Pharmacology Biochemistry and Behavior, Vol. 66, No. 4, pp. 765–770, 2000

0091-3057/00/$–see front matter

ELSEVIER

PII S0091-3057(00)00273-2

Sensitization to Cocaine's Reinforcing Effects Produced by Various Cocaine Pretreatment Regimens in Rats

SUSAN SCHENK AND BRIAN PARTRIDGE

Texas A&M University, Department of Psychology, College Station, TX 77843

Received 10 September 1999; Revised 21 January 2000; Accepted 10 February 2000

SCHENK, S. AND B. PARTRIDGE. *Sensitization to cocaine's reinforcing effects produced by various cocaine pretreatment regimens in rats.* PHARMACOL BIOCHEM BEHAV **66**(4) 765–770, 2000.—A number of studies have demonstrated sensitization to the behavioral effects of cocaine following pretreatment. In most cases, pretreatments have been administered in the test environment. The present study determined the effects of home-cage administrations of cocaine on the acquisition of cocaine self-administration. Initial groups established that the latency to acquisition of cocaine self-administration varied inversely with dose. The effect of cocaine pretreatment on latency to acquisition of cocaine self-administration (0.25 mg/kg/infusion) was then determined in other groups. On each of 5 pretreatment days, separate groups received home-cage administrations of cocaine as either a single injection (20.0 mg/kg), or two (20.0 mg/kg) or three (10.0 mg/kg) injections separated by 1 h. Testing commenced 3 days following the last of the pretreatments. Only the pretreatment consisting of two daily injections of 20.0 mg/kg cocaine decreased the latency to acquisition of self-administration. These data are consistent with a sensitized response to cocaine's reinforcing effects and provide minimum pretreatment conditions for its development.

Sensitization Cocaine Self-administration

PRIOR exposure to a number of stimulants results in an increase in the behavioral response. This sensitized behavioral reponse has been demonstrated following repeated, intermittent exposure to indirect (12,25,33), as well as direct dopamine agonists (11,18,44). The development of sensitization has been proposed relevant to issues concerning variability in the propensity to develop compulsive drug taking (25,26,38,39), and to the ability of various interoceptive and exteroceptive cues to trigger relapse in abstaining abusers (34,40). Studies that have investigated the effects of preexposure on the reinforcing properties of cocaine and other drugs have supported this hypothesis.

Rats that received prior exposure to cocaine demonstrated sensitization to the conditioned reinforcing effects of the drug. These subjects developed a conditioned place preference in response to low cocaine doses that failed to produce this effect in nonexposed animals (17,40–42). The primary reinforcing effects of stimulants also appear to become sensitized as a result of preexposure. For example, following methamphetamine testing, lower doses of the drug maintained reliable self-administration, suggesting a shift to the left in the dose–response curve (48). In tests of the acquisition of stimulant self-administration, preexposure to cocaine decreased the latency to acquisition of self-administration (12), and amphetamine exposure resulted in reliable self-administration of a dose of amphetamine that failed to support operant responding in control rats (20,25,27).

The results of studies on the development of sensitization to cocaine's motor-activating effects have suggested that the environment in which cocaine is administered prior to the test is a critical determinant (1–4,35). Some studies have suggested that pretreatments administered in the test environment may be more effective than pretreatments administered in an alternate environment, or that different preexposure parameters may be required to produce sensitization, depending on the preexposure environment (28–30).

In a previous study, daily test-cage administrations of cocaine decreased the latency to the subsequent acquisition of cocaine self-administration (12,13). Because the latency to acquisition of self-administration is inversely related to the dose

Requests for reprints should be addressed to S. Schenk, Texas A&M University, Department of Psychology, College Station, TX 77843.

of cocaine available for self-administration, this suggests (36,37) that the effects of pretreatment are consistent with sensitization to cocaine's reinforcing effects. Recently, we demonstrated that sensitization to cocaine's locomotor-activating effects produced by pretreatments administered in the home cage reflected a leftward shift in the dose–effect curve, consistent with increased potency (22,23). Minimal effects on the efficacy of cocaine were produced. However, the effect of a similar regimen of home-cage administrations of cocaine on the reinforcing effects have not been examined. Therefore, the present parametric study examined the effect of a number of cocaine pretreatment regimens, administered in the home cage, on the development of cocaine self-administration. Additionally, dose–effect relationships for the latency to acquisition of cocaine self-administration were measured.

