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Nucleus Accumbens Dopamine Release Increases During Instrumental Lever Pressing for Food but not Free Food Consumption

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SALAMONE, J. D., M. S. COUSINS, L. D. McCULLOUGH, D. L. CARRIERO AND R. J. BERKOWITZ. *Nucleus accumbens dopamine release increases during instrumental lever pressing for food but not free food consumption.* PHARMACOL BIOCHEM BEHAV 49(1) 25-31, 1994.—This experiment was undertaken to investigate the role of nucleus accumbens dopamine (DA) in instrumental and consummatory responses for food. In vivo microdialysis methods were used to study DA release and metabolism in the nucleus accumbens of behaving rats. Four behavioral conditions were used: performance on a fixed ratio 5 (FR 5) schedule of food reinforcement, consumption of Bioserve food pellets, consumption of laboratory chow, and food deprivation control. Groups of rats that were previously exposed to these conditions were implanted with dialysis probes in the nucleus accumbens and tested the day after implantation. The rats that pressed a lever on a FR 5 schedule showed significant increases in extracellular DA and DA metabolites compared to food-deprived control rats. In further analyses, rats that responded on the FR5 schedule were divided into three groups based upon their response rates. The rats with low response rates did not significantly differ from control rats, whereas rats with medium and high rates of responding showed significant increases in DA release relative to the control group. Rats that received massed presentation of food pellets or laboratory chow consumed large quantities of food, but showed no significant increases in DA release. This experiment demonstrated that performance of lever pressing behavior is accompanied by an increase in accumbens DA release and metabolism, and that DA release in nucleus accumbens is more closely related to the performance of highly active instrumental responses than it is to consumption of large quantities of food.

Dopamine Behavior Dialysis Reinforcement Operant Feeding Motivation Motor control

DOPAMINE (DA) in nucleus accumbens has been implicated in a number of behavioral functions, including motor activity, reinforcement, and motivation. Interference with dopaminergic activity in nucleus accumbens has been shown to impair performance on a variety of different behavioral tasks. Extensive depletions of accumbens DA produced by injections of 6-hydroxydopamine (6-OHDA) reduced spontaneous and drug-induced locomotor activity (16,18,46). The motor activity induced by periodic food presentation was reduced by accumbens DA depletions (22). Depletions of DA in nucleus accumbens impaired instrumental lever pressing for food reinforcement (7,41,43). However, interference with DA in nucleus accumbens does not affect all food-motivated tasks to the same extent. Injections of the DA antagonist haloperidol directly into the nucleus accumbens did not disrupt food intake, and, in fact, led to slight increases in food consumption (2). Nucleus accumbens DA depletions did not impair food intake, feeding rate, or food handling (18,42). Depletions of DA in nucleus accumbens reduced instrumental lever pressing for food but increased consumption of laboratory chow if both were concurrently available (7,43).

Although several studies have focussed upon the behavioral effects of interference with accumbens DA, there are only a few reported investigations of DA release in behaving animals that were engaged in food-related behaviors. The effects of food consumption on accumbens DA release are somewhat equivocal, with some studies reporting increases in accumbens DA release associated with food consumption (32,52), and other studies reporting little or no change (6,22). Using microdialysis methods, it has been demonstrated that

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nucleus accumbens DA release is increased during periodic food presentation (22) and lever pressing on a continuous reinforcement schedule (13,20). In a study that employed voltammetric methods, it was observed that responding on a variable interval schedule of reinforcement was associated with increases in accumbens DA metabolism (14). The present experiment was undertaken to investigate the role of nucleus accumbens DA in food-related consummatory and instrumental behaviors. In this experiment, microdialysis methods were used to measure extracellular levels of DA, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) in the nucleus accumbens of behaving rats. Four behavioral conditions were used: performance on a fixed ratio 5 (FR 5) schedule of food reinforcement, consumption of Bioserve food pellets, consumption of laboratory chow, and food deprivation control. The FR 5 schedule was employed because this schedule typically generates a relatively high rate of instrumental responding. Because 45 mg Bioserve pellets were used as reinforcement for the FR5 task, one of the food consumption procedures involved presentation of a large quantity (i.e., 15–18 g) of Bioserve pellets. The other food consumption procedure utilized laboratory chow, which is the standard food for the rats used in this experiment. These two food consumption groups were included to compare DA release during food consumption with DA release that occurs during performance of lever-pressing behavior.

METHOD

Animals

A total of 38 male Sprague–Dawley rats (Harlan Sprague–Dawley) were used for this experiment. The rats were group housed in a colony that was maintained at 23°C, and which had a 12L : 12D cycle (lights on 0700 h). After several days of adjustment to the colony, the rats were food deprived to 85% of their free-feeding body weight, and remained deprived throughout the course of the experiment.

