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Dopamine Depletion in Nucleus Accumbens Influences Locomotion But Not Force and Timing of Operant Responding

XIAOQING LIU,* ROBERT E. STRECKER†[1] AND JASPER BRENER*

*Department of Psychology and †Department of Psychiatry, State University of New York at Stony Brook, Stony Brook, NY 11794-2500

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LIU, X., R. E. STRECKER AND J. BRENER. *Dopamine depletion in nucleus accumbens influences locomotion but not force and timing of operant responding.* PHARMACOL BIOCHEM BEHAV **59**(3) 737–745, 1998.—This experiment examined the role of dopamine (DA) in the nucleus accumbens in regulating beam pressing and locomotor responses. Six rats were rewarded with sucrose on a partial reinforcement schedule for pressing force-sensitive beams. Open-field locomotor activity, and the force and timing characteristics of operant motor responses were recorded. It is known that low doses of apomorphine decrease DA tone through activating DA autoreceptors, resulting in suppression of both operant responses and locomotion. Our results showed that DA depletion in the nucleus accumbens, induced by bilateral injection of 6-hydroxydopamine, did not affect the force and timing of operant responses; neither did it reverse the suppressive effects of low doses of apomorphine on the force and timing of operant responses. However, accumbens DA depletion did block the suppressive effect of apomorphine on open-field locomotion. These results were interpreted as support for the hypothesis that the suppressive effects of low doses of apomorphine on locomotion, but not on operant beam pressing, are mediated mainly by DA autoreceptors in the mesolimbic pathway. © 1998 Elsevier Science Inc.

Amphetamine Apomorphine Autoreceptors Dopamine Isometric force Locomotion Nucleus accumbens Operant responses Rats 6-Hydroxydopamine

OPEN-field locomotion is a motor behavior often observed spontaneously in rats and mice (1,53). It can also be induced by certain types of drugs, such as dopamine (DA) agonists (7,13,15,19,21,44,50,52,55). "Stereotypy" is used to describe a group of inappropriate repetitive behaviors such as gnawing, licking, rearing etc., that is usually elicited in rats and mice by high doses of dopamine agonists (19,34). DA agonists increase locomotor activity and this response is blocked by DA antagonists (28,33). Amphetamine, an indirect DA agonist, which increases the release of dopamine from DA terminals, stimulates locomotor activity when low doses are used. When high doses are used, locomotion is suppressed and replaced by stereotyped behaviors (38). Locomotor activity can be suppressed by low doses of DA agonists, such as apomorphine (6,22,39,49). In both rats and mice, systemic injection of apomorphine at doses between 0.02 and 0.2 mg/kg produces suppression of locomotion, while, at doses higher than 3 mg/kg, apomorphine increases locomotion (8,22,37,49). The suppressive effect of apomorphine is mediated by the activation of DA autoreceptors (11), which involves negative feedback control of dopamine metabolism. Thus, the activation of these receptors decreases the synthesis and release of dopamine from the terminals, resulting in a DA antagonistic effect. The stimulant effect of this drug, however, is due to the activation of postsynaptic DA receptors (25,44).

Two different DA pathways in the basal ganglia have been found to mediate different motor responses. Microinjection of DA or amphetamine into the nucleus accumbens increases locomotor activity, while injection of DA or amphetamine into the caudate nucleus produces stereotyped behaviors and does not cause a marked increase in locomotion (12,23,41). Further, destruction of mesolimbic DA terminals by injection of 6-hydroxydopamine (6-OHDA) into the nucleus accumbens blocks the locomotor stimulation but not the stereotyped be-

Requests for reprints should be addressed to Xiaoqing Liu, Department of Psychology, State University of New York at Stony Brook, Stony Brook, NY 11794.

[1]Current address: Harvard Medical School, Veterans Adm. Med Ctr, 151 C, 940 Belmont St., Brockton, MA 02401.

haviors produced by amphetamine. Destruction of nigrostriatal DA terminals in the neostriatum reduces the stereotyped behaviors but not the locomotor stimulant effects of amphetamine (24). These results suggest that mesolimbic DA mediates locomotion, whereas nigrostriatal DA mediates stereotyped behaviors (38).

Unlike spontaneous and drug-induced motor responses (e.g., locomotion), operant motor responses are generated by certain reinforcement contingencies. The role played by dopamine in the performance of operant responses by rats has been investigated through the administration of dopaminergic drugs (14,16–18,29,47). In these studies, rats were required either to press a force-sensitive lever or to lick a force beam under different operant contingencies, or to respond on a fixed ratio schedule. Following training, neuroleptics, such as haloperidol, chlorpromazine, and clozapine, were used as dopamine receptor blockers to reveal the effects of DA on operant responding. It has been shown that small to moderate doses of neuroleptics generally decreased peak force, and lengthened response duration and interpress time. We previously reported (31) that low doses of systemically injected apomorphine suppressed both locomotion and operant responding (i.e., decreased force and lengthened interpress time). Therefore, the performance of operant motor responses is also affected by DA agonists and antagonists.

