Pharmacology Biochemistry & Behavior, Vol. 40, pp. 255–259. © Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/91 $3.00 + .00

Conditioned Place Aversion Following the Central Administration of a Novel Dopamine Release Inhibitor CGS 10746B

DANIEL J. CALCAGNETTI[1] AND MARTIN D. SCHECHTER

Department of Pharmacology, Northeastern Ohio Universities College of Medicine, Rootstown, OH 44272-9989

Received 22 March 1991

CALCAGNETTI, D. J. AND M. D. SCHECHTER. *Conditioned place aversion following the central administration of a novel dopamine release inhibitor CGS 10746B.* PHARMACOL BIOCHEM BEHAV **40**(2) 255–259, 1991.—Numerous drugs of abuse that elevate brain extracellular dopamine concentrations by either increasing the firing rate of dopaminergic neurons or producing dopamine release have been shown to reliably condition a preference for place. If dopamine release is a necessary component for conditioned place preference (CPP), one reciprocal hypothesis may be that inhibition of dopamine release will result in conditioned place aversion (CPA). This hypothesis has been tested pharmacologically by employing CGS 10746B (CGS), a novel neuroleptic known to inhibit the release of dopamine via presynaptic mechanisms. In previous work the peripheral administration of CGS (1.25–20 mg/kg) produced place aversion at doses above 5 mg/kg. However, the contribution of peripheral mechanisms in the production of CGS-induced CPA is unknown. To test whether central administration of CGS would also result in CPA, rats were fitted with chronic intraventricular cannula. Groups of rats subsequently received four conditioning trials with one of four intraventricular (ICV) doses of CGS (1–30 μg) when confined to their preferred side of a place conditioning apparatus. Vehicle was similarly administered on four interspersed days prior to confining these same rats to their nonpreferred side of the apparatus. At the conclusion of these eight conditioning trials, the rats were tested, on separate days, in a nondrugged and a CGS-drugged state. The highest dose of CGS (30 μg) produced a CPA as evidenced by rats spending less time in the environment initially found to be preferred. Locomotor activity was also measured over a 30-min period with and without ICV injection of CGS (1–30 μg). Activity was not reliably decreased at any dose tested in comparison to baseline. In conclusion, centrally administered CGS produces a CPA suggesting that inhibition of dopamine release contributes to place aversion conditioning.

Dopamine CGS 10746B Locomotor activity Conditioned place preference/aversion

SEVERAL drugs of abuse are believed to share a common mechanism of action in that they raise brain extracellular dopamine concentrations (6). This may be accomplished either directly by increasing the firing rate of dopaminergic neurons (7), or indirectly, by increasing the release of dopamine into the synapse via a mechanism independent of neural firing (4). Dopaminergic neural systems are believed to play a major role in the rewarding aspects of feeding (11), male sexual motivation (30), self-stimulation (29,31), drug self-administration (10) and place preference conditioning (12,20) in rats. These and other observations have led to the suggestion that dopamine release is necessary to confer "motivational relevance" in the expression of motivated behaviors (1). In accord with results from animal research, there is much evidence that supports the hypothesis that neural dopaminergic systems play a similar role in the development of stimulant drug abuse in humans [for review see (3, 14, 31)].

Rats conditioned to associate the environmental stimuli of a cue-specific "place" with a rewarding drug will show a significant increase in the time spent in that place when given a choice between the drug-paired place and a nondrug-paired place. Conversely, rats will spend less time in a place when confinement in that place was paired with a drug producing aversive interoceptive effects. In pharmacological research, place preference conditioning (CPP) has been demonstrated to be an effective method to assess the rewarding, as well as the aversive, effects of drugs of abuse, such as cocaine, amphetamine, morphine and nicotine [for review see (12,25)]. Since it has been hypothesized that these drugs of abuse exert their rewarding effects by increasing extracellular dopamine, one reciprocal hypothesis is the possibility that inhibition of dopamine release during place conditioning will result in a conditioned place aversion (CPA).

