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Low Doses of Apomorphine Suppress Operant Motor Performance in Rats

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LIU, X., R. E. STRECKER AND J. M. BRENER. *Low doses of apomorphine suppress operant motor performance in rats.* PHARMACOL BIOCHEM BEHAV 53(2) 335-340, 1996.—The purpose of this study was to examine the effects of low doses of apomorphine on motor performance. Six rats were rewarded with sugar water on a partial reinforcement schedule for pressing force-sensitive beams with a minimum force of 1 g. The kinetics of individual responses and the temporal characteristics of response sequences were measured; open field locomotor activity was also measured in a separate apparatus. Apomorphine (APO), amphetamine (AMP), and haloperidol (HAL) were administered systemically. It was found that low doses of APO (0.03 and 0.1 mg/kg, SC) produced weaker and longer beam presses. These decreases in response peak force resulted from decreases in the rate of rise of force. APO also caused disproportionate lengthening of beam release time. In addition, the low doses of APO increased the time intervals between consecutive components of response sequences. These low doses of APO are known to decrease dopaminergic tone. Hence, the observed pattern of motor dysfunctions produced by APO is similar to the bradykinesia seen in human Parkinson's disease.

Apomorphine Operant response Response sequence Locomotion Parkinsonian bradykinesia Rats

APOMORPHINE, a direct dopamine (DA) receptor agonist (2), elicits spontaneous motor behaviors, such as locomotion, rotation, and stereotyped behaviors, when given to rodents at doses generally greater than 0.5 mg/kg. However, the locomotor stimulating effects of this compound are not exhibited at low doses, such as 0.1 mg/kg. Evidence has shown that apomorphine has biphasic effects on locomotor activities (21), with high doses increasing locomotor activity and low doses decreasing locomotion (22). Although the locomotor stimulant effect is considered to be due to the activation of postsynaptic dopamine receptors in the forebrain (15,19), the locomotor suppressive effect of low doses has been attributed to the selective activation of dopamine autoreceptors present on the dopamine neurons, which results in inhibition of the electrical discharge of dopamine neurons and a reduction of dopamine synthesis and release (4-6,13,20,24). Thus, low doses of apomorphine are thought to produce a decrease in open field locomotor activity via a decrease in dopaminergic tone. This experiment employed a sensitive test of motor performance to determine whether low doses of apomorphine have similar suppressive effects on learned operant behavior.

Neuroleptic drugs, such as haloperidol, which antagonize the effects of dopamine by blocking dopamine receptors, also have depressant effects on motor performance. Haloperidol, clozapine, and pimozide have been shown to produce subtle motor impairments even at low subcataleptic doses (10,11). For example, low to moderate doses of haloperidol decreased the rate of operant responses and increased the durations of individual responses. If low doses of apomorphine also produce their behavioral effects by decreasing dopaminergic tone, then similar effects on operant responding might be expected with apomorphine. Amphetamine was administered to provide behavioral effects that contrast with those of low doses of apomorphine. Amphetamine, an indirect DA agonist, increases locomotor activity in rodents through increasing the release of dopamine (7,8) and may be expected to potentiate some aspects of operant motor responses even at low doses.

In the present study, rats were trained to press a force-

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sensitive beam to get sucrose on a partial reinforcement schedule. The effects of low doses of apomorphine (APO), haloperidol (HAL), and amphetamine (AMP) on performance were examined through recordings of response rate, the kinetic parameters of individual responses, and the organization of response sequences. The effects of AMP and APO on open field locomotor activity were also examined.

METHOD

Subjects

Six naive, male, Long-Evans rats, weighing 302-335 g (mean = 322 g) at the beginning of the experiment, were drawn from the colony maintained in the State University of New York at Stony Brook. Before operant training, the animals were handled and weighed every day for 2 weeks to familiarize the animals with the experimenter. The animals were maintained at about 92% of their free-feeding body weights by supplemental feeding of standard lab chow after the daily experimental session. They were housed under reversed lighting conditions with lights on from 2000 h to 0800 h. Room temperature was maintained constant at 20°C. Training or testing started at 1000 h daily, in a dark room next to the rat housing room.

Drugs

Apomorphine hydrochloride (Sigma) was dissolved in dilute ascorbic acid (0.2 mg/ml saline), injected SC in the neck with a dose of 0.03, 0.1, or 0.3 mg/kg, and the subjects were placed in the operant box 7 min after injection. Haloperidol (McNeil) was dissolved in a small volume of 2% lactic acid, diluted with saline, and the final pH corrected with dilute NaOH to above pH 5.0. Haloperidol was given IP in doses of 0.03, 0.1, or 0.3 mg/kg, 45 min prior to placement in the operant box. D-Amphetamine sulfate (Sigma) was dissolved in saline and injected IP at doses of 0.3, 1.0, or 3.0 mg/kg, followed by operant testing 15 min later. Doses of HAL and AMP were given at 72-h intervals and APO at 24-h intervals (16). All subjects received the three drug sequences in the same order: APO, HAL, and AMP. The intervals between the administration of each drug series was 7 weeks. Within each drug sequence the order of doses was counterbalanced across subjects. Control injections used the vehicle appropriate for each drug series.