METHOD

Subjects

Male Sprague–Dawley rats (Harlan, TX), weighing 325–350 g, were used. They were housed individually in hanging polycarbonate cages. The humidity and temperature controlled colony at Texas A&M University was kept on a 12:12-h light condition, with lights on at 0800 h. Food and water were freely available except during testing.

Surgery

A chronic indwelling Silastic catheter was implanted in the right jugular vein. The rats were deeply anesthetized with ketamine (60.0 mg/kg) and pentobarbital (20.0 mg/kg). The external jugular vein was isolated, the catheter inserted and the distal end (22 ga stainless steel tubing) was passed subcutaneously to an exposed portion of the skull where it was fixed to embedded jeweler's screws with dental acrylic. Each day, the catheters were infused with 0.1 ml of a sterile saline solution containing heparin (1.25 U/ml), penicillin G Potassium (250,000 U/ml), and streptokinase (8000 IU/ml) to prevent infection and the formation of clots and fibroids. The rats were allowed 5 days afte surgery for recovery. Sample sizes for each group are indicated in the Procedures section, and represent the number of subjects (generally 75–80%) that completed testing with patent catheter lines. At the completion of testing, patency was confirmed by the immediate loss of the righting reflex following an infusion of sodium pentobarbital (15.0–20.0 mg/kg, IV).

Apparatus

Self-administration testing was carried out in operant chambers (Med Associates, ENV-001) equipped with two levers. Depression of one lever (the active lever) resulted in an intravenous infusion of cocaine HCl, dissolved in sterile physiological saline and heparin (3 U/ml). Depression of the other lever (the inactive lever) was without programmed consequence. Drug delivery and data acquisition were controlled by the OPN software package (43,45). Cocaine deliveries were made via mechanical pumps (Razel Model A with 1 rpm motor equipped with 20.0-ml syringes) in a volume of 0.1 ml over 12.0 s. Coincident with drug delivery was the illumination of a stimulus light located above the active lever.

Procedures

Experiment 1: Acquisition of cocaine self-administration as a function of dose. Three groups of rats were used to determine the effect of cocaine dose on latency to acquisition of self-administration. Each of these groups received a different dose of cocaine [0.125 (n = 15), 0.25 (n = 12), or 0.5 (n = 15) mg/kg/infusion) during 8 (0.5 mg/kg/infusion) or 10 (0.125 and 0.25 mg/kg/infusion) daily 2-h tests. Each daily test began with an experimenter-delivered infusion of the available dose of cocaine (0.125, 0.25, or 0.50 mg/kg/infusion). Thereafter, infusions were delivered according to an FR-1 schedule of reinforcement by depression of the active lever. Responses on both the active and inactive levers were recorded for each daily session.

Experiment 2: Effects of cocaine pretreatment on acquisition of self-administration. retreatment phase—separate groups of rats received preexposure to cocaine or the saline vehicle in the home cage during 5 pretreatment days. Groups received either a single daily intraperitoneal injection of 20.0 mg/kg (n = 18), three daily intraperitoneal injections of 10.0 mg/kg (n = 15), or two daily intraperitoneal injections of 20.0 mg/kg (n = 11) cocaine. Multiple daily injections, delivered in a volume of 1.0 ml/kg, were separated by 1 h. An additional group received a single daily injection of 40.0 mg/kg cocaine during the pretreatment phase. However, 50% of the rats developed seizures or died prior to completion of the 5-day pretreatment period and, therefore, data from this group are not included.

Acquisition of cocaine self-administration—3 days following the last of the pretreatment injections, the acquisition of cocaine self-administration (0.25 mg/kg/infusion) was measured during eight daily 2-h sessions. On these days, the session began with an experimenter administered priming infusion of cocaine (0.25 mg/kg/infusion). Thereafter, infusions were delivered according to an FR-1 schedule of reinforcement by depression of the active lever. Inactive lever responses were recorded but had no programmed consequences.

Data Analysis

Repeated-measures ANOVAs were conducted on the number of active and inactive lever responses as a function of days. When appropriate, pairwise comparisons were conducted using Tukey post hoc tests.

Acquisition data were obtained by applying a criterion consisting of a minimum of 7.5 mg/kg/day intake and a minimum of 2:1 ratio active:inactive lever responses to the self-administration data. Acquisition was defined as the first day that this criterion was met for 3 consecutive days. The cumulative percentage of subjects that acquired cocaine self-administration over days was compared for various groups using chi-square analysis. Additionally, the number of days to acquisition of cocaine self-administration was compared for the saline-pretreated rats and rats from each of the cocaine pretreatment conditions.