There is much debate on the role of accumbens and caudate DA in the mediation of operant responding. It has been shown that during operant lever pressing, nucleus accumbens DA was increased (26,45), and ibotenic acid or 6-OHDA lesion in the accumbens impaired lever-pressing performance (3,9). However, some studies demonstrated that the caudate nucleus was more involved in operant responding than the nucleus accumbens. For example, while DA depletion in the accumbens only produced a mild effect on lever pressing (46), DA blocking in the caudate produced significant declines in operant responding (4), and ibotenic acid lesions in the lateral caudate yielded performance deficits in lever pressing (42). So it is unclear whether mesolimbic and/or nigrostriatal DA are involved in the regulation of operant responding.

The present experiment aimed at understanding the role played by accumbens DA in the mediation of force and timing of operant responding. As discussed above, because the activation of postsynaptic DA receptors in the mesolimbic pathway increased locomotor activity (25,44), it was inferred that the suppressive effect of apomorphine on locomotion was produced by the activation of DA autoreceptors in the mesolimbic pathway. The issue addressed in this article was whether the suppressive effects of apomorphine on force and timing could also be accounted for by the activation of DA autoreceptors in the nucleus accumbens. Rats were trained to press one of three force-sensitive beams to get sucrose rewards. Following training, 6-OHDA was bilaterally injected into the nucleus accumbens to produce DA depletion in the mesolimbic pathway. After the lesion, the rats were systemically injected with apomorphine and amphetamine, and tested in both operant performance and locomotion.

If the mesolimbic DA pathway mediates force and timing, accumbens DA depletion should have the same suppressive effects as observed by Liu et al. (31) for low doses of apomorphine injected systemically in intact animals. Further, after 6-OHDA accumbens lesions, the suppressive effects of low doses of apomorphine should be reversed because of loss of DA autoreceptors in the mesolimbic DA terminals. Conversely, if the accumbens DA pathway does not mediate force and timing, DA depletion of accumbens should have no effects. Low doses of apomorphine should continue to produce suppressive effects on performance in accumbens-lesioned animals. However, given that the mesolimbic DA pathway is involved in locomotor activity, accumbens DA depletion should eliminate the suppressive effects of apomorphine on locomotion or even stimulate locomotion due to the development of supersensitivity of postsynaptic DA receptors. In contrast, the stimulant effects of amphetamine on locomotion should be reduced or eliminated because of partial or complete DA terminal loss in the mesolimbic pathway.

METHOD

Subjects

Six male Long–Evans rats, which completed the experiment described in Liu et al. (31), were used as subjects. The animals were maintained between 90–95% of their free-feeding body weights by supplementing standard lab food pellets after daily sessions. They were housed under reversed lighting conditions with lights on from 2000–0800 h. Training or testing started at 1000 h daily, in a dark room next to the rat vivarium.

Apparatus and Operant Procedures

Operant apparatus and procedures are described in greater detail in Liu et al. (31). Briefly, three aluminum force-sensitive beams were mounted to the front panel of the operant box. A food tray was housed below each beam. Strain gauges were bonded to the shaft of the beam. Force applied to the beams resulted in changes of the electrical resistance of the strain gauges that was converted to voltage changes and amplified by using high-stability DC amplifiers. Responses on each beam that exceeded the "recognition criterion" of 1 g were recorded using a computer that was programmed to record the response parameters described below and to apply the reinforcement criterion. A stepper motor, positioned outside the sound-attenuating chamber in which the experimental box was housed, was used to deliver a fixed amount of liquid food (16.66 μl of 0.32 g/ml sucrose) into the central food tray. A clicker mounted outside the operant box delivered feedback click as each reward was delivered.

Subjects were trained on a schedule of partial reinforcement (probability of reward = 0.75). On each session they were allowed to earn 200 reinforcements by pressing the central beam (beam 2) with a minimum peak force of 1 g. Presses on the other two beams were recorded but were not rewarded. Rewards were always delivered to the central tray (tray 2), which was immediately below beam 2.

The open field box described in Liu et al. (31), was also used in the current experiment for testing locomotor activity.

Surgery

The six animals used in Liu et al. (31) were randomly divided into two groups: a 6-OHDA lesion group, and a sham-lesion group. All six rats were anesthetized with a mixture of ketamine and xylazine (57 mg ketamine and 8.7 mg xylazine per ml, 1.5 ml/kg, IP) prior to surgery. One group of three rats were bilaterally injected with 6 μg 6-OHDA in 1.5 μl ascorbate-saline into the nucleus accumbens of both hemispheres over a period of about 4 min. The cannula was left in place for another 4 min before it was withdrawn. Stereotaxic coordinates (40) were as follows: tooth bar: +5.0 mm; AP: +3.2 mm from bregma; ML: ±1.7 mm; DV: −7.5, −7.0, and −6.5 mm

(from dura; 0.5 μl at each DV coordinate). The other three were injected with ascorbate-saline in the same volume, using the same coordinates as the 6-OHDA animals. Behavioral tests were suspended for 9 days after the lesions for the effects of axon destruction to reach its maximum.

