bar= 1 mm. Sections were photographed pre-Nissel staining to optimally view fluorescence and to ensure that infusions remain undisturbed for measurement

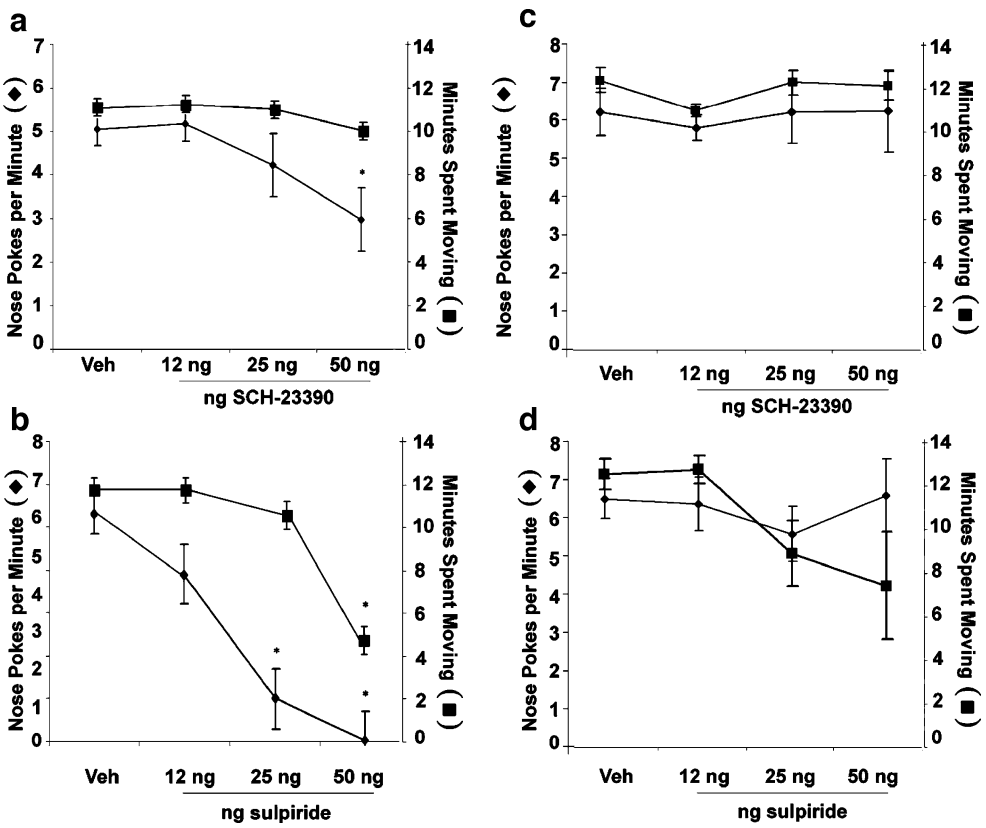

Fig. 3 The effect of SCH-23390 (a D1-like DA receptor antagonist) on nose pokes per minute for access to aggression (*filled diamonds*) and minutes spent moving during experimental sessions (*filled squares*) for cannula placements within the NAc (**a**) and outside the NAc (**c**). The effect of sulpiride (a D2-like DA receptor antagonist) on nose pokes per minute for access to aggression (*filled diamonds*) and minutes spent moving during experimental sessions (*filled squares*) for cannula placements within the NAc (**b**) and outside the NAc (**d**). All *data points* represent the mean scores across mice, and the *vertical lines* represent ±1 SEM. *$p<.05$ in relation to comparison with vehicle injections

Dopamine antagonist effects on movement during aggression tests

For cannula placements within the NAc, SCH-23390 produced no differences from vehicle in the total time spent moving. However, grooming, at both the 25- and 50-ng dosages was different from vehicle ($F_{(3,37)}=46.76$, $p<.001$). Rearing was also different between 50 ng SCH-23390 and vehicle ($F_{(3,37)}=4.62$, $p<.01$; see Table 2). For cannula placements within the NAc, sulpiride resulted in reductions from vehicle only at the 50-ng dosage ($F_{(3,44)}=31.40$, $p<.0001$). Walking, grooming, and rearing were different from vehicle only at the 50-ng dosage ($F_{(3,44)}=27.35$, $p<.001$; $F_{(3,44)}=6.44$, $p<.001$; and $F_{(3,44)}=32.72$, $p<.001$; respectively). For cannula placements outside the NAc, no dosage of SCH-23390 (Fig. 3c) or sulpiride (Fig. 3d) affected movement.