Drugs

Cocaine HCl (National Institute of Drug Abuse) was dissolved in sterile physiological saline. Intravenous infusions were delivered in a volume of 100 μl, and intraperitoneal injections were delivered in a volume of 1.0 ml/kg.

RESULTS

Figure 1 shows the mean number of active (top panel) and inactive (bottom panel) lever responses as a function of days and cocaine dose during the acquisition of self-administration. For all dosage groups, active lever responding gradually increased over days, whereas inactive lever responses remained fairly low. A repeated-measures ANOVA (dose ×

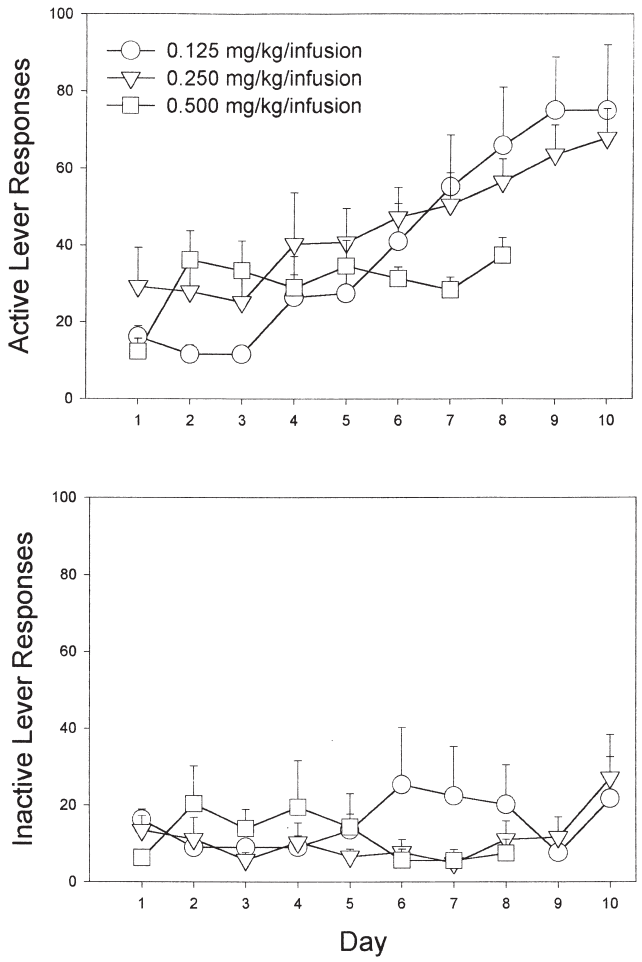

FIG. 1. Effect of cocaine dose on cocaine self-administration. Top panel shows the number of active lever responses as a function of test day and cocaine dose. Bottom panel shows the number of inactive lever responses as a function of test day and cocaine dose. The effect of increasing cocaine dose was to increase the number of active lever responses during the early test sessions and to decrease the number of active lever responses during the latter test sessions.

days) on the active lever responses from the first 8 days of testing revealed a significant effect of day, $F(7, 273) = 9.047$, $p < 0.001$, as well as a significant interaction between day and dose, $F(7, 273) = 2.553$, $p = 0.011$. Responding for the 0.25 and 0.50 mg/kg/infusion groups was higher than responding of the 0.125 mg/kg/infusion group on days 2 and 3 ($p < 0.05$). On days 7 and 8, responding of the 0.5 mg/kg/infusion group was lower than responding of either the 0.125 or 0.25 mg/kg/infusion groups ($p < 0.05$).

Figure 2 shows the cumulative percentage of subjects that acquired cocaine self-administration as a function of days and cocaine dose. The curve for the 0.50 mg/kg group is displaced to the left of the curve for the 0.25 mg/kg/infusion group, which is displaced to the left and up of the curve for the 0.125 mg/kg/infusion group. A higher percentage of subjects acquired cocaine self-administration during the early test days when the higher dose of cocaine was available. Whereas 50% of the subjects in the higher dose group acquired cocaine self-administration by the third test day, 5 and 9 days were required for 50% of the subjects to acquire self-administration in the 0.25 and 0.125 mg/kg/infusion groups, respectively. Chi-square analysis confirmed that the latency to acquisition for the 0.5 and 0.25 mg/kg/infusion groups was shorter than for the 0.125 mg/kg/infusion group, $\chi^2(2) = 18.294$, $p < 0.001$.