This hypothesis has been tested through the use of an atypical antipsychotic of the benzothiadiazepine class labelled CGS 10746B (CGS). CGS has been reported to inhibit dopamine release without interfering with dopamine metabolism or occupying dopamine receptors (2,32). Intraperitoneally administered CGS (1.25–20 mg/kg) has recently been shown to produce a place preference aversion at doses above 5.0 mg/kg (16). Thus peripheral administration of CGS leads to aversive interoceptive

[1]Requests for reprints should be addressed to Daniel J. Calcagnetti, Ph.D., Department of Pharmacology, Northeastern Ohio Universities College of Medicine, P.O. Box 95, 4209 S.R. 44, Rootstown, OH 44272-9989.

cues as indexed by place testing. However, it remains unknown to what degree peripheral and/or central mechanisms are involved in the development of CGS-induced place aversion. To test whether the effects of CGS have a centrally mediated component, rats were fitted with chronic intracerebroventricular (ICV) cannula and confined to their preferred side of a place conditioning apparatus following the administration of one of four doses of CGS (1.0, 5.0, 15 and 30 μg/rat) chosen as 1/100th (8,18) of the effective peripheral dose (16). Peripherally administered CGS was also reported to significantly decrease locomotor behavior (16). Therefore, locomotor activity was also measured with, and without, ICV administered CGS.

METHOD

Subjects

Adult male rats of Sprague-Dawley descent, weighing 175–195 g upon arrival, were purchased from Zivic-Miller Laboratories Inc. (Allison Park, PA). All subjects were individually housed in stainless steel hanging cages equipped for ad lib access to food (Purina 5008) and water. They were maintained in a colony room with a constant temperature and humidity on a 12:12-h light:dark cycle (dark onset at 18:00 h). Place aversion conditioning/testing was conducted in a room separate from the colony room.

Cannula Implantation Surgery and Drug Administration

Rats, 240–330 g at the time of surgery, were anesthetized using 100 mg/kg of ketamine hydrochloride in combination with 0.15 ml injection of xylazine (10 mg/ml, Sigma Chemical). Under aseptic conditions, a stainless steel outer guide cannula (22 gauge; Plastics One, Roanoke, VA) was stereotaxically implanted into the right lateral ventricle using the coordinates: 0.5 mm posterior to bregma, 1.5 mm lateral to midline, and 3.2 mm ventral to the surface of the dura, with the skull level between lambda and bregma. Subjects were allowed a 7-day postsurgical recovery interval prior to the start of conditioning. All manipulations with the rats complied with the "Guide for the Care and Use of Laboratory Animals," Department of Health, Education and Welfare Publication, 1985.

Intracerebroventricular (ICV) injections were performed by backloading the drug solution up a 28-gauge internal cannula (Plastics One, Roanoke, VA) via a length of PE-20 tubing affixed to a 25 μl Hamilton microsyringe. The internal cannula was cut to extend 0.5 mm beyond the guide cannula.

CGS 10746B [5-(4-methyl-1 piperazinyl)-imidazol(22, 1-b) [1,3,5] benzothiadiazepine maleate] (CIBA-GEIGY Corp., Summit, NJ) was dissolved in sterile 0.9% saline which also served as the vehicle control injection. All doses tested (1, 5, 15 and 30 μg/rat) are expressed as the salt and were administered in an injection volume of 5 μl. Drug solution was delivered at a rate of 1 μl/5 s while each subject was gently held by hand. The inner cannula remained in place for 10 s after the drug injection to allow for pressure equalization and for the complete delivery of the drug.

Testing of Cannula Patency and Histological Verification of Placement

In order to test cannula patency behaviorally, subjects underwent several postsurgical treatment phases: the determination of baseline angiotensin II (AGII)-induced drinking, followed by place preference conditioning/testing with CGS and, in the last phase, subjects underwent a second measurement of AGII dipsogenic activity to reconfirm cannula patency. Thus cannula patency was tested by measuring water intake following ICV angiotensin II administration (40 ng/5 μl) before and after CPP testing. Rats that failed to drink at least 5 ml of water by 15 min after AG II administration were excluded from subsequent testing.