Dopamine antagonist effects on movement in open-field tests

The distance traveled in the SCH-23390 open-field test yielded an overall significant effect ($F_{(3,37)}=3.67$, $p<.05$). The mean distance traveled in the SCH-23390 groups was 1,903 cm for mock-injections (SEM=213), 1,662 cm for vehicle (SEM=189), 1,701 cm for 25 ng (SEM=195), and 1,630 cm for 50 ng (SEM=200). Tukey–Kramer post hoc analyses revealed that there were no significant differences

Table 1 Effects of SCH-23390 and sulpiride on percent time spent in aggression during intruder encounters

Behavior	Vehicle	12 ng SCH-23390	25 ng SCH-23390	50 ng SCH-23390	12 ng Sulpiride	25 ng Sulpiride	50 ng Sulpiride
Tail rattle	7.8±1.6	10±1*	8.2±1.2	9.3±1.2	7.9±1.3	5.3±1*	0*
Sideways threat	12.1±2.1	10.1±2.7	12.3±1.3	15.2±3.3	13±2.1	12.6±1	11.2±1
Boxing	23.2±2	24.3±2.4	20±2.3	20.2±1.7	24.6±1.8	26.2±1.7	19.4±1.5*
Biting	54.3±1.9	53.5±1.8	53±2	48.1±2*	51.7±1.9	46.9±1.5*	25.2±1.9*
Total	97.4±4	97.9±4.3	93.6±4.9	92.9±5.4	97.2±4.4	90.9±3.1	55.7±3*

Data for each behavior are the means±SEM. Values that are significantly different from average vehicle are noted with an asterisk ($p<.01$).

Table 2 Effects of SCH-23390 and sulpiride on walking, grooming, rearing, and total movement

	Mock-injection	Vehicle	12 ng SCH-23390	25 ng SCH-23390	50 ng SCH-23390	12 ng sulpiride	25 ng sulpiride	50 ng sulpiride
Walking	8.91±0.47	8.58±0.40	7.9±0.39	6.35±0.41	6.64±0.49	8.13±0.45	7.67±0.48	3.65±0.47*
Grooming	0.84±0.09	0.83±0.10	0.79±0.14	2.87±0.15*	1.98±0.15*	0.82±0.05	0.73±0.03	0.58±0.05*
Rearing	3.32±0.27	2.65±0.25	3.06±0.22	2.20±0.26	1.73±0.19*	2.89±0.28	2.01±0.26	0.54±0.24*
Total	12.90±0.52	11.88±0.50	11.71±0.44	11.43±0.42	10.42±0.37	11.85±0.61	10.41±0.59	4.77±0.63*

Data for each behavior are the means±SEM. Values that are significantly different from average vehicle are noted with an asterisk ($p<.05$).

between drug dosages and vehicle (see Fig. 4). The distance traveled in the sulpiride open-field test yielded an overall effect ($F_{(5,54)}=4.37$, $p<.05$). The mean distance traveled in the sulpiride group was 2,246 cm for mock-injections (SEM=220), 1,691 cm for vehicle (SEM=223), 1,573 cm for 25 ng (SEM=184 cm), and 1,291 cm for 50 ng (SEM=207). Results of the Tukey–Kramer post hoc analyses revealed that the 50-ng dosage differed from vehicle ($p<.05$; see Fig. 4).