Dialysis Probe Construction and Implantation

The active (exposed) surface of the dialysis probe consisted of a loop of 200 μm diameter dialysis tubing (15000 M.W. cutoff) with a strand of 0.002 inch diameter stainless steel wire inserted through the tubing for structural support. Both ends of the dialysis tubing were glued (Duro Super Glue Gel) to polyethylene tubing (PE-10), and the probe was formed into a very tight loop. The tip of the loop of dialysis tubing had 1.5 mm of exposed surface that was not glued and, therefore, was available for exchange across the dialysis membrane. Super glue was used to support the dialysis fiber and PE tubing, and to attach the PE tubing to a stainless steel casing (18 ga.) that was used for structural support. The edge of the metal tubing was 5–8 mm from the tip of the exposed dialysis fiber, so that with the probe implanted in the brain the metal tubing was several mm dorsal to the nucleus accumbens. This type of probe generally has shown 13–18% recovery of DA, DOPAC, and HVA when tested for recovery of standard solutions in beakers with a flow rate of 1.5 μl/min.

Dialysis probes were implanted unilaterally in the core region of the nucleus accumbens [see (25,53,54)] at the following coordinates: AP 2.8 mm from bregma, ML 1.4 mm, V −7.8 mm from skull, with the incisor bar was elevated 5.0 mm above interaural line [see (30)]. The number of rats operated for each group were as follows: control (n = 9), lab chow (n = 7), pellets (n = 10), FR5 (n = 12). The probe was anchored to the skull using machine screws and cranioplastic cement that was applied after implantation. The two strands of PE-10 from each end of the probe were fed through a metal tether and connected to a fluid swivel (Harvard Apparatus) at one end and to an open sample collection tube at the other end. The probe was perfused with artificial CSF [147.2 mM NaCl, 4.0 mM KCl, and 2.3 mM $CaCl_2$; which represents a relatively high calcium level, see (28)] at 1.5 μl/min by a Hamilton syringe driven with a Harvard Apparatus syringe pump. The collection tubes contained 1.0 μl of 11 N perchloric acid as an antioxidant. Rats were placed in the operant chamber (28 × 23 × 23 cm; Lafayette Instruments, Lafayette, IN) and allowed 1 day to recover before the behavioral test.

Neurochemical Analysis of DA, DOPAC, and HVA

The dialysis samples were analyzed using a high performance liquid chromatography (HPLC) system that consisted of a Waters dual-piston pump, a reverse phase column, a Coulochem electrochemical detector, and a chart recorder. The mobile phase was a pH 4.5 phosphate buffer that also contained 7.0% methanol, EDTA, and sodium octyl sulphate as an ion pairing agent. The oxidation potential (working vs. reference electrode) was 0.2 V. Standards of DA, DOPAC, HVA (Sigma Chemical Co.), were assayed along with the dialysis samples.

Histology

After completion of the experiment, rats were anesthetized with sodium pentobarbital and perfused with saline followed by 10% formalin. The dialysis probes were removed after perfusion, and then the brains were removed from the skull and stored in the formalin solution. Brains were cut in 50 μm coronal sections in the vicinity of the dialysis probe, mounted on gelatin-coated microscope slides, and stained with cresyl violet.

Experimental Procedure

All rats were food deprived to 85% of normal body weight. Prior to surgery, rats were trained for 4 weeks on one of the four following behavioral conditions: performance on a fixed ratio 5 (FR 5) schedule of food reinforcement, massed presentation of 15–18 g Bioserve food pellets (Bioserve Inc., Frenchtown, NJ), massed presentation of 15–18 g laboratory chow (Wayne Rodent Blox, Teklad Premier), and food deprivation control. The amount of food given to the chow and pellet groups (15–18 g) was enough to ensure unlimited access to food during the test session. Rats in the FR5 group were initially trained to press a lever on a continuous schedule, and then were switched to the FR5 schedule. On the last few training days, rats in all groups were placed in the operant chamber in the morning, and received their behavioral treatment in a 45-min session during the afternoon, after which the rats remained in the operant chamber for 3–4 h. This procedure was used to prepare all rats for the day during which dialysis testing would take place. All rats were implanted with dialysis probes, and each rat received a small amount of lab chow in the chamber immediately after surgery to maintain their deprived body weight. Implanted rats were tested the next day (20–24 h after implantation). Dialysis samples and behavioral data were collected in 45-min periods. The 45-min dialysis sampling period has been used in previous studies from this laboratory (20–24,46) and, thus, was employed in the present work so that these results could be comparable to those from

previous dialysis studies. A neurochemical baseline was established over four to five samples. Baseline levels of DA (mean (±SEM) pg DA/60 μl sample) were as follows: control 23.8 (±3.0), chow 32.3 (±3.0), pellets 22.5 (±4.0), FR5 27.9 (±3.1). There were no significant differences between groups in the baseline levels of DA. After the baseline period, the rats were exposed to the condition in which they had been trained (performance on a FR 5 schedule of food reinforcement, consumption of Bioserve food pellets, consumption of laboratory chow, and food deprivation control) for a single 45-min period (test time was usually between 1200 and 1400 h). Three more dialysis samples were collected after behavioral treatment. After the dialysis test, rats were perfused and their brains were used for histological analyses, as described above.