After the last phase of AGII testing, all subjects underwent histological verification of cannula placements. Each subject was overdosed with sodium pentobarbital (200 mg/kg) and injected ICV with 4 μl of Staedtler (#C745) ink. Approximately 10 min after injection of the ink, each subject was perfused transcardially with physiological (0.9%) saline followed by a solution of buffered formalin (10%). The brains were rapidly removed and bathed in formalin. Twenty-four h later, coronal sections were made in the brains along the cannula tract. Positive cannula placement was verified visually by the presence of ink throughout the ventricles. Only those subjects for which positive placement was visually verified were included in the results. Several subjects were excluded from the analyses resulting in unequal group sizes and differences in baselines among matched CPP dose groups. However, the exclusions failed to produce statistically significant differences between the matched baseline group means.

Conditioned Place Preference Apparatus and Procedure

Place conditioning/testing was conducted in one of four modular test component units (Lafayette Inst. Co., IN). The three-chambered stainless steel apparatus consisted of a center section through which the subjects were allowed access into two end sections. A constraint wall served to restrict a subject's egress from the right or left side of the apparatus during conditioning.

The right and left end sections ($20.5 \times 30.5 \times 20$ cm), originally identical, were altered in three sensory modalities to provide the following discriminable cues: the "dark" side of each unit was illuminated by a 6-W, 30-V red light bulb and had a smooth black plastic floor. The "light" side had white plastic walls, was illuminated with a 6-W, 30-V white light bulb and had a grid floor over pine shavings in the drop pan. Location throughout the chamber was detected by weight pivot sensors connected to a computer that automatically recorded the time (in s) spent in each section of the apparatus.

Subjects underwent three treatment phases: habitation/baseline testing, drug conditioning and place preference testing. All subjects were given 2 days of habituation to the conditioning room and 15 min of free access in the place testing apparatus. On the third day, 15 min of free access served to establish a "preconditioning baseline" of place preference per subject. The side in which the rats spent more time (in s) was considered its preferred side for the remainder of the study. Given the establishment of side preference baseline, the subjects were ranked from the highest to lowest time (in s) spent in their preferred side in blocks of four. Subjects were then randomly assigned to one of four dose groups (1.0, 5.0, 15 or 30 μg/rat). Place conditioning was then initiated and conducted daily for 30 min.

The drug conditioning phase consisted of four days of confinement in the preferred side after administration of CGS, alternated with four days of confinement in the nonpreferred side after vehicle injection. Rats were placed in the apparatus immediately after ICV administration of vehicle or drug. Twenty-four h following the 8th (last) day of conditioning, each subject was allowed free access, as on the baseline day, for 15 min to determine place preference in a nondrugged state. On the following

TABLE 1

MEAN AND STANDARD ERROR OF THE MEAN (SEM), TIME (S) SPENT IN THE PREFERRED SIDE OF THE CPP APPARATUS DURING BASELINE, TESTING WITHOUT CGS AND TESTING WITH ICV ADMINISTERED CGS

		Dose of ICV Administered CGS (μg/rat)			
		1.0 (n=8)	5.0 (n=8)	15 (n=8)	30 (n=10)
Baseline	Mean	472.1	450.4	448.6	536.2
	SEM	(58.8)	(38.2)	(56.9)	(55.1)
Without CGS	Mean	362.5	335.4	471.5	288.1*
	SEM	(33.7)	(33.7)	(35.9)	(43.2)
% Change		−23.3	−25.5	+5.1	−46.3
With CGS	Mean	380.5	360.7	350.0	359.9*
	SEM	(47.7)	(39.8)	(41.0)	(47.3)
% Change		−19.4	−20.0	−22.0	−33.1

*Significant difference from baseline, Newman-Keuls test; $p<0.05$.