Discussion

We established contingent access to aggression as a positively reinforcing stimulus for male Swiss Webster mice. Administration into the NAc of a D1-like DA receptor antagonist (SCH-23390) or a D2-like DA receptor antagonist (sulpiride) decreased responding for aggression at dosages not disrupting general motor behavior. Administration of SCH-23390 or sulpiride outside of the NAc did not affect contingent aggression or movement. Open-field tests also demonstrated that SCH-23390 and sulpiride dosages reducing aggression in the operant conditioning task did not impair general movement. These findings suggest that mesocorticolimbic DA is involved in the rewarding effects of aggression in mice. In addition, we have demonstrated a technique for local administration of DAergic antagonists into the NAc that avoids previous confounds in regard to general motor suppression.

Previous experiments have established the viability of the operant conditioning task used in this experiment to study aggression as positive reinforcement. De Almeida and Miczek (2002), Fish et al. (2002), and May et al. (submitted for publication) have used contingent access to aggression under a range of response- and time-based positive reinforcement schedules. An important aspect of this method is the separation of ethologically evoked aggression elicited from the introduction of a conspecific into the resident cage from the motivation of the resident mouse to earn access to aggression as a stimulus event by emitting instrumental behavior. This paradigm allowed us to analyze the motivational properties of aggression as a rewarding stimulus separate from other behavioral processes evoked by conspecific encounters (Michael 1982; Laraway et al. 2003).

Several previous studies have implicated mesocorticolimbic DA in relation to the rewarding properties of aggression. The most direct evidence for the involvement of the "reward pathway" comes from microdialysis experiments showing that extracellular levels of DA increase in the NAc after agonistic encounters, a finding that parallels microdialysis studies of other positively reinforcing stimuli (Ferrari et al. 2003; Van Erp et al. 2000). In our experiment, we were able to further the microdialysis findings by directly suppressing DAergic activity in the NAc. This NAc DAergic receptor antagonism resulted in mice no longer engaging in instrumental behavior to earn access to aggression, further implicating NAc DA in the rewarding properties of aggression.

For other positively reinforcing stimuli, DA is the most strongly implicated neurotransmitter (Wise 2004). Drugs of abuse, including cocaine, amphetamine, heroine, and

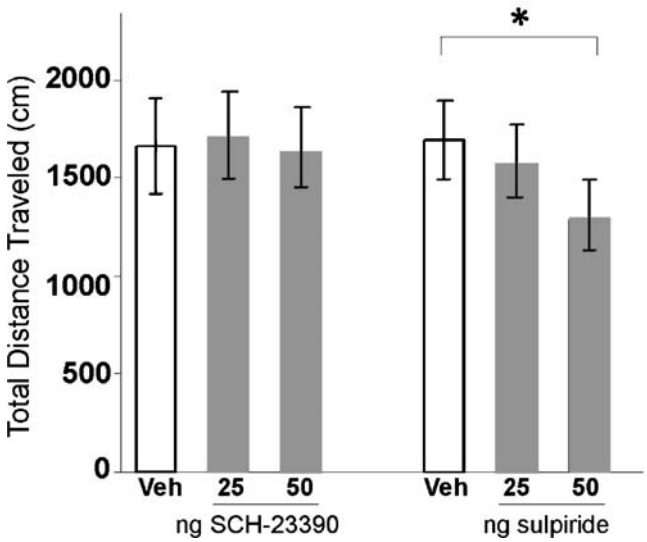

Fig. 4 The effect of SCH-23390 (a D1-like DA receptor antagonist) and sulpiride (a D2-like DA receptor antagonist) on total distance traveled in open-field testing. All *vertical bars* represent the mean scores across mice, and the *vertical lines* represent ±1 SEM. *$p<.05$ in relation to comparison with vehicle injections