Drugs

The animals were tested in the operant box with apomorphine (APO) and amphetamine (AMP) consecutively after the lesions. The doses used after the lesions were the same as those in the experiment described by Liu et al. (31). Briefly, apomorphine hydrochloride (Sigma) was dissolved in dilute ascorbic acid (0.2 mg/ml saline) and injected (SC) at doses of 0.03, 0.1, and 0.3 mg/kg. D-Amphetamine sulfate (Sigma) dissolved in saline, was injected (IP) at 0.3, 1.0, and 3.0 mg/kg. The rats were tested in the operant box, 7 or 15 min after either APO or AMP injection. Every drug injection day was preceded by a vehicle injection day. Each drug series lasted for 7 days. The dose order for each drug was counterbalanced across rats.

A few days after the operant testing, the rats were tested in the open field after injection of APO, AMP, and saline. The doses for APO and AMP were 0.1 mg/kg (SC) and 1.0 mg/kg (IP), respectively.

Biochemical Analysis

Upon the completion of the experiment, all of the rats with either sham or 6-OHDA lesion were sacrificed for biochemical analysis of tissue DA concentrations. The rats were decapitated following anesthetization with chloral hydrate. The brains were immediately dissected and sampled at the following structures: central nucleus accumbens (NAc), middle caudate putamen (CPm), and dorsal lateral caudate putamen (CPdl). Tissue samples were frozen on dry ice and stored at −70°C until later analysis for dopamine concentrations using computerized high-performance liquid chromatography (HPLC).

Before performing HPLC, the tissue samples were homogenized in 0.1 M perchloric acid containing 50 μM EDTA (ratio of tissue to perchloric acid: 1 mg/50 μl), followed by centrifugation. Ten microliters of sample supernatant for each sample were directly injected via a refrigerated autoinjector (CMA 200, CMA/Microdialysis, Stockholm) into the HPLC.

Sample supernatant was analyzed by HPLC (35) using a dual potentiostat electrochemical detector (BAS 200 Bioanalytical Systems, W. Lafayette, IN). The glassy carbon electrodes were set in parallel at applied potentials of 600 mV and 450 mV relative to an Ag/AgCl reference electrode. The mobile phase composition was 50 mM NaH_2PO_4 monobasic, 0.1 mM EDTA, 1 mM Sodium Octyl Sulfate (SOS), 9.5% methanol, pH 4.0. Mobile phase was delivered as a flow rate of 1.0 ml/min onto a 10-cm × 3.2-mm chromatography column with ODS 3-μm packing (BAS, W. Lafayette, IN). Extracellular levels of dopamine per 10-μl sample were identified in this assay, and converted to picogram (pg) amounts by comparing the peak heights of the compound to that of a known DA standard.

Measures and Data Analyses

Peak force, the highest force reached during a single beam press, was recorded, as well as its two determinants, time to peak force, the time interval from the onset of the beam press to the moment when peak force was achieved, and the rate of rise of force (dF/dt), the average rate of rise of force during time to peak force (36). Beam release time, a measure of response termination, was recorded as the time from peak force to the moment at which force fell below the recognition criterion (1 g). The interresponse timing measures were 1) interpress time: the time from the onset of preceding beam press to the onset of the current beam; 2) the B2T2 interval: the time from the release of beam 2 to entering tray 2, indexed switching from one component to the next component in the same sequence; and 3) the T2B2 interval: measured as the time from exiting tray 2 to the onset of pressing beam 2, indexed switching from the terminal component of one sequence to the first component of the next sequence. Each of these measures was averaged over responses recorded during each daily session to provide session means for the parameters.

Force and timing data from the 5 days preceding and 5 days following either sham or 6-OHDA lesion was used to assess prelesion and postlesion performance for the sham and 6-OHDA groups. After either sham or 6-OHDA lesion, the day prior to each drug series was taken as a control baseline (no-injection) for that drug series. Data from the 3 days preceding the three dose days in each drug series were averaged to provide means for the vehicle injection condition (0 mg/kg). Data for the highest doses of both drugs are not reported due to unreliability of data at those doses. The differences between drug doses and the no-injection conditions were calculated separately for APO and AMP, and the means across subjects for each drug series are presented in the figures. Force and timing data obtained from APO and AMP injections, reported in Liu et al. (31), were separately analyzed for the sham and 6-OHDA groups and were used as prelesion conditions in this article.