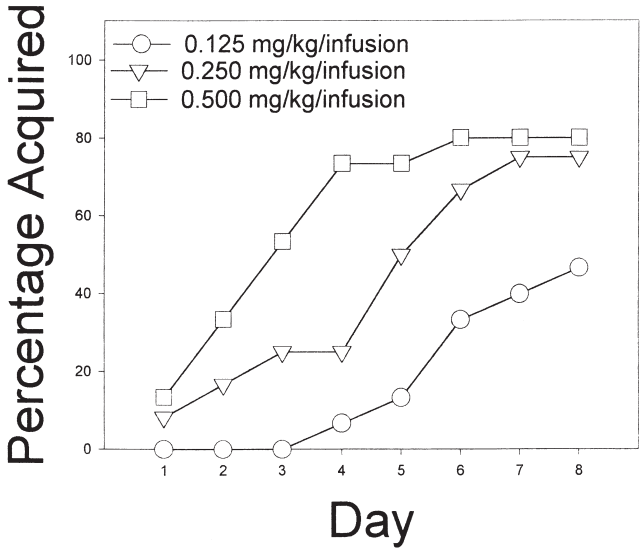

FIG. 2. Cumulative percentage of subjects that acquired cocaine self-administration on each day as a function of cocaine dose. A higher percentage of rats acquired self-administration during the early days of testing when a higher dose of cocaine was available.

Figure 3 shows the number of active (top panel) and inactive (bottom panel) lever responses as a function of pretreatment regimen and day of testing. Inactive lever responding was low for all groups. There was a tendency for active lever responding to be higher in the groups that received cocaine pretreatment when compared to the group that received saline pretreatment. An ANOVA (pretreatment condition $\times$ day) on the number of active lever responses revealed a main effect of day, $F(7, 441) = 2.208$, $p = 0.033$, and an interaction between day and pretreatment, $F(7, 441) = 2.870$, $p = 0.006$. Active lever responses for the group that received the pretreatment consisting of 2×20 mg/kg cocaine was higher than the group that received saline on days 5, 6, 7, and 8 ($p < 0.05$). A higher rate of responding was also obtained for the group that received the pretreatment consisting of 1×20.0 mg/kg cocaine on days 7 and 8 when compared to the saline-pretreated group.

Figure 4 shows the cumulative percentage of subjects that acquired cocaine self-administration as a function of days and pretreatment condition. There was a tendency for a higher percentage of cocaine-pretreated rats to acquire cocaine self-administration during the early days of testing. However, the acquisition curves for the saline pretreated rats and for the groups that received 1×20.0 mg/kg cocaine ($\chi^2 = 1.53$, NS), or 3×10.0 mg/kg cocaine ($\chi^2 = 2.24$, NS) were not significantly different. In contrast, rats that received the pretreatment regimen consisting of two daily injections of 20.0 mg/kg cocaine acquired cocaine self-administration with a shorter latency than rats that received saline pretreatment ($\chi^2 = 8.14$, $p < 0.01$).

Table 1 shows the average number of days required for the acquisition of cocaine self-administration for the various groups. Latency to acquisition was significantly shorter for the 2×20.0 mg/kg, $t(11, 21) = 129.5$, $p = 0.041$, pretreatment group.

