

BRIEF COMMUNICATION

Preferential Stimulation of D1 or D2 Receptors Disrupts Food-Rewarded Operant Responding in Rats

DIANE C. HOFFMAN¹ AND RICHARD J. BENINGER*Department of Psychology, Queen's University, Kingston, Ontario K7L 3N6*

Received 3 February 1989

HOFFMAN, D. C. AND R. J. BENINGER. *Preferential stimulation of D1 or D2 receptors disrupts food-rewarded operant responding in rats*. PHARMACOL BIOCHEM BEHAV 34(4) 923-925, 1989. — Rats were trained to lever-press for food on a variable interval 30-sec schedule. Following stabilization of response rates, separate groups of rats were treated with saline, the nonselective DA agonists amphetamine or apomorphine, the D1 agonist SKF 38393, or the D2 agonist quinpirole prior to placement in the operant chamber. Treatment with SKF 38393 or quinpirole produced dose-dependent reductions in overall response rates which were similar to those observed with either amphetamine or apomorphine. In addition, treatment with the D2 agonist produced a gradual decline in responding within each test session. These data suggest that preferential stimulation of either D1 or D2 receptors is sufficient in disrupting food-reinforced lever-pressing; furthermore, the extinction-like intrasession decline in responding induced by the D2 agonist suggests that this drug, unlike the others, may have disrupted responding by reducing the reinforcing efficacy of the food.

D2 receptor	D1 receptor	Operant behavior	Amphetamine	Apomorphine
-------------	-------------	------------------	-------------	-------------

A large number of studies have examined the effects of dopaminergic agonists on behavior maintained by the delivery of reinforcing stimuli such as food or water. The effects of (+)-amphetamine, cocaine, and methylphenidate have been described as rate-dependent; these compounds enhance low rates of responding and suppress high rates (3,6). In contrast, treatment with the direct-acting agonist apomorphine results in a uniform reduction regardless of baseline rate (3).

Variable interval (VI) schedules of reinforcement tend to produce high levels of responding, and although exceptions do exist (4,5), recent studies have demonstrated predominantly dose-dependent decreases in responding in animals treated with (+)-amphetamine (7). Two different DA receptor subtypes have been identified, and the present series of experiments investigated the involvement of D1 and D2 receptors in the disruption of operant behavior. Thus, the effects of the selective D1 agonist SKF 38393 and the D2 agonist quinpirole on food-reinforced lever-pressing were assessed and compared to the effects of the nonselective DA agonists amphetamine and apomorphine.

Currently, there is disagreement over whether the suppressant action of dopaminergic agonists results from a motor impairment or an effect on reinforcement mechanisms [cf. (2,5)]. To provide further information regarding this issue, the present study also

looked at the temporal pattern of response rates throughout the session (intrasession profile) and over repeated test sessions (intersession profile) in drug-treated animals. This approach has previously been useful when interpreting the rate-reducing effects of DA receptor *antagonists* [cf. (8)]. For example, in rats treated with DA antagonists, responding was affected relatively little at the beginning of the session, but gradually declined over the remaining time period; in addition, with repeated daily tests of the same dose, there was a day to day decline in response rates. These intra- and intersession declines resemble responding during extinction suggesting that the reinforcing stimulus was losing its effectiveness in maintaining the lever-press response. Furthermore, because the drug-treated animals were capable of responding in the initial portion of the session, a nonspecific motor impairment seemed to be an inadequate explanation for the disruption of response rates. The intra- and intersession response profiles of animals treated with DA receptor *agonists* have not been reported previously, and, therefore, were examined in the current experiments in an attempt to discriminate between possible interpretations.

METHOD

Food-deprived male Wistar rats (maintained at 80% of free-

¹Requests for reprints should be addressed to Diane C. Hoffman, Ph.D., Center for Studies in Behavioral Neurobiology, Department of Psychology, Concordia University, 1455 de Maisonneuve Blvd. West, Montreal, Canada H3G 1M8.

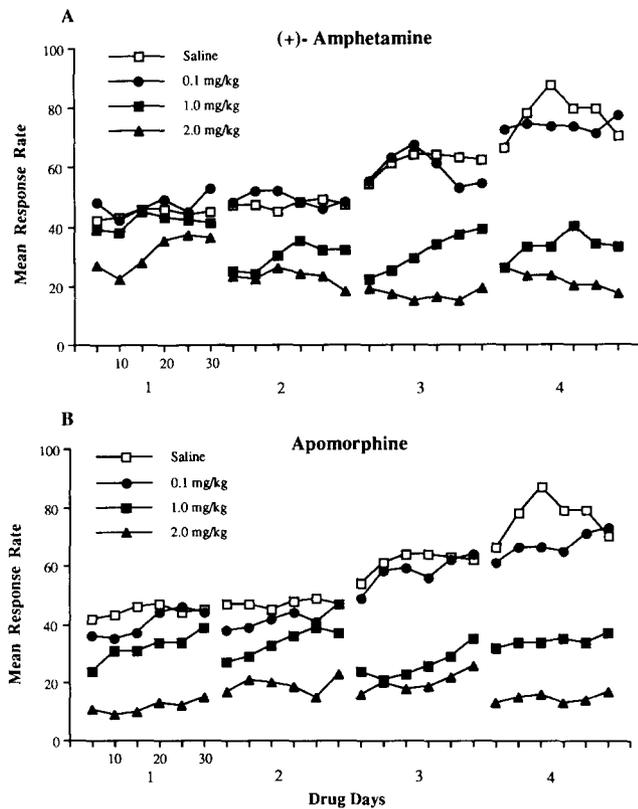


FIG. 1. Mean responses per min for each 5-min segment of the four 30-min drug tests in rats treated with amphetamine (A) or apomorphine (B). The saline group is shown in both panels.