To test the lesion effects, two-way mixed analyses of variance (ANOVA) were performed for each of the force and timing measures, using group (6-OHDA and sham) as the between-subject factor and lesion condition (prelesion and postlesion) as the within-subject factor. To test for differences in the APO and AMP baselines (no-injection) before and after the lesions, three-way ANOVA was used with the factors: group (6-OHDA and sham), drug condition (APO and AMP), and prelesion and postlesion conditions. To test the main hypothesis that the lesion affected operant performance under different doses of drugs, the differences across doses of each drug in pre- and postlesion conditions for the two groups were tested by three-way mixed ANOVAs, using the three factors: group (6-OHDA and sham), lesion condition (pre- and postlesion), and dose (control baseline, vehicle injection, doses 1 and 2). The Duncan test was used for post hoc comparisons.

The number of times a rat moved from one quadrant of the open-field box to another during a 45-min period, starting 15 min after injections, was subjected to statistical analysis. Two-way mixed ANOVAs were used to compare locomotor activity between 6-OHDA and sham groups, using the two factors: group (6-OHDA and sham) and condition (saline, and APO or AMP). Significant effects were further examined using the Duncan test.

DA concentrations were expressed in nanograms per milligram of wet brain tissue. Student's *t*-tests were used to examine the differences in DA concentrations between the 6-OHDA and sham groups. The degree of DA depletion on each side of the brain was obtained by subtracting the mean DA concentrations of tissue samples of the 6-OHDA group from the mean DA concentrations of the corresponding sample of the sham group, and then dividing it by the mean of DA concentrations in the sham group.

TABLE 1

DA CONCENTRATIONS (ng/mg) OF TISSUE SAMPLES OBTAINED FROM THE CENTRAL NUCLEUS ACCUMBENS (NAc), MIDDLE AND DORSAL LATERAL CAUDATE PUTAMEN (CPm AND CPdl) FOR SHAM (n = 3) AND 6-OHDA (n = 3) RATS

		Sham				6-OHDA					
Rat #		1	4	5	Means	2	3	6	Means	t-Value	DAdep
Nac	L	20	30	19	24.64	11	8	8	10.35	5.66*	58.0%
	R	26	20	33		11	12	11			
CPm	L	18	57	47	33.49	20	29	26	29.23	0.52	12.9%
	R	8	28	43		33	42	26			
CPdl	L	57	50	65	62.85	106	49	47	60.95	0.15	3.0%
	R	100	48	56		36	67	60			

L: left side,; R: right side. Means are obtained across both sides of three rats in each group. t-Values were obtained from comparing the means for the sham lesioned with those for the 6-OHDA lesioned rats and the degree of DA depletion (DA dep) for the 6-OHDA rats was expressed relative to the sham-lesioned rats.

*$p < 0.01$.

RESULTS

Biochemical Data

Table 1 presents the DA concentrations (ng/mg) of tissue assays from the central nucleus accumbens (NAc), the middle caudate putamen (CPm), and the dorsal lateral caudate putamen (CPdl) for each subject and the degree of DA depletion for the 6-OHDA animals. The means of DA concentration of the three areas for the sham animals across the left and right hemispheres were 24.64, 33.49, and 62.85 ng/mg, and those for the 6-OHDA animals were 10.35, 29.23, and 60.95 ng/mg, respectively. Student's t-tests showed that only in the NAc was the DA concentration for the 6-OHDA group significantly lower than that in the sham group. On average, the means of DA depletion of the 6-OHDA group in NAc, CPm, and CPdl were 58, 12.95, and 3%, respectively.

Drug and Lesion Effects on Locomotion

In Fig. 1, it is shown that APO did not suppress locomotion in the 6-OHDA group, while it did suppress locomotor activity in the sham-lesioned rats. This was supported by a significant interaction between group (6-OHDA and sham) and condition (APO and saline) in the ANOVA, $F(1, 4) = 10.79$, $p < 0.05$. Duncan tests indicated that locomotor activity after APO for the 6-OHDA group was significantly higher than that for the sham group ($p < 0.05$) but was not different from the locomotor of either group in the saline condition.

An ANOVA performed using the two factors: group (6-OHDA and sham) and condition (AMP and saline) yielded a highly significant main effect of condition, $F(1, 4) = 563.72$, $p < 0.001$. This was due to the substantial increase in locomotor activity stimulated by AMP in both groups (Fig. 1). However, as indicated by a marginally significant interaction effect between group and condition, $F(1, 4) = 6.9$, $p = 0.058$, DA depletion in the 6-OHDA group slightly blocked this stimulant effect of AMP. Duncan tests indicated that in the AMP condition, the 6-OHDA group showed significantly less ($p < 0.05$) locomotor activity than the sham group.