The exclusion of subjects based on histological results resulted in unequal group sizes which failed to produce significant differences in the baseline matched CPP dose groups.

day, subjects were again allowed free access in the place apparatus immediately after an ICV injection of CGS. This allowed for a comparison between nondrugged and drugged-state performance of place preference/aversion testing.

Spontaneous Locomotor Activity

Activity was measured by the interruption of one of four photosensor light sources placed in the wall of a 45.5 × 35.5 × 20.5 cm Plexiglas cage. The sensors were oriented 5.5 cm above the floor and 9.5 cm apart along the wall of the longer side. Each photocell interruption constituted one activity count. Activity counts were recorded from four cages by a computer at 5-min intervals throughout the 30-min testing sessions. Activity testing was conducted in the light and began immediately after the ICV administration of vehicle on the day of nondrug CPP testing. On the day after CPP + drug testing, locomotor activity was again measured following the ICV administration of CGS (1.0, 5.0, 15 and 30 μg/rat). Rats remained in their assigned dose groups and received the same dose of CGS as they did during CPA conditioning. Once again, rats were placed into the apparatus immediately after ICV administration of drug.

Measurements and Statistics

The critical measurement was the actual time (in s) that the subjects spent in the preferred side of the apparatus during CPP testing without and, then, with CGS compared to their baseline. Thus measurements of the time spent in the preferred chamber of the place apparatus were analyzed by two-factor analysis of variance (ANOVA) with four levels of dose and repeated measures on the three levels of days of place testing (28). Where appropriate, these measurements were compared post hoc by Newman-Keuls test (28). Additionally, ANOVA and Newman-Keuls were used to analyze activity measurements given a similar design. The level of statistical significance was set at $p<0.05$.

RESULTS

The time (s) that rats in each of four CGS dose groups spent in the preferred side of the CPP apparatus were subjected to two-factor ANOVA with repeated measures on the days of CPP testing (baseline testing and postconditioning with and without CGS). The factor for dose failed to reveal a reliable main effect, $F(3,30)=0.27$, $p=0.84$, whereas the main effects of the repeated factor for days of CPP testing revealed significant differences, $F(2,60)=12.0$, $p<0.01$. The interaction was also significant, $F(6,60)=2.3$, $p<0.05$.

As dose was not a reliable factor, Newman-Keuls analyses were conducted only between treatment days within each dose of CGS. The baseline s spent in the preferred side of the place preference apparatus, failed to reliably differ ($qs<3.0$; $ps>0.05$) for rats given the three lowest doses of CGS (1.0, 5.0 and 15 μg/rat) tested. However, Newman-Keuls comparisons revealed significant differences from CPP baseline and postconditioning CPP testing without ($q=5.1$, $p<0.01$) and with ($q=3.6$, $p<0.05$) CGS for rats in the 30 μg dose group. These results demonstrate that rats in the CGS 30 μg dose group spent significantly less time in the preferred side of the apparatus when tested with (a 43.6% decrease) and without (a 33.1% decrease) CGS compared to baseline. Thus it appears that conditioning with the 30 μg dose of CGS produced a place aversion that was maintained regardless of whether the rats were tested without CGS or just following the ICV injection of CGS. The mean (and standard error of the mean) of the s spent in the preferred side of the CPP apparatus during baseline and postconditioning with and without ICV administered CGS are presented in Table 1.

Two-factor ANOVA on activity scores revealed a significant main effect for dose, $F(3,30)=6.2$, $p<0.003$. However, the main effect of measurements from drug and vehicle treatment days failed to reveal significant differences, $F(1,30)=0.38$, $p=0.12$. The interaction was also nonsignificant. Subsequent analyses with Newman-Keuls failed to reveal reliable differences between vehicle and drug treatments within dose groups. As it was not possible to equate baseline activity between dose groups because the groups were already matched by CPP baseline, post hoc tests between dose groups were not performed. The important comparisons were between vehicle and drug treatments within each dose. As the simple main effects between vehicle and drug treatments failed to show reliable differences, these results demonstrate that CGS did not significantly decrease activ-