feeding weight) were trained to lever press for 45-mg food pellets (Bioserv) on a VI 30-sec schedule of reinforcement [see (1) for description of operant conditioning chambers]. Following stabilization of response rates (i.e., responding on 3 consecutive days did not deviate more than 10% from the average rate of those 3 days), separate groups of rats ($n=8$) were treated with saline, the nonselective agonists (+)-amphetamine sulphate (0.1, 1.0, 2.0 mg/kg IP) or apomorphine hydrochloride (0.1, 1.0, 2.0 mg/kg IP), the D1 agonist SKF 38393 hydrochloride (1.0, 10.0, 20.0 mg/kg IP), or the D2 agonist quinpirole hydrochloride (0.01, 0.1, 1.0 mg/kg IP) prior to placement in the operant chamber. All drugs were dissolved in distilled water except apomorphine which was dissolved in 0.1% ascorbic acid in distilled water. Each group of animals received only one dose, but the effects of the one dose were repeated on three additional days; each drug day was separated by 2 intervening baseline days during which no drug was given.

RESULTS

Response rates at 5-min intervals within each of the four repeated drug sessions are illustrated in Fig. 1 for the nonselective agonists and in Fig. 2 for the selective receptor agonists. In general, treatment with SKF 38393 and quinpirole produced significant dose-dependent reductions in responding ($p<0.05$) which were similar to those observed with amphetamine and apomorphine.

In either the 2.0 mg/kg amphetamine group or the 10.0 mg/kg SKF 38393 group, a progressively larger drug effect occurred over repeated tests ($p<0.05$). It was observed, however, that

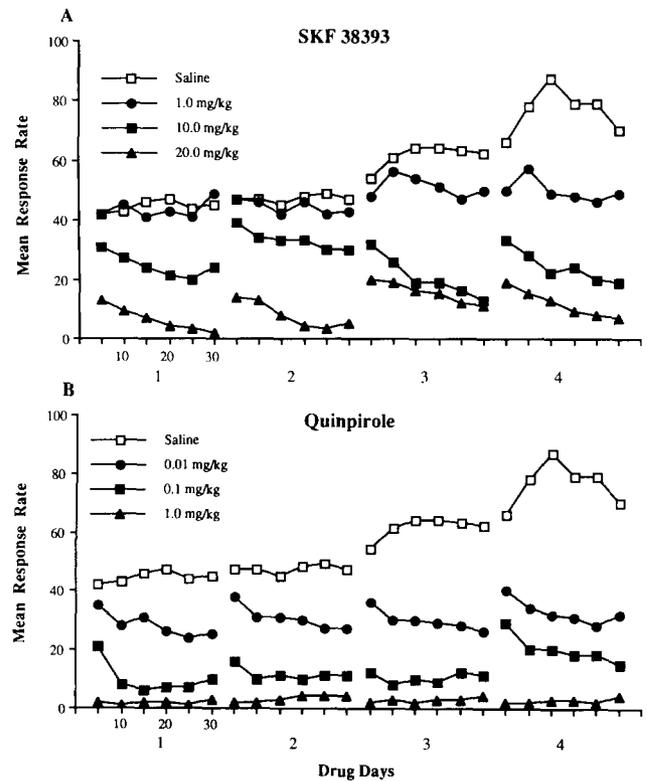


FIG. 2. Mean responses per min for each 5-min segment of the four 30-min drug tests in rats treated with SKF 38393 (A) or quinpirole (B). The saline group is shown in both panels and is the same group shown in Fig. 1.

response rates on the intervening baseline days tended to increase (data not shown). Accordingly, the phenomenon of rate-dependency (i.e., that some drugs produce a greater disruption of response rates when baseline responding is high rather than low) may explain the augmentation of the drug effect over days. To test this possibility, two control groups ($n=8$) were included in which rates were allowed to increase and stabilize before repeated drug testing with 2.0 mg/kg amphetamine or 10.0 mg/kg SKF 38393 was initiated. In each case, on the first drug test, a large decrease in response rates was observed, and, furthermore, the magnitude of the decrease remained consistent over repeated drug tests (data not shown).

Responding over time *within* each drug session (i.e., intrasession responding) was also analysed. In contrast to the nonselective agonists, the two lowest doses of quinpirole as well as the two highest doses of SKF 38393 demonstrated significant gradual decreases in responding from the beginning to the end of the 30-min session (Fig. 2).