Data Analysis

The data from this experiment were analyzed using analysis of variance (ANOVA). The mean baseline levels for DA, DOPAC and HVA were calculated for the last two samples prior to the behavioral session. For data analysis, levels of DA, DOPAC, and HVA in the baseline samples, the sample collected during food presentation, and the three samples collected after the behavioral test session were recalculated as percent of the mean baseline. Percent baseline transformations of dialysis data have been used previously in our laboratory (20-24,46), and this method is useful because it reduces variability in the data [see also (50) for a discussion of statistical analyses of changes from baseline]. Simple ANOVA was performed on the data from each sample for DA, DOPAC, and HVA. Planned comparisons [see (17), pp. 106-118] were used to test for differences between each of the food presentation groups vs. the control group, and the Tukey test was used for comparisons between all possible pairs of means. To assess the relation between the lever pressing response and increases in extracellular DA, the group of 12 rats that responded on the FR5 schedule were subdivided into three groups (low responders, medium responders, high responders; $n = 4$ per group) based upon the number of lever pressing responses, and the DA data obtained during the behavioral performance were analyzed with ANOVA. In addition, linear and hyperbolic correlations were performed between the number of responses and the percent increase in DA for the 12 rats in the FR5 group.

RESULTS

Performance on a FR5 schedule of reinforcement increased extracellular levels of DA, DOPAC, and HVA. Figures 1-3 depict the results of the analyses of dialysis samples. Figure 1 shows the effects of the behavioral treatments on DA levels in dialysis samples expressed as a percent of the baseline period. There was a significant overall effect of behavioral treatment on DA content in accumbens dialysis samples that were collected during the behavioral test sessions, $F(3, 34) = 14.3$, $p < 0.01$. Planned comparison demonstrated that the FR5 group differed from the control group, and Tukey test analysis of these data demonstrated that the FR5 group showed increases in DA over baseline that were significantly different from the other two groups that received food in the sample collected during behavioral performance. In terms of picogram quantities, the FR5 group increased from a mean baseline of 27.9 (±3.1) pg to a mean of 44.9 (±5.0) pg during the FR5 session. In the three samples collected after the behavioral tests, there were no significant differences in DA content between the control group and any of the groups that received food.

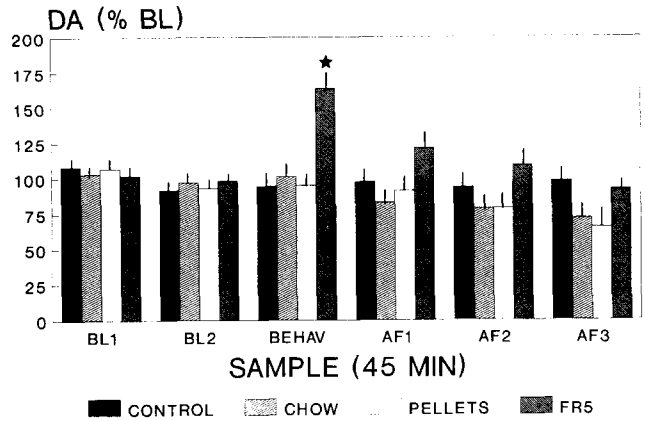

FIG. 1. Mean (±SEM) DA content (expressed as percent of baseline) in accumbens dialysis perfusates for all four groups. Data are from the last two baseline samples (BL), the sample obtained during the behavioral treatment (BEHAV), and the three samples obtained after treatment (AF1-3). (*$p < 0.05$, different from the control group).

Data on the mean (±SEM) DOPAC content (expressed as percent of baseline) in accumbens dialysis samples are shown in Fig. 2. There was a significant overall effect of behavioral treatment on DOPAC content in accumbens dialysis samples that were collected during the behavioral test sessions, $F(3, 34) = 2.96$, $p < 0.05$, and planned comparisons indicated that only the FR5 group showed a significant increase in extracellular DOPAC relative to control rats. In the three samples after the behavioral test sessions, there were no significant effects of behavioral treatment on DOPAC levels. Mean (±SEM) HVA content in accumbens dialysis samples is depicted in Fig. 3. There was no significant effect of behavioral treatment on HVA levels during the behavioral tests, but there was a significant overall effect of behavioral treatment during the first sample collected after the behavioral test sessions, $F(3, 34) = 3.82$, $p < 0.05$. Planned comparisons indicated that only the

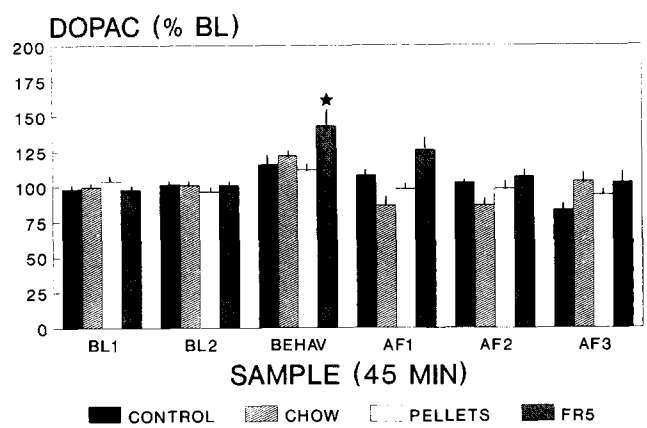

FIG. 2. Mean (±SEM) DOPAC content (expressed as percent of baseline) in accumbens dialysis perfusates for all four groups. Data are from the last two baseline samples, the sample obtained during the behavioral treatment, and the three samples obtained after treatment. (*$p < 0.05$, different from the control group).