Lesion Effects on Force and Timing

Figure 2 shows the force and timing measures during the prelesion and postlesion conditions for the 6-OHDA and sham groups. Bilateral 6-OHDA lesion in the NAc did not influence peak force: No differences were found between groups or between prelesion and postlesion conditions. However, both the 6-OHDA and sham groups exhibited increases in dF/dt and shortening of time to peak force and beam release time after the lesion (dF/dt (Fig. 2B): $F(1, 4) = 14.24$, $p < 0.05$; time to peak force (Fig. 2C): $F(1, 4) = 7.86$, $p < 0.05$; beam release time (Fig. 2D): $F(1, 4) = 8.30$, $p < 0.05$). Other timing measures, such as interpress time, B2T2 interval, and T2B2 interval, were all unchanged after both 6-OHDA and sham lesions.

Drug Effects on Force and Timing

Table 2 provides the means of force and timing measures for the control baselines (no-injection) in the APO and AMP series, before and after 6-OHDA and sham lesion for the two groups. Peak force and dF/dt, before and after lesion for both groups in the APO series, were slightly higher than those in

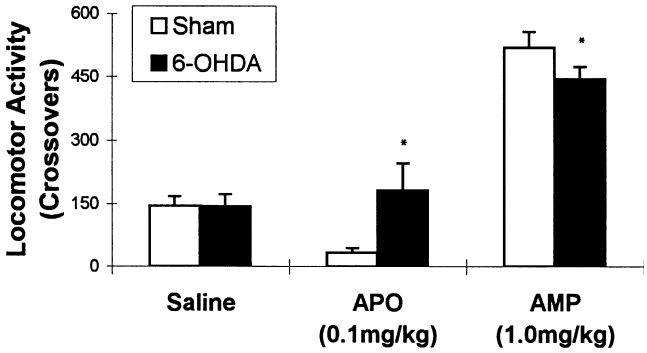

FIG. 1. Locomotor activities after either 6-OHDA or sham lesion. They were measured as the total numbers of crossovers from one quadrant to another in an open field box, during a 45-min period, starting 15 min following injection of either saline, APO (0.1 mg/kg, SC) and AMP (1.0 mg/kg, IP). Sham: the sham lesioned group; 6-OHDA: the group bilaterally injected with 6-OHDA into the nucleus accumbens. Level of significance: *$p < 0.05$, compared with the sham group in the same drug condition. Brackets show standard error of the mean (SEM).