The possibility that these within-session declines reflected slow absorption of the drug was tested in two control groups ($n=8$) which were administered 0.01 mg/kg quinpirole or 10.0 mg/kg SKF 38393 30 min prior to the test session (rather than immediately before). Quinpirole was no longer effective in reducing total response rates when administered at this time and, thus, not surprisingly, the response rates at 5-min intervals failed to show a decline over time (data not shown). In contrast, a significant decrease in total response rates was observed in the SKF 38393 30-min condition, however, the intrasession decline was no longer evident (data not shown).

DISCUSSION

Both the direct- and indirect-acting dopaminergic agonists apomorphine and amphetamine, respectively, produced dose-dependent decreases in food-rewarded lever-pressing in rats. This is consistent with previous reports that illustrated the rate-reducing effects of DA agonists (2, 3, 7). The present study also demonstrated similar overall response decrements when either D1 or D2 receptors were preferentially stimulated with SKF 38393 or quinpirole, respectively.

When analysing the intersession data, it appeared in two instances (2.0 mg/kg amphetamine and 10.0 mg/kg SKF 38393) that the drug effect increased (i.e., there was a greater disruption in response rates) with repeated testing. In both instances, however, the apparent increasing effectiveness of the drug was probably due to rising control response rates on the intervening baseline days. Thus, if drug testing was initiated only when response rates had stabilized at a higher level, the magnitude of the effect remained consistent across repeated tests.

The intrasession pattern of responding was also examined. Both SKF 38393 and quinpirole produced a gradual decline in response rates within the test session. The within-session decline with SKF 38393 may have been due to slow absorption of the drug because when SKF 38393 was administered 30 min prior to the test, responding was reduced uniformly (i.e., to the same extent) throughout the session. This was not the case with quinpirole. When this drug was administered 30 min prior to the test, it was no longer effective in reducing lever-pressing. This suggests that most of the drug effect occurred during the initial 30 min following

injection; it therefore seems unlikely that the intrasession declines observed in the original quinpirole groups were due to slow absorption of the drug.

In the present study, where nonselective DA agonists produced dose-dependent reductions in responding, extinction-like intra- and intersession profiles were not observed. This suggests that the reduction in rates was not primarily related to a decrease in the reinforcing efficacy of the food. A similar conclusion can also be drawn for the D1 agonist SKF 38393 which also failed to produce extinction-like response profiles. There may be a number of alternative interpretations for the rate-reducing effects of these drugs, motor impairment being only one. In contrast, rats treated with the D2 receptor agonist quinpirole demonstrated a gradual decline in response rates over the 30-min session, suggesting that this drug may be affecting reinforcement mechanisms. However, some caution is warranted in accepting this conclusion because rats treated with this drug, unlike DA receptor antagonists, did *not* show an intersession decline in response rates, a result that would be expected if reinforcement mechanisms were affected by the drug.

ACKNOWLEDGEMENTS

We thank Smith, Kline and French for the gifts of amphetamine and SKF 38393. We also thank Lilly Research Laboratories and Nordic for their generous supply of quinpirole and apomorphine, respectively. This research was supported by grants from the Natural Sciences and Engineering Research Council of Canada and the Ontario Ministry of Health to R.J.B.

REFERENCES

1. Beninger, R. J.; Cheng, M.; Hahn, B. L.; Hoffman, D. C.; Mazurski, E. J.; Morency, M. A.; Ramm, P.; Stewart, R. J. Effects of extinction, pimoizide, SCH 23390 and metoclopramide on food-rewarded operant responding of rats. *Psychopharmacology (Berlin)* 92:343-349; 1987.
2. Bradshaw, C. M.; Ruddle, H. V.; Szabadi, E. Relationship between response rate and reinforcement frequency in variable-interval schedules: III. The effect of d-amphetamine. *J. Exp. Anal. Behav.* 36:29-39; 1981.
3. Harris, R. A.; Snell, D.; Loh, H. H. Effects of stimulants, anorectics, and related drugs on schedule-controlled behavior. *Psychopharmacology (Berlin)* 56:49-55; 1978.
4. Heyman, G. M. A parametric evaluation of the hedonic and motoric effects of drugs: Pimoizide and amphetamine. *J. Exp. Anal. Behav.* 40:113-122; 1983.
5. Heyman, G. M.; Seiden, L. S. A parametric description of amphetamine's effect on response rate: Changes in reinforcement efficacy and response topography. *Psychopharmacology (Berlin)* 85:154-161; 1985.
6. Lucki, I. Rate-dependent effects of amphetamine on responding under random-interval schedules of reinforcement in the rat. *Pharmacol. Biochem. Behav.* 18:195-201; 1983.
7. Morley, M. J.; Bradshaw, C. M.; Szabadi, E. The effect of d-amphetamine on operant behavior maintained under variable-interval schedules of reinforcement. *Psychopharmacology (Berlin)* 87:207-211; 1985.
8. Wise, R. A. Neuroleptics and operant behavior. The anhedonia hypothesis. *Behav. Brain Sci.* 5:39-87; 1982.