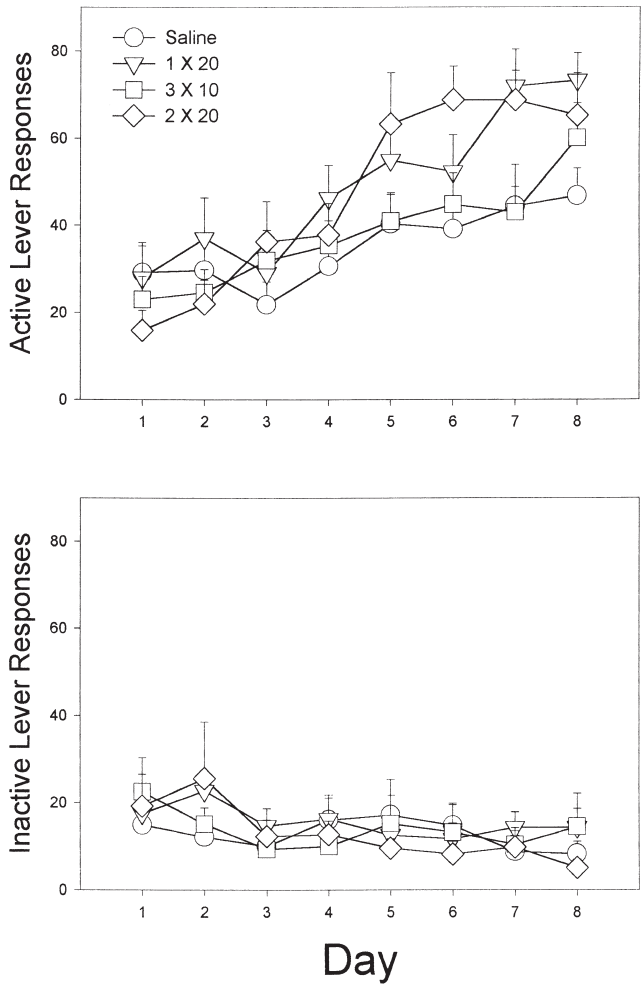

FIG. 3. Effect of cocaine preexposure on acquisition of self-administration. Rats received saline or cocaine during 5 pretreatment days. Either single (20.0 mg/kg), double (20.0 mg/kg each), or triple (10.0 mg/kg each) daily injections were administered during preexposure. Acquisition of cocaine self-administration began 3 days following the last of the pretreatments. Top panel shows active lever responses and bottom panel shows inactive lever responses during each day of an 8-day test period. The pretreatment consisting of two daily injections of cocaine (20.0 mg/kg) increased actgivve lever responding for cocaine during the later test days.

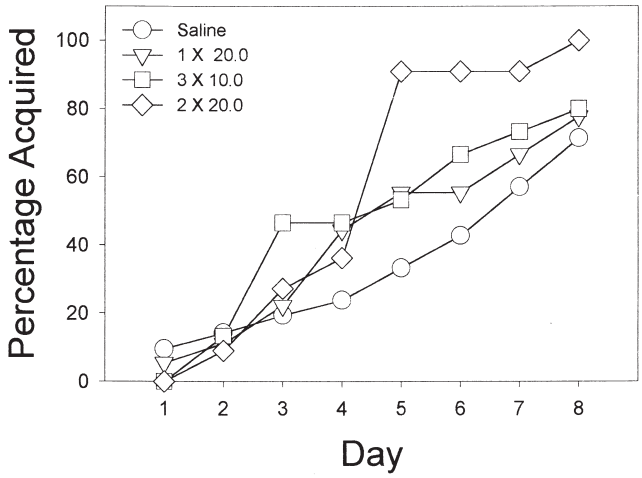

FIG. 4. Cumulative percentage of subjects from each pretreatment group that acquired cocaine self-administration on each test day. Pretreatment with two daily injections of cocaine shifted the acquisition curve for cocaine self-administration to the left of saline pretreated rats.

DISCUSSION

During acquisition of cocaine self-administration, active lever responses increased gradually over days. During the early test days, the number of responses was greater when the higher dose (0.50 mg/kg/infusion) was available than when the lower cocaine dose (0.125 mg/kg/infusion) was available. Acquisition curves for cocaine self-administration indicated an inverse relationship between cocaine dose and latency to acquisition. These data are consistent with those reported previously (10,36,37). With extended testing, a higher percentage of subjects generally acquire cocaine self-administration (10,21). The protracted development of cocaine self-administration suggests that for some subjects, cocaine, while not initially very effective in reinforcing operant behavior, becomes an effective reinforcer with repeated exposure.

A major effect of increasing the dose of cocaine available for self-administration was a shift to the left in the acquisition curve; more rats acquired self-administration during the early test days. That is, higher doses of cocaine resulted in faster acquisition rates. This same effect was obtained for rats that received the pretreatment consisting of 2 daily injections of 20.0 mg/kg cocaine for 5 days. The decreased latency to acquisition of self-administration is consistent with the effect of increasing the dose of cocaine available for self-administration.

The decreased latency to acquisition of cocaine self-administration suggests that cocaine preexposure sensitized rats to the reinforcing effects of cocaine. However, an alternate possibility is that anxiogenic effects of cocaine initially prevented the acquisition of the lever press operant and that tolerance to these effects, as a function of exposure to cocaine, resulted in a decrease in the latency to acquisition. The aversive effects of cocaine are well-documented, but there are data to suggest that these effects become sensitized rather than tolerant following cocaine exposure.