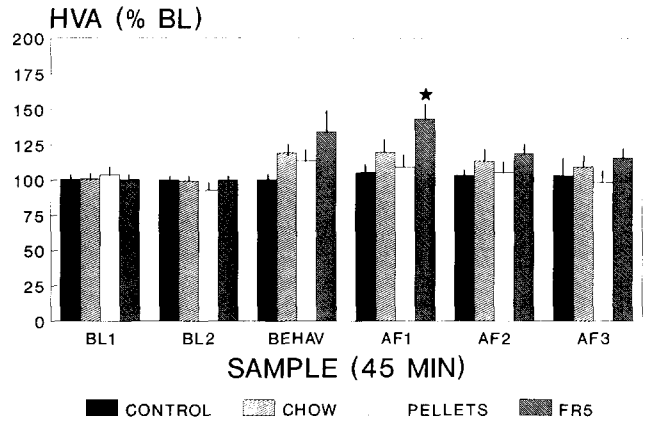

FIG. 3. Mean (±SEM) HVA content (expressed as percent of baseline) in accumbens dialysis perfusates for all four groups. Data are from the last two baseline samples, the sample obtained during the behavioral treatment, and the three samples obtained after treatment. (*$p < 0.05$, different from the control group).

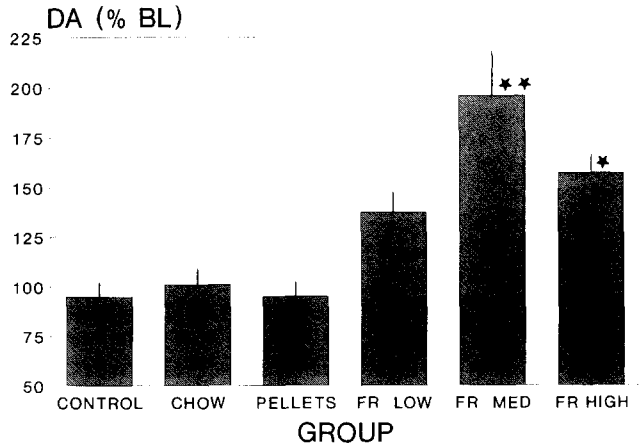

FIG. 4. Mean (± SEM) DA content (expressed as percent of baseline) in accumbens dialysis perfusates for the control group, the two food consumption groups, and the FR5 animals split into three different behavioral response categories (FR low = low response rate, FR med = medium response rate, FR high = high response rate). Data are from the sample obtained during the behavioral treatment. (*$p < 0.05$, different from the control group, chow consumption group and pellet consumption group; **$p < 0.05$, different from the control group, chow consumption group, pellet group, and FR low group).

FR5 group showed a significant increase in extracellular HVA compared to rats in the control group in the first sample after the behavioral test.

The mean (±SEM) number of lever presses for the FR5 group was 748.4 (±123.8). Because each Bioserve pellet weighed 45 mg, the group that responded on the FR5 consumed 6.74 (±1.1) g of food. The mean (±SEM) food consumption for the group that had chow available was 5.32 (±1.0), and the group that had Bioserve pellets available consumed 10.13 (±0.8) g of food. ANOVA demonstrated that there was a significant overall difference between groups in food consumption, $F(2, 26) = 5.32$, $p < 0.05$. Post hoc comparisons indicated that the group that received massed presentation of Bioserve pellets ate significantly more food than the rats that received lab chow. The FR5 group did not differ from either of the other two groups that received food in terms of how much food was consumed.

Figure 4 shows the results of the analysis in which the FR5 group was divided into three separate groups based upon the lever-pressing response rate. This figure depicts the DA content in dialysis samples obtained during the behavioral test session for animals in the control group, the two food consumption groups, and the three different FR5 groups (low, medium, and high responders). There was an overall significant group effect, $F(5, 32) = 12.64$, $p < 0.01$. Post hoc comparisons with the Tukey test demonstrated that the rats that responded at a low rate on the FR5 task (318.0 ± 124.9 responses) did not significantly differ from the control group or the two food consumption groups. The rats that responded at a medium rate on the FR5 task (727.8 ± 64.9 responses) had significantly higher levels of DA relative to the control group, the two food consumption groups, and the low responding FR5 group. The rats that responded at a high rate on the FR5 task (1199.5 ± 138.0 responses) significantly differed from the control group and the two food consumption groups. Regressional analyses also were performed on lever pressing and DA release data from the 12 rats in the FR5 group. There was not a significant linear relation between lever pressing rate and increases in DA, but there was a significant hyperbolic relation between the number of responses and increases in DA, $F(2, 10) = 22.2$, $p < 0.01$; corrected hyperbolic correlation = 0.50; see Fig. 5).