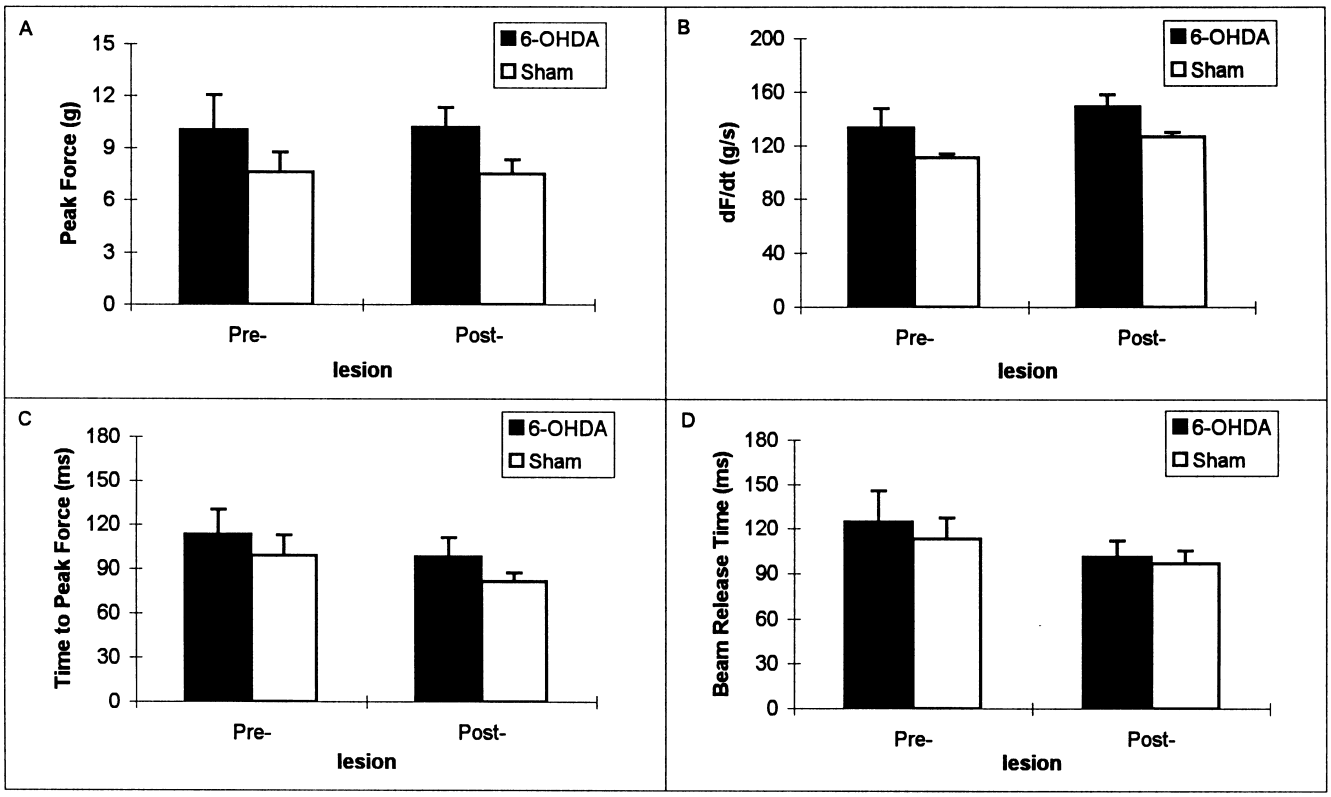

FIG. 2. Force and timing before and after bilateral 6-OHDA or sham lesion in the nucleus accumbens. (A) Peak force. (B) dF/dt: the rate of rise of force. (C) Time to peak force. (D) Beam release time. The data for the 6-OHDA lesioned group are indicated by filled bars (6-OHDA), while those for the sham lesioned group are open bars (sham). Pre: before 6-OHDA or sham lesion. Post: after 6-OHDA or sham lesion. Brackets show SEM.

the AMP series, shown by significant main effects of drug series (peak force: $F(1, 4) = 15.2, p < 0.05$; dF/dt: $F(1, 4) = 18.2$, $p < 0.05$.

APO. DA depletion in the nucleus accumbens did not reverse the suppressive effects of APO on force and timing (Fig. 3). APO decreased peak force in both the 6-OHDA and sham groups after lesion (Fig. 3A), indicated by a significant main effect of dose, $F(3, 12) = 8.0, p < 0.01$. The Duncan test indicated that peak force at 0.1 mg/kg of APO was significantly lower than peak forces in all other conditions ($p < 0.01$). The

TABLE 2

MEANS OF FORCE AND TIMING MEASURES FOR BASELINE CONTROL (NO-INJECTION) CONDITIONS BEFORE AND AFTER EITHER SHAM OR 6-OHDA LESION IN THE NUCLEUS ACCUMBENS

	APO				AMP			
	Sham		6-OHDA		Sham		6-OHDA	
Measures	pre-	post-	pre-	post-	pre-	post-	pre-	post-
Peak force (g)	5.88 (1.25)	7.16 (1.69)	7.23 (2.11)	10.66 (0.74)	5.21 (0.38)	6.14 (1.49)	6.75 (0.47)	8.20 (2.49)
dF/dt (g/s)	129 (39)	128 (9)	127 (24)	165 (23)	96 (18)	108 (3)	120 (12)	122 (13)
Time to peak Force (ms)	85 (22)	77 (18)	79 (13)	95 (34)	87 (14)	75 (17)	77 (9)	91 (23)
Beam release Time (ms)	84 (22)	86 (12)	84 (2)	88 (18)	88 (11)	85 (14)	97 (18)	100 (34)
B2T2 interval (s)	0.19 (0.09)	0.14 (0.03)	0.12 (0.02)	0.09 (0.05)	0.15 (0.06)	0.15 (0.04)	0.15 (0.01)	0.09 (0.07)
T2B2 interval (s)	0.47 (0.20)	0.46 (0.13)	0.47 (0.10)	0.35 (0.06)	0.55 (0.26)	0.49 (0.17)	0.43 (0.07)	0.46 (0.12)
Interpress Time (s)	0.16 (0.09)	1.12 (0.25)	1.07 (0.33)	1.10 (0.11)	1.20 (0.15)	1.34 (0.29)	1.21 (0.14)	1.23 (0.12)

APO: apomorphine series; AMP: amphetamine series. Standard deviations are in parentheses.