An elegant demonstration of sensitization to the aversive as well as positive effects of cocaine was demonstrated in rats trained to run a runway to receive cocaine infusions. Trials were conducted once daily, and intravenous cocaine was administered in a goal box at the end of a straight alley. Start latencies were short, but with repeated testing the rats would retreat from the goal box rather than entering it, thereby leading to long run times (8). These data suggest that with repeated exposures, the anxiogenic effects of cocaine increased.

TABLE 1

AVERAGE NUMBER OF DAYS TO ACQUISITION OF COCAINE SELF-ADMINISTRATION (SEM) FOR THE VARIOUS PRETREATMENT GROUPS

Saline	6.85 (0.74)
1 × 20.0	6.05 (0.78)
3 × 10.0	5.60 (0.86)
2 × 20.0	4.54 (0.47)*

*$P < 0.05$ compared to saline pretreatment group.

Therefore, the decreased latency to acquisition of cocaine self-administration cannot be attributed to tolerance to the aversive effects of cocaine. Rather, these data are consistent with sensitization to cocaine's positive effects.

The decreased latency to acquisition of cocaine self-administration was only produced following pretreatment with the regimen consisting of two daily injections of 20.0 mg/kg cocaine; three daily injections of 10.0 mg/kg or a single daily injection of 20.0 mg/kg were insufficient to produce sensitization. Because the pretreatments were administered in the home cage, these data provide a minimum preexposure requirement for the development of sensitization when preexposure was administered in an environment distinct from the test environment.

Both the reinforcing (6,7,31,32) and motor activating (16,47) effects of cocaine have been attributed to the ability of cocaine to block the reuptake of mesolimbic dopamine. The development of sensitization to cocaine's motor behavioral effects has been attributed to increased effects within this neurochemical system (10,14,15). A similar mechanism may underlie the development of sensitization to cocaine's reinforcing effects observed in the present study and in a previous study (12). Additionally, sensitization may also reflect cocaine-produced alterations of neurotransmission in areas that underlie associative learning processes such as the amygdala (19,24), which has been implicated in cocaine seeking (5,9,46). If so, the ability to learn the lever-press operant to obtain cocaine infusions may have been facilitated through a cocaine-produced strengthening of these associative processes.

ACKNOWLEDGEMENTS

This research was supported by DA 10084.