DISCUSSION

Performance on a FR5 schedule of reinforcement was accompanied by increases in extracellular DA, DOPAC, and HVA in nucleus accumbens. These results are consistent with previous studies, which have demonstrated that DA release in nucleus accumbens is increased under conditions related to appetitive motivation. Lever pressing for food reinforcement on continuous or variable interval reinforcement schedules (13,14,20) as well as periodic presentation of food (22), and exposure to stimuli associated with food (3), all have been shown to increase accumbens DA release or metabolism. It was observed that the increase in HVA shown by the FR5 group lagged behind the period of behavioral performance

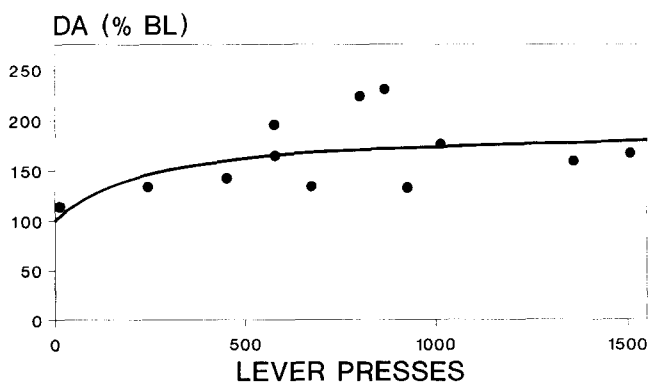

FIG. 5. Scatterplot showing the relation between number of lever presses and extracellular levels of DA in nucleus accumbens (as percent of baseline). The curve shown is a hyperbolic function, with the asymptote equal to 92.0% above baseline, and the response number that generates half maximal increases in DA equal to 242 responses (origin set at 100%).

and, in fact, was only significantly different from the control group during the sample collected after the behavioral test session (see Fig. 3). This delayed increase in extracellular HVA is consistent with previous reports (14,24,40). In the present study, consumption of Bioserve pellets or lab chow did not significantly increase extracellular DA, DOPAC, or HVA relative to the control group. Thus, it is difficult to explain the increases in extracellular DA, DOPAC, and HVA that were shown by rats performing the FR5 schedule simply in terms of the presentation and consumption of large quantities of food. Previous work has indicated that the effects of food consumption on accumbens DA release are somewhat equivocal. Some studies have reported increases in accumbens DA release associated with food consumption (32,52), yet other studies have reported little or no change (6,22). Each of these studies has employed different behavioral methods, and it is possible that subtle differences in the behavioral conditions, such as the degree of training or other factors, can lead to different neurochemical results. In the present experiment, most rats that consumed chow or pellets did show small increases in DOPAC or HVA relative to their own baseline (14 of 17 for DOPAC, 15 of 17 for HVA). Yet these two groups did not differ from the control group, and the two food consumption groups had significantly lower levels of extracellular DA (as percent of baseline) compared to the FR5 group. In the present study, all of the rats that received food were food deprived, were exposed to comparable degrees of training, and were tested under conditions that were virtually identical except for the behavioral task itself. Thus, the present results suggest that all conditions related to food motivation do not produce comparable increases in accumbens DA release. Because there may be differences in the extent to which various food-related conditions affect accumbens DA release, it does not seem accurate to state simply that DA release is instigated by food or motivation or reward.

The precise conditions that stimulate DA release in nucleus accumbens remain poorly understood. Periodic presentation of food, which induces large increases in motor activity, has been show to increase accumbens DA release and metabolism (22). The present results, together with other studies (13,14, 20), indicate that performance of appetitively motivated instrumental lever pressing is accompanied by substantial increases in accumbens DA release and metabolism. In addition, a variety of conditions related to aversive motivation increase accumbens DA release. Exposure to aversive or stressful conditions such as shock (1,34) or tailpinch (8) increase accumbens DA release or metabolism. Although considerable emphasis has been placed on the finding that drugs of abuse increase accumbens DA release (10), it also has been reported that anxiogenic drugs that have aversive properties also increase accumbens DA release and metabolism (23). In considering the present results, in which lever pressing for food was shown to increase accumbens DA release, it is important to note that lever pressing to avoid shock also is accompanied by increases in accumbens DA release and metabolism (24). Changes in accumbens DA release are related to a variety of motivational stimuli, including both appetitive and aversive conditions. There is no evidence that increases in accumbens DA are selectively linked to positive reinforcement, or to states of pleasure. Thus, it is possible that DA in nucleus accumbens is related to functions that are common to appetitive and aversive motivation.