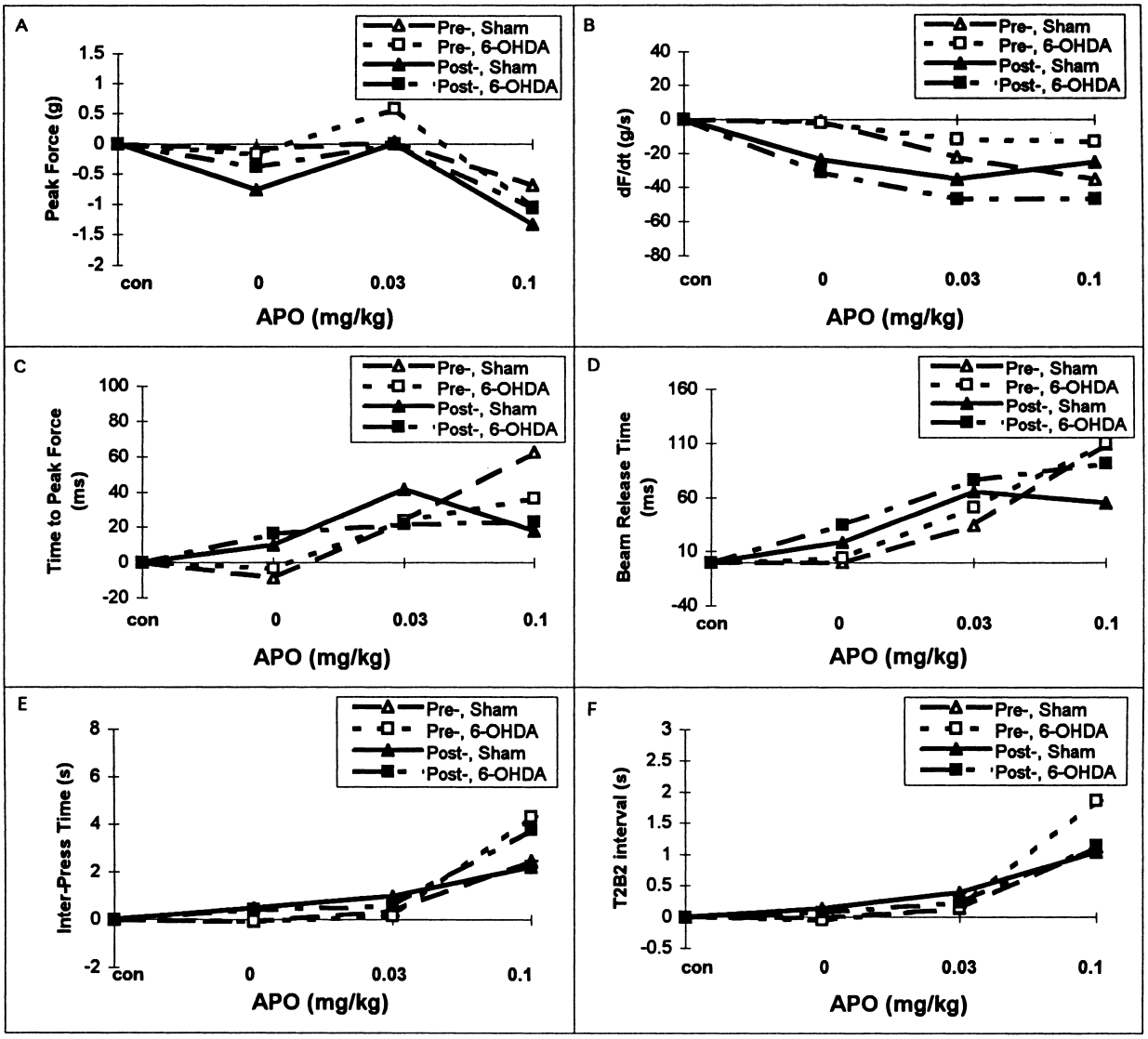

FIG. 3. Force and timing measures between groups and lesion conditions in the APO series (control, 0, 0.03, and 0.1 mg/kg, SC). The difference scores for peak force (A), dF/dt (B), time to peak force (C), mean release time (D), interpress time (E), and T2B2 interval (F) were obtained by subtracting the mean values for the control baseline from the means in each dose condition. Triangle markers represent data for the sham lesioned group, with open and filled triangles for prelesion and postlesion conditions, respectively. Square markers indicate data for the 6-OHDA lesioned group, with open and filled squares for the prelesion and postlesion conditions respectively.

decrease in peak force at 0.1 mg/kg can be attributed to the decrease in dF/dt (Fig. 3B). In both 6-OHDA and sham groups, dF/dt was lower than that in the prelesion condition, indicated by a significant two-way interaction between lesion condition and dose, $F(3, 12) = 3.53, p < 0.05$, and a significant main effect for dose, $F(3, 12) = 21.92, p < 0.001$ (Fig. 3B).

Time to peak force (Fig. 3C) showed significant lengthening after APO, independent of group and prelesion and postlesion condition [main effect of dose: $F(3, 12) = 8.64, p < 0.01$]. Beam release time (Fig. 3D) also increased as shown by a dose main effect, $F(3, 12) = 25.1, p < 0.001$. However, because there were no group effects, these changes in response timing are independent of DA depletion in the nucleus accumbens.

As reflected by main effects for dose, all other timing measures were lengthened significantly at 0.1 mg/kg of APO [interpress time, Fig. 3E: $F(3, 12) = 41.92, p < 0.001$; the B2T2 interval, not plotted in the figure: $F(3, 12) = 9.31, p < 0.01$; the T2B2 interval, Fig. 3F: $F(3, 12) = 17.94, p < 0.001$]. A significant lesion condition by dose interaction, $F(3, 12) = 5.65$, $p = 0.01$, was also found. However, no group effect was significant.