TABLE 2

MEAN (SEM) PHOTOCELL INTERRUPTIONS PER 30-MIN PERIOD AFTER VEHICLE AND CGS ADMINISTRATION AS A MEASURE OF ACTIVITY

		Dose of ICV Administered CGS (μg/rats)			
		1.0 (n=8)	5.0 (n=8)	15 (n=8)	30 (n=10)
Vehicle	Mean	316.1	277.1	205.8	230.3
	SEM	(30.1)	(32.5)	(47.1)	(28.1)
CGS	Mean	323.1	359.6	219.1	186.4
	SEM	(19.7)	(34.3)	(29.2)	(24.2)
% Difference		+2.2	+22.5	+6.1	−26.2

ity scores compared to vehicle injections. Table 2 shows the mean and SEM for activity scores following the ICV injection of vehicle and CGS, as measured by photocell interruptions over a 30-min period immediately after ICV administration of vehicle and CGS.

DISCUSSION

Several dopamine receptor antagonists have been found to produce neutral effects when tested for place preference affects. Thus spiroperidol and d-butaclamol (13), haloperidol (15, 21–23), pimozide (3) and sulpiride (9) have all been shown to produce neither a CPP nor a CPA. In addition, all of these agents have been systemically administered. CGS 10746B is an atypical antipsychotic which has been reported to decrease dopamine release without either changing dopamine metabolism or occupying dopaminergic receptors (2). Thus this agent may allow for a third mechanism to decrease dopaminergic activity, i.e., one differing from inhibition of catecholamine biosynthesis or postsynaptic dopaminergic blockade.

The three lowest doses of CGS tested had no significant effect upon place preference. Central administration of 30 μg of CGS in rats confined to their preferred side in a place testing apparatus resulted in a significant ($p<0.05$) CPA, with a reduction of the time spent in the initially preferred side. CPA was observed regardless of whether or not rats received an ICV administration of CGS just prior to testing suggesting that the shift in preference was not due to the presence of drug during testing (17). That is, it is possible that the inability to express a preference for a cue specific place may reside in the fact that training and testing are conducted in different drug states. Previous work found that amphetamine produced a robust CPP when the testing occurred in a drug or nondrugged state (19). Similar results were reported from other investigators when either morphine (17) or diazepam (24) were used as drugs to produce CPP. In reference to producing a CPA, Swerdlow et al. (27) found that CCK produced a place aversion when rats were tested with or without the drug. A similar CPA produced by ethanol was clear whether the subjects were drugged or undrugged (5). It is of interest to note that the CPA obtained with the 30 μg dose of CGS during place preference testing without drug was slightly larger than during testing with drug.

It has been reported that peripheral administration of CGS (5.0–20 mg/kg) produced both a CPA and a significant decrease in locomotor activity (16). It is unknown to what degree this decrease in activity contributes to place aversion. In contrast, many reports have linked the production of a CPP with increased locomotor behavior after conditioning with psychostimulants (12). In fact, one group of investigators has suggested that preference may be related to increased exploration due to hypermotility (26). Importantly, there was no significant change in activity at any dose of CGS tested and this suggests that the place aversion produced by the 30 μg dose of CGS was not due to a decrease in the subjects' activity level. To our knowledge, there have been no reports of ICV administered drugs which act at dopaminergic neural systems to produce CPA without attenuating locomotor behavior. In general, dopaminergic antagonists (e.g., haloperidol and pimozide), at doses which produce place aversions, also decrease activity (3, 21, 23).