Previous studies of the relation between lever pressing behavior and accumbens DA release reported that there was a significant linear correlation between the number of lever pressing responses and the increases in extracellular DA (20,24). In those studies, the rate of operant responding was relatively low compared to that generated by an FR5 schedule. In the present study, there was not a simple linear relation between response rate on the FR5 schedule and increases in DA release. Animals with low response rates showed small increases in extracellular DA that were not significantly different from the control or food consumption groups. The group of rats with medium rates of responding showed significantly higher increases in DA release than the group with low rates of responding. However, rats with the highest rates of responding did not differ from rats with medium response rates in terms of increases in DA release. The present results suggest that the relation between response rate and DA release across a broad range of response rates is probably not linear, and instead shows curvilinear (e.g., hyperbolic) characteristics. For several reasons, it seems unlikely that there is a simple linear relation between lever pressing and accumbens DA release over a wide range of responses. A linear model implies that there is no limit to the magnitude of the increases in accumbens DA release that one can observe, and that the relation between responding and DA release is the same at all levels of responding. In contrast, the present results suggest that at moderate levels of responding the increases in DA release reach some maximal level, beyond which further increases in responding are not associated with additional increases in accumbens DA release.

Nucleus accumbens DA has been implicated in a number of behavioral processes. It has been suggested that accumbens DA is involved in preparatory behavior, and may have less direct involvement in consummatory behavior (3,31). Accumbens DA has been implicated in secondary reinforcement and conditioned incentive processes (5,11,45,49). DA in nucleus accumbens is involved in the prepulse inhibition of the startle response, which also involves associative functions (48). Considerable evidence indicates that accumbens DA is involved in aspects of motor activity (7,9,16,18,19,21,22,27,46), and that nucleus accumbens sends projections to other brain areas that are known to be involved in motor function (12,27,47,51). However, there is little evidence that DA release in nucleus accumbens directly mediates the phasic output of motor activity. In one study in which the activity of ventral tegmental DA neurons was recorded during operant responding for food on a FR20 schedule, the activity of most DA neurons was not closely related to motor output (29). Enhanced release of DA from nucleus accumbens may not directly stimulate specific motor acts but, instead, may modulate motor function so that some stimuli become more likely to elicit movement (20,22, 39). In discussing the motor functions of nucleus accumbens, and the involvement of accumbens DA in motivational processes, it should be emphasized that there are areas of overlap between motor and motivational functions (4,35–39). Possibly, DA in nucleus accumbens is involved in processes that are common to both motor control and motivation. Several investigators have suggested that DA in nucleus accumbens is involved in the behavioral activation produced by motivationally relevant stimuli (19,20,22,26,35–39). A variety of motivational conditions, involving both conditioned and unconditioned stimuli, appear to increase the release of accumbens DA. The behavioral function of this increased DA release may be to facilitate aspects of motor function and enhance responsiveness to some stimuli. This type of action could be important for naturalistic instrumental behaviors such as hoarding or foraging (15,37), as well as lever pressing to obtain food in laboratory conditions. Evidence indicates that

depletion of accumbens DA results in a slowing of the local rate of responding on an FR5 schedule (41). In addition, accumbens DA depletions that decrease lever pressing on a FR5 schedule have been shown to increase consumption of lab chow if both the operant schedule and the lab chow are available concurrently (7,43). It is possible that one of the major behavioral functions of accumbens DA release is to facilitate the ability of organisms to overcome the obstacles that separate them from significant stimuli such as food (7,39,43). The increases in extracellular DA in nucleus accumbens that accompany FR5 performance may reflect this type of behavioral function.