nicotine, are associated with elevated mesocorticolimbic DA in the NAc, and this elevated brain DA is thought to be involved in the abuse process. Blockade of mesocorticolimbic DA receptors by DA antagonists results in significantly reduced self-administration of drugs of abuse (Corrigall et al. 1992; de Wit and Wise 1977; Di Chiara and Imperato 1988; McFarland and Ettenberg 1995; Yokel and Wise 1975). Similarly, positively reinforcing stimuli other than drugs of abuse have been consistently attributed to elevations in mesocorticolimbic DA (e.g., food, water, sex). For example, Wise et al. (1978) demonstrated attenuation of food reward with the administration of pimozide (a potent mixed DA receptor antagonist). Thus, there is strong evidence for the role of mesocorticolimbic DA in stimulus contingencies involving reward, although the specific behavioral mechanism of that effect is unclear (Berridge 2007). Our results suggest a similar mechanism for aggression that is operative for other positively reinforcing stimuli.

The results of our experiments indicate a role for D1- and D2-like DA receptors in the reinforcing properties of aggression. However, what role each DA receptor subtype serves in contingent aggression is yet to be determined. Experiments administering apomorphine (a semiselective D2-like DA receptor agonist) and *N*-propylnorapomorphine (a potent D2-like DA receptor agonist) have shown a facilitative agonistic effect under predatory, foot shock, and isolation-induced aggression paradigms (Baggio and Ferrari 1980; Miczek et al. 2002; Siegel et al. 1999). Complementing the findings of these experiments are studies using haloperidol and raclopride (D2-like DA receptor antagonists), which decreased aggression in rodents and humans, although the findings are problematic due to undesired motor side effects (Miczek et al. 2002; Siegel et al. 1999). Experiments demonstrating a role for D1-like DA receptors in the modulation of aggression are also present in the literature. SCH-23390 and SKF-38393 (a selective D1-like DA receptor agonist) have been reported to reduce aggression in rodents, although movement confounds limit the interpretation of previous studies (Miczek et al. 2002; Rodriguez-Arias et al. 1998) and interspecies replication has been limited (Siegel et al. 1999).

However, the ambiguity regarding mesocorticolimbic DA receptor specialization in aggression is also an issue in the larger positive reinforcement literature. Like the literature on DA receptors for other positive reinforcers (e.g., drugs of abuse, food, sex), it is unclear how the activation of each receptor subtype contributes to positive reinforcement. Various data support D1-like DA receptor activation, D2-like DA receptor activation, or activation of both receptor types. Supporting a role for D2-like DA receptor activation in positive reinforcement is research demonstrating NAc D2-like DA receptor control for food, cocaine, and intracranial self-stimulation (Pezze et al. 2007). Combining these data with anatomical findings demonstrating high levels of other D2-like DA receptors in the NAc shell, an area commonly associated with reward, there is support for a role of D2-like DA receptor activation in positive reinforcement.

It is also possible that the D1-like DA receptor association with reward involves an interaction with serotonin (5-HT). The 5-HT receptor subtype most implicated in aggression has been the 5-HT 1B receptor, although data have also implicated the 5-HT 2A receptor (De Almeida and Miczek 2002; De Almeida et al. 2006; de Boer and Koolhaas 2005). It is possible that SCH-23390 reduced responding for aggression through a serotonergic mechanism involving 5-HT 2A receptors. However, the doses required for 5-HT 2A receptor responses are tenfold higher than those blocking the D1-like DA receptor (Bourne 2001). Therefore, the dose range in the current experiment is unlikely to have affected the 5-HT 2A receptor.

In our experiments, we were not able to isolate the role of the nucleus accumbens core vs shell. Although our histological data demonstrated consistent, isolated microinjections not exceeding the boundaries of the NAc, it was not possible to isolate core vs shell injections due to the size of the mouse ventral striatum. However, research with other species with other positive reinforcers suggests that the medial shell is strongly associated with the rewarding effects of a stimulus, whereas the core contributes to behavioral activation. This hypothesis is strongly supported by a variety of evidence ranging from c-*fos* mRNA expression studies to studies utilizing 6-hydroxydopmaine lesions in conjunction with a variety of reward–response analysis paradigms (Floresco et al. 2006; Hara and Pickle 2005; Sellings and Clark 2003, 2006; Shram et al. 2007). In regard to the current findings, given our data on injection spread in the NAc, it is best to conclude that the behavioral effects we observed were due to DA receptor antagonism throughout the ventral striatum.