REFERENCES

1. Badiani, A.; Browman, K. E.; Robinson, T. E.: Influence of novel verses home environments on sensitization to the psychomotor stimulant effects of cocaine and amphetamine. Brain Res. 674:291–298; 1995.
2. Browman, K. E.; Badiani, A.; Robinson, T. E.: The influence of environment on the induction of sensitization to the psychomotor activating effects of intravenous cocaine in rats is dose-dependent. Psychopharmacology (Berlin) 137:90–98; 1998.
3. Carey, R. J.; Gui, J.: Cocaine conditioning and cocaine sensitization: What is the relationship?. Behav. Brain Res. 92:67–76; 1998.
4. Carroll, M. E.; Lac, S. T.: Acquisition of IV amphetamine and cocaine self-administration in rats as a function of dose. Psychopharmacology (Berlin) 129:206–214; 1997.
5. Childress, A. R.; Mozley, P. D.; McElgin, W.; Fitzgerald, J.; Reivich, M.; O'Brien, C. P.: Limbic activation during cue-induced cocaine craving. Am. J. Psychiatry 156:11–18; 1999.
6. DeWitt, H.; Wise, R. A.: 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; 1997.
7. DiChiara, G.: The role of dopamine in drug abuse viewed from the perspective of motivation. Drug Alcohol Depend. 38: 345–348; 1995.
8. Ettenberg, A.; Geist, T. D.: Animal model for investigating the anxiogenic effects of self-administered cocaine. Pharmacol. Biochem. Behav. 103:455–461; 1991.
9. Grant, S.; London, E. D.; Newlin, D. B.; Villemagne, V. L.; Liu, X.; Contoreggi, C.; Phillips, R. L.; Kimes, A. S.; Margolin, A.: Activation of memory circuits during cue-elicited cocaine craving. Proc. Natl. Acad. Sci. USA 93:12040–12045; 1996.
10. Henry, D. J.; Hu, X. T.; White, F. J.: Adaptations in the mesoaccumbens dopamine system resulting from repeated administration of dopamine D1 and D2 receptor-selective agonists: Relevance to cocaine sensitization. Psychopharmacology (Berlin) 140:233–242; 1998.
11. Hoffman, D. C.; Wise, R. A.: Locomotor-activating effects of the D2 agonist bromocriptine show environment-specific sensitization following repeated injections. 107:277–284; 1992.
12. Horger, B. A.; Shelton, K.; Schenk, S.: Preexposure sensitizes rats to the rewarding effects of cocaine. Pharmacol. Biochem. Behav. 37:707–711; 1990.
13. Horger, B. A.; Giles, M. K.; Schenk, S.: Preexposure to amphetamine and nicotine predisposes rats to self-administer a low dose of cocaine. Psychopharmacology (Berlin) 107:271–276; 1992.
14. Kalivas, P. W.; Duffy, P.; DuMars, L. A.; Skinner, L.: Behavioral and neurochemical effects of acute and daily cocaine administration in rats. J. Pharmacol. Exp. Ther. 245:485–492; 1988.
15. Kalivas, P. W.; Stewart, J.: Dopamine transmission in the initiation and expression of drug- and stress-induces sensitization to motor activity. Brain Res. Rev. 16:223–244; 1991.
16. Kelley, P. H.; Iversen, S. D.: Selective 6-OHDA-induced destruction of mesolimbic dopamine neurons; Abolition of psychostimulant-induced locomotor activity in rats. Eur. J. Pharmacol. 40:45–56; 1976.
17. Lett, B. W.: Repeated exposures intensify rather than diminish the rewarding effects of amphetamine, morphine and cocaine. Psychopharmacology (Berlin) 98:357–362; 1989.
18. Mattingly, B. A.; Gotsick, J. E.: Conditioning and experiential factors affecting the development of sensitization to apomorphine. Behav. Neurosci. 103:1311–1317; 1989.
19. Mcintosh, A. R.; Gonzalez-Lima, F.: Large-scale functional connectivity in associative learning: Interrelations of the rat auditory, visual, and limbic systems. J. Neurophysiol. 80:3148–3162; 1998.
20. Mendrek, A.; Blaha, C. D.; Phillips, A. G.: Preexposure of rats to amphetamine sensitizes self-administration of this drug under a progressive ratio paradigm. Psychopharmacology (Berlin) 135: 416–422; 1998.
21. Miczek, K. A.; Mutschler, N. H.: Activational effects of social stress on IV cocaine self-administration in rats. Psychopharmacology (Berlin) 128:256–264; 1996.
22. Mitchell, J. A.; Hall, G.: Learning in rats with caudate-putamen lesions: Unimpaired classical conditioning and beneficial effects of redundant stimulus cues on instrumental and spatial learning deficits. Behav. Neurosci. 102:504–514; 1988.
23. Partridge, B.; Schenk, S.: Context-independent sensitization to the locomotor activating effects of cocaine. Pharmacol. Biochem. Behav. 63:543–548; 1999.
24. Phillips, G. D.; Morutto, S. L.: Post-session sulpiride infusions within the perifornical region of the lateral hypothalamus enhance consolidation of associative learning. Psychopharmacology (Berlin) 140:354–364; 1998.
25. Piazza, P. V.; Deminiere, J. M.; Le Moal, M.; Simon, H.: Factors that predict individual vulnerability to amphetamine self-administration. Science 245:1511; 1989.
26. Piazza, P. V.; Deminiere, J. M.; Le Moal, M.; Simon, H.: Stress and pharmacologically-induced behavioral sensitization increases vulnerability to acquisition of amphetamine self-administration. Brain Res. 514:22–26; 1990.
27. Pierre, P. J.; Vezina, P.: Predisposition to self-administer amphetamine: The contribution of response to novelty and prior exposure to the drug. Psychopharmacology (Berlin) 129:277–284; 1997.
28. Post, R. M.; Lockfield, A.; Squillace, K. M.; Contel, N. R.: Drug-environment interaction: Context dependency of cocaine induced behavioral sensitization. Life Sci. 28:755–760; 1991.
29. Post, R. M.; Weiss, S.; Pert, A.: The role of context and conditioning in behavioral sensitization to cocaine. Psychopharmacol. Bull. 23:423–429; 1987.