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REFERENCES

1. Abercrombie, E. A.; Keefe, K. A.; DiFrischia, D. A.; Zigmond, M. J. Differential effect of stress on in vivo dopamine release in striatum, nucleus accumbens and medial frontal cortex. J. Neurochem. 52:1655-1658; 1989.
2. Bakshi, V. P.; Kelley, A. E. Dopaminergic regulation of feeding behavior: I. Differential effects of haloperidol microinjection in three striatal subregions. Psychobiology 19:223-232; 1991.
3. Blackburn, J. R.; Phillips, A. G.; Jakubovic, A.; Fibiger, H. C. Dopamine and preparatory behavior: II. A neurochemical analysis. Behav. Neurosci. 103:15-23; 1989.
4. Broekkamp, C. L.; van Dongen, P. A.; van Rossum, J. M. Neostriatal involvement in reinforcement and motivation. In: Cools, A. R.; Lohman, A. M.; van den Berken, J. H., eds. Psychobiology of the striatum. Amsterdam: Elsevier North Holland; 1977.
5. Cador, M.; Robbins, T. W.; Everitt, B. J. Involvement of the amygdala in stimulus-reward associations: Interactions with the ventral striatum. Neuroscience 30:77-86; 1989.
6. Cenci, M. A.; Kalen, P.; Mandel, R. J.; Bjorklund, A. Regional differences in the regulation of dopamine and noradrenaline release in medial frontal cortex, nucleus accumbens and caudate-putamen: A microdialysis study in the rat. Brain Res. 581:217-228; 1992.
7. Cousins, M. S.; Sokolowski, J. D.; Salamone, J. D. The role of brain dopamine in instrumental response selection: Different effects of dopamine depletions in the nucleus accumbens, medial striatum and ventrolateral striatum on lever pressing and feeding in the rat. Pharmacol. Biochem. Behav. 46:943-951; 1993.
8. D'Angio, M. D.; Serrano, A.; Rivy, J. P.; Scatton, B. Tail-pinch stress increases extracellular DOPAC levels (as measured by in vivo voltammetry) in rat nucleus accumbens but not frontal cortex: Antagonism by diazepam and zolpidem. Brain Res. 409:169-174; 1987.
9. Delfs, J. M.; Schreiber, L.; Kelley, A. E. Microinjection of cocaine into the nucleus accumbens elicits locomotor activation in the rat. J. Neurosci. 10:303-310; 1990.
10. 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.
11. Everitt, B. J.; Morris, K. A.; O'Brien, A.; Robbins, T. W. The basolateral amygdala-ventral striatal system and conditioned place preference: Further evidence of limbic-striatal interactions underlying reward-related processes. Neuroscience 42:1-18; 1991.
12. Garcia-Rill, E. The basal ganglia and the locomotor regions. Brain Res. Rev. 11:47-63; 1986.
13. 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.
14. Joseph, M. H.; Hodges, H. Lever pressing for food reward and changes in dopamine turnover and uric acid in rat caudate and nucleus accumbens studied chronically by in vivo voltammetry. J. Neurosci. Methods 34:143-149; 1990.
15. Kelley, A. E.; Stinus, L. Disappearance of hoarding behavior after 6-hydroxydopamine lesions of the mesolimbic dopamine neurons and its reinstatement with L-DOPA. Behav. Neurosci. 99:531-543; 1985.
16. Kelly, P. H.; Seviour, P. W.; Iversen, S. D. Amphetamine and apomorphine responses in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum. Brain Res. 94: 507-522; 1975.
17. Keppel, G. Design and analysis: A researchers handbook. Englewood Cliffs, NJ: Prentice Hall; 1982.
18. Koob, G. F.; Riley, S. J.; Smith, S. C.; Robbins, T. W. Effects of 6-hydroxydopamine lesions of the nucleus accumbens septi and olfactory tubercle on feeding, locomotor activity, and amphetamine anorexia in the rat. J. Comp. Physiol. Psychol. 92:917-927; 1978.
19. Koob, G. F.; Swerdlow, N. R. The functional output of the mesolimbic dopamine system. Ann. NY Acad. Sci. 537:216-227; 1988.
20. McCullough, L. D.; Cousins, M. S.; Salamone, J. D. The role of nucleus accumbens dopamine in responding on a continuous reinforcement operant schedule: A neurochemical and behavioral study. Pharmacol. Biochem. Behav. 46:581-586; 1993.
21. McCullough, L. D.; Salamone, J. D. Increases in extracellular dopamine levels and locomotor activity after direct infusion of phencyclidine into the nucleus accumbens. Brain Res. 577:1-9; 1992.
22. McCullough, L. D.; Salamone, J. D. Involvement of nucleus accumbens dopamine in the motor activity induced by periodic food presentation: A microdialysis and behavioral study. Brain Res. 592:29-36; 1992.
23. McCullough, L. D.; Salamone, J. D. Anxiogenic drugs beta-CCE and FG 7142 increase extracellular dopamine levels in nucleus accumbens. Psychopharmacology (Berlin) 109:379-382; 1992.
24. McCullough, L. D.; Sokolowski, J. D.; Salamone, J. D. A neurochemical and behavioral investigation of the involvement of nucleus accumbens dopamine in instrumental avoidance. Neuroscience 52:919-925; 1993.
25. Meredith, G. E.; Blank, B.; Groenewegen, H. J. The distribution and compartmental organization of the cholinergic neurons in the nucleus accumbens of the rat. Neuroscience 31:327-345; 1989.
26. Mitchell, J. B.; Gratton, A. Opioid modulation and sensitization of dopamine release elicited by sexually relevant stimuli: A high speed chronoamperometric study in freely behaving rats. Brain Res. 551:20-27; 1991.
27. Mogenson, G.; Jones, D.; Yim, C. Y. From motivation to action: Functional interface between the limbic system and the motor system. Prog. Neurobiol. 14:69-97; 1980.
28. Moghaddam, B.; Bunney, B. S. Ionic composition of microdialysis perfusing fluid alters the basal release and pharmacological responsiveness of striatal dopamine. J. Neurochem. 53:652-654; 1989.
29. Nishino, H.; Ono, T.; Muramoto, K.; Fukuda, M.; Sasaki, K. Neuronal activity in the ventral tegmental area (VTA) during motivated bar press feeding in the monkey. Brain Res. 413:302-313; 1987.
30. Pellegrino, L. J.; Cushman, A. J. A stereotaxic atlas of the rat brain. New York: Appelton-Century-Crofts; 1967.
31. Pfaus, J. G.; Phillips, A. G. Role of dopamine in anticipatory and consummatory aspects of sexual behavior in the male rat. Behav Neurosci. 105:727-743; 1991.
32. Radhakishun, F. S.; van Ree, J. M.; Westerink, B. H. C. Scheduled eating increases dopamine release in the nucleus accumbens of food-deprived rats as assessed with on-line brain dialysis. Neurosci. Lett. 85:351-356; 1988.
33. Robbins, T. W.; Everitt, B. J. Functional studies of central catecholamines. Int. Rev. Neurobiol. 23:303-364; 1982.