AMP. Neither peak force nor dF/dt were changed by AMP in either group. Time to peak force, $F(3, 12) = 22.71$, $p < 0.001$, and beam release time, $F(3, 12) = 11.61, p < 0.001$, were longer at 1.0 mg/kg than those recorded in the no-injection conditions (time to peak force: mean increase = 21 ms, SD = 6 ms; beam release time: mean increase = 27 ms, SD =

9 ms). However, these changes were independent of group and lesion. None of the timing measures, interpress time, the B2T2, and T2B2 intervals, were changed significantly by any dose of AMP across groups and lesion conditions.

DISCUSSION

Contrary to the observations of Liu et al. (31), who found that low doses of apomorphine had suppressive effects on force and timing, it was found in this experiment that neither of these performance features were influenced by accumbens DA depletion (58%). In contrast, dF/dt was increased, and both time to peak force and beam release time were shortened in both the 6-OHDA and sham groups. Similar changes across sessions, resulting in decreases in the area under the force-time curve, have been observed to occur after extensive training (5,36). In the present experiment they probably reflect training effects, too. Because the amount of energy expended in isometric muscle responses is positively correlated with the area under the force–time curve (20), the changes in performance imply an improvement in response efficiency over sessions.

It was assumed that the suppressive effects of low doses of apomorphine on locomotion and force and timing were mediated by DA autoreceptors in the accumbens (31). On this basis, it would be expected that the destruction of DA terminals in the accumbens would block or reverse the suppressive effects of low doses of apomorphine on locomotion and force and timing. However, the results indicated that the same degree of accumbens DA depletion reversed the suppressive effect of low doses of apomorphine on locomotion but did not influence that on force and timing of operant responding. Apomorphine resulted in similar decreases in peak force and dF/dt, and increases in time to peak force and beam release time in both the 6-OHDA and sham groups. As reflected by a comparison between the 6-OHDA and sham groups, the effects of apomorphine on timing measures, such as interpress time, were uninfluenced by accumbens DA depletion. On the other hand, apomorphine suppressed open-field locomotor activity in the sham group but not in the 6-OHDA group. However, because an increase in locomotion after apomorphine was not observed in the 6-OHDA group compared to saline treatment, it may be inferred that the supersensitivity of postsynaptic DA receptors induced by DA depletion was not fully developed. Moreover, accumbens DA depletion did not completely block the stimulant effect of amphetamine on locomotion as would be expected if all DA terminals in the accumbens had been destroyed (24). These observations indicated that 6-OHDA partially destroyed dopamine terminals in the accumbens and thereby partially blocked the action of apomorphine on dopamine autoreceptors.

The nucleus accumbens has been implicated in the mediation of motivational behaviors (27). Locomotion, as an element of exploratory behavior, is an expression of this class of behavior. For example, rats exhibit more locomotion in a new environment than in an environment to which they are habituated (37). However, in the current experiment, the force and timing measures of reinforced behavior were unaffected by accumbens dopamine depletion that was sufficient to affect locomotor activity. Thus, lesions affected one class of motivated behavior (locomotion) but not the other (beam pressing).

One possibility could be that the involvement of accumbens dopamine in the current beam pressing task was training dependent so that during the initial learning period accumbens dopamine was necessary for learning the task, and when the task was well learned, the importance of accumbens dopamine was greatly reduced. Some studies have indicated that during acquisition of lever-pressing tasks, microinjections of dopamine antagonists (4,54), or 6-OHDA lesion (43) to the accumbens impaired lever-pressing behaviors. Cell recording studies in monkeys (32,48) also demonstrated that more dopamine neurons in the midbrain fired in response to conditioning stimuli during the initial learning phase, and when the behavioral task was learned, these neurons greatly decreased their firing. In this experiment, the task was well learned, because the rats had been trained on the schedule for over 3 months before surgery was performed. Perhaps at the time of postlesion operant testing the importance of accumbens DA was greatly reduced.

Another possibility is that locomotion is mediated by accumbens dopamine, while beam pressing is not. By this argument, our finding was consistent with the observation by Amalric and Koob (2) that dopamine depletion (75%) in the accumbens did not impair reaction time performance. Moreover, in the same study, they demonstrated that dopamine depletion (59%) in the posterior caudate produced reaction time deficit. Similarly, Spirduso et al. (51) observed that dopamine depletion (11–14%) in the nigrostriatal pathway resulted in reaction time deficits, and Salamone et al. (47) found that dopamine in the ventrolateral striatum was more necessary for a normal interpress time distribution than that in the nucleus accumbens (10). Our recent data (30) also showed that dopamine depletion in the nigrostriatal pathway, induced by injection of 6-OHDA into the substantia nigra, produced operant response deficits in force and reaction time. Thus, it may be that dopamine in the mesolimbic pathway is not crucial in regulating force and timing measured in the present experiment, while dopamine in the other pathways might be more involved in force and timing.

We interpret our results as a support for the hypothesis that the suppressive effect of low doses of apomorphine on locomotion, but not on the force and timing of operant responding, is mediated by DA autoreceptors in the mesolimbic pathway.

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