30. Post, R. M.; Weiss, S. R.; Fontana, D.; Pert, A.: Conditioned sensitization to the psychomotor stimulant cocaine. Ann. NY Acad. Sci. 654:386–399; 1992.
31. Ritz, M.; Lamb, R. J.; Goldberg, S. R.; Kuhar, M. J.: Cocaine self-administration appears to be mediated by dopamine uptake inhibition. Prog. Neuropsychopharmacol. Biol. Psychiatry 12:233–239; 1988.
32. Ritz, M.; Lamb, R. J.; Goldberg, S. R.; Kuhar, M. J.: Cocaine receptors in dopamine transporters are related to self-administration of cocaine. Science 237:1219–1223; 1987.
33. Robinson, T. E.; Becker, J. B.: Enduring changes in brain and behavior produced by chronic amphetamine administration: A review and evaluation of animal models of amphetamine psychosis. Brain Res. Rev. 11:157–198; 1986.
34. Robinson, T. E.; Berridge, K. C.: The neural basis of drug craving: An incentive-sensitization theory of addiction. Brain Res. 18:247–291; 1993.
35. Robinson, T. E.; Browman, K. E.; Crombag, H. S.; Badiani, A.: Modulation of the induction or expression of psychostimulant sensitization by the circumstances surrounding drug administration. Neurosci. Biobehav. Rev. 22:347–354; 1998.
36. Schenk, S.; Horger, B. A.; Peltier, R.; Shelton, K.: Supersensitivity to the reinforcing effects of cocaine following 6-hydroxydopamine lesions to the medial prefrontal cortex in rats. Brain Res. 543:227–235; 1991.
37. Schenk, S.; Valdez, A.; McNamara, C.; House, D. T.; Higley, D.; Bankson, M. G.; Gibbs, S.; Horger, B. A.: Development and expression of sensitization to cocaine's reinforcing properties: role of NMDA receptors. Psychopharmacology (Berlin) 111:332–338; 1993.
38. Schenk, S.; Partridge, B.: Sensitization and tolerance in psychostimulant self-administration. Pharmacol. Biochem. Behav. 57: 543–550; 1997.
39. Schenk, S.; Davidson, E. S.: Stimulant preexposure sensitizes rats and humans to the rewarding effects of cocaine. NIDA Res. Monogr. 169:56–82; 1998.
40. Shippenberg, T. S.; Heidbreder, Ch.: Sensitization to the conditioned rewarding effects of cocaine: Pharmacological and temporal characteristics. J. Pharmacol. Exp. Ther. 273:808–815; 1995.
41. Shippenberg, T. S.; Le Flour, A.; Thompson, Ch.: K-opioid agonists prevent sensitization to the conditioned rewarding effects of cocaine. J. Pharmacol. Exp. Ther. 276:545–554; 1996.
42. Shippenberg, T. S.; LeFevour, A.; Thompson, A. C.: Sensitization to the conditioned rewarding effects of morphine and cocaine: differential effects of the k-opioid receptor agonist U69593. Eur. J. Pharmacol. 345:27–34; 1998.
43. Spencer, D. G.; Emmett-Oglesby, M. W.: Parallel processing strategies in the application of microcomputers to the behavioral laboratory. Behav. Res. Methods Instrum. 17:294–300; 1985.
44. Szechtman, H.; Dai, H.; Mustafa, S.; Einat, H.; Sullivan, R. M.: Effects of dose and interdose interval on locomotor sensitization to the dopamine agonist quinperole. Pharmacol. Biochem. Behav. 48:921–928; 1994.
45. Szumlinski, K. K.; Allan, M.; Talangbayan, H.; Tracey, A.; Szechtman, H.: Locomotor sensitization to quinperole: Environment-modulated increase in efficacy and context-dependent increase in potency. Psychopharmacology (Berlin) 134:193–200; 1997.
46. Whitelaw, R. B.; Markou, A.; Robbins, T. W.; Everitt, B. J.: Excitotoxic lesions of the basolateral amygdala impair the acquisition of cocaine-seeking behaviour under a second-order schedule of reinforcement. Psychopharmacology (Berlin) 127:213–224; 1996.
47. Wise, R. A.; Bozarth, M. A.: A psychomotor stimulant theory of addiction. Psychol. Rev. 94:469–492; 1987.
48. Woolverton, W. L.; Cervo, L.; Johanson, C. E.: Effects of repeated methamphetamine administration on methamphetamine self-administration in rhesus monkeys. Pharmacol. Biochem. Behav. 21:737–741; 1984.