34. Robinson, T. E.; Becker, J. B.; Young, E. A.; Akil, H.; Castenada, E. The effects of foot shock stress on regional brain dopamine metabolism and pituitary beta-endorphin release in rats previously sensitized to amphetamine. Neuropharmacology 26:679-691; 1987.
35. Salamone, J. D. Different effects of haloperidol and extinction on instrumental behaviors. Psychopharmacology (Berlin) 88:18-23; 1986.
36. Salamone, J. D. The actions of neuroleptic drugs on appetitive instrumental behaviors. In: Iversen, L. L.; Iversen, S. D.; Snyder, S. H., eds. Handbook of psychopharmacology. New York: Plenum Press; 1987:575-608.
37. Salamone, J. D. Dopaminergic involvement in activational aspects of motivation: Effects of haloperidol on schedule-induced activity, feeding and foraging in rats. Psychobiology 16:196-206; 1988.
38. Salamone, J. D. Behavioral pharmacology of dopamine systems: A new synthesis. In: Willner, P.; Scheel-Kruger, J., eds. The mesolimbic dopamine system: From motivation to action. Cambridge: Cambridge University Press; 1991:599-613.
39. Salamone, J. D. Complex motor and sensorimotor functions of accumbens and striatal dopamine: Involvement in instrumental behavior processes. Psychopharmacology (Berlin) 107:160-174; 1992.
40. Salamone, J. D.; Keller, R. W.; Zigmond, M. J.; Stricker, E. M. Behavioral activation in rats increases striatal dopamine metabolism measured by dialysis perfusion. Brain Res. 487:215-224; 1989.
41. Salamone, J. D.; Kurth, P.; McCullough, L. D.; Sokoloski, J. D.; Cousins, M. S. The role of brain dopamine in response initiation: Effects of haloperidol and regionally specific dopamine depletions on the local rate of instrumental responding. Brain Res. 628:218-226; 1993.
42. Salamone, J. D.; Mahan, K.; Rogers, S. Ventrolateral striatal dopamine depletions impair feeding and food handling in rats. Pharmacol. Biochem. Behav. 44:605-610; 1993.
43. Salamone, J. D.; Steinpreis, R. E.; McCullough, L. D.; Smith, P.; Grebel, D.; Mahan, K. Haloperidol and nucleus accumbens dopamine depletion suppress lever pressing for food but increase free food consumption in a novel food-choice procedure. Psychopharmacology (Berlin) 104:515-521; 1991.
44. Salamone, J. D.; Zigmond, M. J.; Stricker, E. M. Characterization of the impaired feeding behavior in rats given haloperidol or dopamine-depleting brain lesions. Neuroscience 39:17-24; 1990.
45. Schultz, W.; Apicella, P.; Ljungberg, T. Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task. J. Neurosci. 13: 900-913; 1993.
46. Steinpreis, R. E.; Salamone, J. D. The role of nucleus accumbens dopamine in the neurochemical and behavioral effects of phencyclidine: A microdialysis and behavioral study. Brain Res. 612: 263-270; 1993.
47. Swanson, L. W.; Mogenson, G. J.; Gerfen, C. R.; Robinson, P. Evidence for a projection from the lateral preoptic area and substantia innominata to the "mesencephalic locomotor region." Brain Res. 295:161-178; 1984.
48. Swerdlow, N. R.; Caine, S. B.; Geyer, M. A. Regionally selective effects of intracerebral dopamine infusion on sensorimotor gating of the startle reflex in rats. Psychopharmacology (Berlin) 108: 189-185; 1992.
49. Taylor, J. R.; Robbins, T. W. 6-Hydroxydopamine lesions of the nucleus accumbens but not the caudate nucleus attenuate responding with reward-related stimului produced by intra-accumbens D-amphetamine. Psychopharmacology (Berlin) 90: 390-397; 1986.
50. Wainer, H. Adjusting for differential base rates: Lord's paradox again. Psychol. Bull. 109:147-151; 1991.
51. Yang, C. R.; Mogenson, G. J. Hippocampal signal transmission to the pedunculopontine nucleus and its regulation by dopamine D_2 receptors in the nucleus accumbens: An electrophysiological and behavioral study. Neuroscience 23:1041-1055; 1987.
52. Yoshida, M.; Yokoo, H.; Mizoguchi, K.; Kawahara, H.; Tsuda, A.; Nishikawa, T.; Tanaka, M. Eating and drinking cause increased dopamine release in the nucleus accumbens and ventral tegmental area in the rat: Measurement by in vivo microdialysis. Neurosci. Lett. 139:73-76; 1992.
53. Zahm, D. S.; Brog, J. S. On the significance of subterritories in the "accumbens" part of the rat ventral striatum. Neuroscience 50:751-767; 1992.
54. Zahm, D. S.; Heimer, L. Two transpallidal pathways originating in the rat nucleus accumbens. J. Comp. Neurol. 302:437-446; 1990.