One research group has hypothesized that increased brain dopamine release confers "motivational relevance" to a given situation (1). One assumption of CPP testing is that drugs of abuse interact with neural mechanisms via specific biochemical mechanisms that produce their rewarding effects which, in turn, result in the formation of a preference so that subjects spend more time in the drug-paired environment. Thus the mechanism of action by which amphetamine and related stimulants are believed to produce condition place preference is by increasing the extracellular levels of neural dopamine (16,20). Additional support for this view resides in the observation that drugs which block dopamine receptors (SCH 23390, sulpiride, haloperidol and alpha-flupenthixol) effectively prevent amphetamine conditioning of place preference [for review see (12)]. Furthermore, results from 6-hydroxydopamine produced lesions in the mesolimbic dopaminergic pathway has been found to likewise attenuate place conditioning (21). Taken together, these results support the notion that dopaminergic systems have a definite role in the development of CPP.

In conclusion, the present data are consistent with the hypothesis that ICV administration of CGS, which may act by inhibiting neural dopamine release presynaptically, produces CPA. CGS may, therefore, serve as a tool to study the blockade of amphetamine and related stimulant-induced CPP. However, other mechanisms by which CGS may produce CPA, that are not reflected in a change in activity level, cannot yet be ruled out, e.g., toxicity or general malaise.

ACKNOWLEDGEMENTS

We wish to thank Dr. Richard Lovell of the CIBA-GEIGY Corp., Summit, NJ for the generous gift of CGS 10746B. This research was funded by the National Institute of Drug Abuse grant No. 3591 to M.D.S.