In summary, we showed that mesocorticolimbic DA is involved in the positively reinforcing effects of agonistic encounters. The localized microinjection technique we used was successful in avoiding general motor impairments resulting from systemic injection of DA antagonists. In addition, our findings suggest that both D1- and D2-like DA receptors serve a functional role in the rewarding properties of aggression.

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References

Baggio G, Ferrari F (1980) Role of brain dopaminergic mechanisms in rodent aggressive behavior: influence of (±, −)*N*-*n*-propylnorapomorphine on three experimental models. Psychopharmacology (Berl) 70:63–68

Berridge KC (2007) The debate over dopamine's role in reward: the case for incentive salience. Psychopharmacology (Berl) 191:391–431

Bourne JA (2001) SCH 23390: the first selective dopamine D1-like receptor antagonist. CNS Drug Rev 7:399–414

Chaplin EH (2006) Forensic aspects in people with intellectual disabilities. Curr Opin Psychiatry 19:486–491

Cherek D, Thompson T, Heistad GT (1973) Responding maintained by the opportunity to attach during an interval food reinforcement schedule. J Exp Anal Behav 19:113–123

Corrigall WA, Franklin KB, Coen KM, Clarke PB (1992) The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. Psychopharmacology (Berl) 107:285–289

De Almeida RMM, Miczek KA (2002) Aggression escalated by social instigation or by discontinuation of reinforcement ("frustration") in mice. Neuropsychopharmacology 27:171–181

De Almeida RM, Rosa MM, Santos DM, Saft DM, Benini Q, Miczek KA (2006) 5-HT(1B) receptors, ventral orbitofrontal cortex, and aggressive behavior in mice. Psychopharmacology (Berl) 185: 441–450

de Boer SF, Koolhaas JM (2005) 5-HT1A and 5-HT1B receptor agonists and aggression: a pharmacological challenge of the serotonin deficiency hypothesis. Eur J Pharmacol 526:125–139

de Wit H, Wise RA (1977) Blockade of cocaine reinforcement in rats with the dopamine receptor blocker pimozide, but not with the noradrenergic blockers phentolamine or phenoxybenzamine. Can J Psychol 31:195–203

Di Chiara G, Imperato A (1988) Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci U S A 85:5274–5278

Drago J, Padungchaichot P, Accili D, Fuchs S (1998) Dopamine receptors and dopamine transporter in brain function and addictive behaviors: insights from targeted mouse mutants. Dev Neurosci 20:188–203

Ferrari PF, Van Erp AAM, Tornatzky W, Miczek KA (2003) Accumbal dopamine and serotonin in anticipation of the next aggressive episode in rats. Eur J Neurosci 17:371–378

Fish EW, De Bold JF, Miczek KA (2002) Aggressive behavior as a reinforcer in mice: activation by allopregnanolone. Psychopharmacology (Berl) 163:459–466

Fish EW, DeBold JF, Miczek KA (2005) Escalated aggression as a reward: corticosterone and GABA(A) receptor positive modulators in mice. Psychopharmacology (Berl) 182:116–127

Floresco SB, Ghods-Sharifi S, Vexelman C, Magyar O (2006) Dissociable roles for the nucleus accumbens core and shell in regulating set shifting. J Neurosci 26:2449–2257

Hara Y, Pickel VM (2005) Overlapping intracellular and differential synaptic distributions of dopamine D1 and glutamate *N*-methyl-D-aspartate receptors in rat nucleus accumbens. J Comp Neurol 492:442–55

Kudryavtseva NN, Lipina TV, Koryakina LA (1999) Effects of haloperidol on communicative and aggressive behavior in male mice with different experiences of aggression. Pharmacol Biochem Behav 63:229–236