REFERENCES

1. Acquas, E.; Carboni, E.; Leone, P.; Di Chiara, G. SCH 23390 blocks drug-conditioned place preference and place aversion: anhedonia (lack of reward) and apathy (lack of motivation) after dopamine-receptor blockade. Psychopharmacology (Berlin) 99:151–155; 1989.
2. Altar, C. A.; Wasley, A. M.; Liebman, J.; Gerhardt, S.; Kim, H.; Welch, J. J.; Wood, P. L. CGS 10746B: an atypical antipsychotic candidate that selectively decreases dopamine release at behavioral effective doses. Life Sci. 39:699–705; 1986.
3. Bozarth, M. A.; Wise, R. A. Heroin reward is dependent on a dopaminergic substrate. Life Sci. 29:1881–1886; 1981.
4. Carboni, E.; Acquas, E.; Frau, R.; Di Chiara, G. Differential inhibitory effects of a 5-HT_3 antagonist on drug-induced stimulation of dopamine release. Eur. J. Pharmacol. 164:515–519; 1989.
5. Cunningham, C. L. Flavor and location aversions produced by ethanol. Behav. Neural Biol. 27:362–367; 1979.
6. Di Chiara, G. In-vivo dialysis of neurotransmitters. Trends Pharmacol. Sci. 11:116–121; 1990.
7. Di Chiara, G.; Imperato, A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc. Natl. Acad. Sci. USA 85:5274–5278; 1988.
8. Feldberg, W.; Sherwood, S. L. Injections of drugs into the lateral ventricle of the cat. J. Physiol. 123:148–167; 1954.
9. Gilbert, D. B.; Dembski, J. E.; Stein, L.; Belluzzi, J. D. Dopamine and reward: conditioned place preference induced by dopamine D2 receptor agonist. Soc. Neurosci. Abstr. 12:938; 1986.
10. Goeders, N. E.; Smith, J. E. Intracranial self-administration methodologies. Neurosci. Biobehav. Rev. 11:319–329; 1984.
11. Hernandez, L.; Hoebel, B. G. Food reward and cocaine increase extracellular dopamine in the nucleus accumbens as measured by microdialysis. Life Sci. 42:1705–1712; 1988.
12. Hoffman, D. C. The use of place conditioning in studying the neuropharmacology of drug reinforcement. Brain Res. Bull. 23:373–387; 1989.
13. Iwamoto, E. T. Place-aversion conditioned by phencyclidine in rats: development of tolerance and pharmacologic antagonism. Alcohol Drug Res. 6:265–276; 1986.
14. Kalix, P. Pharmacological properties of the stimulant khat. Pharmacol. Ther. 48:397–416; 1990.
15. Leone, P.; Di Chiara, G. Blockade of D-1 receptors by SCH 23390 antagonizes morphine- and amphetamine-induced place preference conditioning. Eur. J. Pharmacol. 135:251–255; 1987.
16. Meehan, S. M.; Schechter, M. D. Effect of dopamine release inhibition upon conditioned place preference produced by the psychostimulant cathinone. Pharmacol. Biochem. Behav. Submitted.
17. Mucha, R. F.; Iverson, S. D. Reinforcing properties of morphine and naloxone revealed by conditioned place preferences: a procedural examination. Psychopharmacology (Berlin) 82:241–247; 1984.
18. Rech, R. H. The relevance of experiments involving injection of drugs into the brain. In: Tedeschi, D. H.; Tedeschi, P. R., eds., Importance of fundamental principles in drug evaluation. New York: Raven Press; 1968;325–360.
19. Reicher, M. A.; Holman, E. W. Location preference and flavor aversion reinforced by amphetamine in rats. Anim. Learn. Behav. 5:343–346; 1977.
20. Schechter, M. D. Effect of learned behavior upon conditioned place preference to cathinone. Pharmacol. Biochem. Behav. 38:7–11; 1991.
21. Spyraki, C.; Fibiger, H. C.; Phillips, A. G. Dopaminergic substrate of amphetamine-induced place preference conditioning. Brain Res. 253:185–193; 1982.
22. Spyraki, C.; Fibiger, H. C.; Phillips, A. G. Cocaine-induced place preference conditioning: lack of effects of neuroleptics and 6-hydroxydopamine lesions. Brain Res. 253:195–203; 1982.
23. Spyraki, C.; Fibiger, H. C.; Phillips, A. G. Attenuation of heroin reward in rats by disruption of the mesolimbic dopamine system. Psychopharmacology (Berlin) 79:278–283; 1983.
24. Spyraki, C.; Kanzandjian, A.; Varonos, D. Diazepam-induced place preference conditioning: appetitive and antiaversive properties. Psychopharmacology (Berlin) 87:225–232; 1985.
25. Swerdlow, N. R.; Gilbert, D.; Koob, G. F. Conditioned drug effects on spatial preference. In: Boulton, A. A.; Baker, G. B.; Greenshaw, A. J., eds. Neuromethods series 1—psychopharmacology, vol. 13. Clifton, NJ: Humana Press; 1989:399–446.
26. Swerdlow, N. R.; Koob, G. F. Restrained rats learn amphetamine-conditioned locomotion, but not place preference. Psychopharmacology (Berlin) 84:163–166; 1984.
27. Swerdlow, N. R.; van der Kooy, D.; Koob, G. F.; Wenger, J. R. Cholecystokinin produces conditioned place-aversions, not place-preferences in food-deprived rats: evidence against involvement in satiety. Life Sci. 32:2087–2093; 1983.
28. Tallarida, R. J.; Murray, R. B. Manual of pharmacologic calculations, 2nd ed. New York: Springer-Verlag, 1987.
29. Van Wolfswinkle, L.; Seifert, W. F.; Van Ree, J. Catecholamines and endogenous opioids in ventral tegmental self-stimulation reward. Pharmacol. Biochem. Behav. 30:589–595; 1988.
30. Warner, R. K.; Thompson, J. T.; Markowski, V. P.; Loucks, J. A.; Bazzett, T. J.; Eaton, R. C.; Hull, E. M. Microinjection of the dopamine antagonist cis-flupenthixol into the MPOA impairs copulation, penile reflexes and sexual motivation in male rats. Brain Res. 540:177–182; 1991.
31. Wise, R. A. Brain dopamine reward. In: Cooper, S. J., ed. Theories in psychopharmacology. New York: Academic Press; 1981:103–121.
32. Wood, P. L.; Altar, C. A.; Kim, H. S. Presynaptic inhibition of nigrostriatal dopamine release in the mouse: Lack of cross tolerance between apomorphine, GBL and CGS 10746B. Life Sci. 42:1503–1506; 1988.