Laraway S, Snycerski S, Michael J, Poling A (2003) Motivating operations and terms to describe them: some further refinements. J Appl Behav Anal 36:407–414

McFarland K, Ettenberg A (1995) Haloperidol differentially affects reinforcement and motivational processes in rats running an alley for intravenous heroin. Psychopharmacology (Berl) 122:346–350

Michael J (1982) Distinguishing between discriminative and motivational functions of stimuli. J Exp Anal Behav 37:149–155

Miczek KA, Fish EW, De Bold JF, De Almeida RM (2002) Social and neural determinants of aggressive behavior: pharmacotherapeutic targets at serotonin, dopamine and gamma-aminobutyric acid systems. Psychopharmacology (Berl) 163:434–548

Miczek KA, Maxson SC, Fish EW, Faccidomo S (2001) Aggressive behavioral phenotypes in mice. Behav Brain Res 125:167–181

Miczek KA, O, 'Donnell JM (1978) Intruder-evoked aggression in isolated and nonisolated mice: effects of psychomotor stimulants and l-DOPA. Psychopharmacology (Berl) 57:47–55

Nelson J (2006) Biology of aggression. Oxford University, New York

Nestler EJ (2004) Molecular mechanisms of drug addiction. Neuropharmacology 47(Suppl 1):24–32

Paxinos G, Franklin KBJ (2001) The mouse brain in stereotaxic coordinates. Academic, New York

Pezze MA, Dalley JW, Robbins TW (2007) Differential roles of dopamine D1 and D2 receptors in the nucleus accumbens in attentional performance on the five-choice serial reaction time task. Neuropsychopharmacology 32:273–283

Rodriguez-Arias M, Minarro J, Aguilar MA, Pinazo J, Simon VM (1998) Effects of risperidone and SCH 23390 on isolation-induced aggression in male mice. Eur Neuropsychopharmacol 8:95–103

Scott JP (1958) Aggression. University of Chicago, Chicago

Sellings LH, Clarke PB (2003) Segregation of amphetamine reward and locomotor stimulation between nucleus accumbens medial shell and core. J Neurosci 23:6295–6303

Sellings LH, Clarke PB (2006) 6-Hydroxydopamine lesions of nucleus accumbens core abolish amphetamine-induced conditioned activity. Synapse 59:374–377

Shram MJ, Funk D, Li Z, Le AD (2007) Acute nicotine enhances c-*fos* mRNA expression differentially in reward-related substrates of adolescent and adult rat brain. Neurosci Lett 418:286–291

Siegel A, Roeling TAP, Gregg T, Kruk MR (1999) Neuropharmacology of brain-stimulation-evoked aggression. Neurosci Biobehav Rev 23:359–389

Sokolov BP, Cadet JL (2006) Methamphetamine causes alterations in the MAP kinase-related pathways in the brains of mice that display increased aggressiveness. Neuropsychopharmacology 31:956–966

Steiner H, Saxena K, Chang K (2003) Psychopharmacologic strategies for the treatment of aggression in juveniles. CNS Spectr 8:298–308

Thompson T (1963) Visual reinforcement in Siamese fighting fish. Science 141:55–57

van Erp AM, Miczek KA (2000) Aggressive behavior, increased accumbal dopamine, and decreased cortical serotonin in rats. J Neurosci 20:9320–9325

van Erp AM, Miczek KA (2007) Increased accumbal dopamine during daily alcohol consumption and subsequent aggressive behavior in rats. Psychopharmacology (Berl) 191:679–688

Wise RA (2004) Dopamine, learning, and motivation. Nat Rev Neurosci 5:483–495

Wise RA, Spindler J, deWit H, Gerberg GJ (1978) Neuroleptic-induced "anhedonia" in rats: pimozide blocks reward quality of food. Science 201:262–264

Yokel RA, Wise RA (1975) Increased lever pressing for amphetamine after pimozide in rats: implications for a dopamine theory of reward. Science 187:547–549