Operant Apparatus and Procedures

The operant conditioning environment consisted of a Plexiglas box, 18 cm wide × 28.3 cm deep × 16 cm high. The front panel was made of sheet metal on which were mounted three aluminum force beams. A circular disc, 1.5 cm in diameter, horizontally fixed to the end of each beam, protruded 1.7 cm into the box. The disc was shielded in such a way that it was accessible to the subjects only from the top. A food tray was housed below each beam. Responses on each beam that exceed the "recognition criterion" of 1 g were recorded. A videocamera and monitor allowed observation of the animal's performance during each session.

Strain gauges were bonded to the shaft of the beam. Force applied to the disc caused small movements (< 1 mm) of the shaft and also resulted in changes of the electrical resistance of the strain gauges. These resistance changes, which were directly related to the force applied to the disc, were converted to voltage changes and amplified by using high stability DC amplifiers. Amplifier output was sampled at 1000 Hz via a 12-bit analog-to-digital (A/D) converter by a microcomputer, permitting force to be measured in units of less than 0.1 g. The computer was programmed to record and calculate the response parameters described below and to apply the reinforcement criterion. Only beam presses that exceeded a peak force of 1 g (9.76×10^{-3} N) were classified as responses. This measure was adopted to distinguish clearly the animal's activities from spurious signals induced, for example, by amplifier drift.

A stepper motor, which was positioned outside the sound-attenuating chamber in which the experimental box was housed, was used to deliver a fixed amount of liquid food (0.32 g/ml sugar solution) into the second tray directly below the central beam. The volume of each food reward was 16.66 μl and had an energy value of 37 calories. 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 subjects were allowed to earn 200 reinforcements by pressing the central beam (beam 2) with a minimum peak force of 1 g. Sessions were also terminated after 45 min, although drug-free trained subjects generally collected the 200 reinforcements in 10-15 min. Presses on the other two beams were recorded but were not rewarded. Rewards were always delivered to the central tray (tray 2), which was situated immediately below beam 2. Training continued on a daily basis until the kinetic and sequential properties of beam pressing performance were stable (approximately 2 weeks).

Operant Measures and Data Analysis

Four kinetic measures illustrated in Fig. 1 were recorded for each operant beam press. These are peak force (PF), the highest force reached during a single response, and its two determinants, time to peak force (TPF) and the rate of rise of force (dF/dT) (17). The TPF is the time interval from the onset of the response to the moment when PF was achieved and dF/dT is the average rate of rise of force during TPF. Beam release time (BRT), a measure of operant response termination, was measured as the time from PF to the moment at which force fell below the recognition criterion. Each of these measures was averaged over responses recorded during each session to provide session means for the kinetic parameters.

The temporal and sequential measures were: 1) interresponse time (IRT), the time from the onset of preceding beam response to the onset of the current beam response; 2) the B2T2 interval was measured as the time from the release of

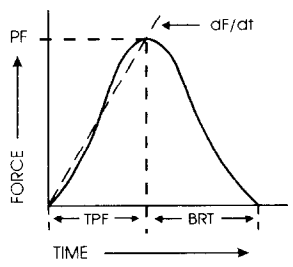

FIG. 1. A diagramatic illustration of the kinetic and temporal measures used to describe individual beam presses. Abbreviations are defined in the Method section.

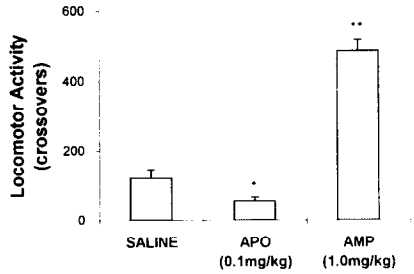

FIG. 2. Open field locomotor activity was measured as the total numbers of crossovers from one quadrant to another during a 45-min observation period, starting 15 min after injection of AMP (1.0 mg/kg, IP), APO (0.1 mg/kg, SC), or saline. Levels of significance: $*p < 0.05$ and $**p < 0.01$ compared with saline condition. Bracket shows SEM.

beam 2 to entering tray 2 and indexed switching from one component to the next component in the same sequence; 3) the T2B2 interval was measured as the time from exiting tray 2 to the onset of pressing beam 2 and indexed switching from the terminal component of one sequence to the first component of the next sequence.

For the analysis of the operant measures, means were obtained for no injection, vehicle injection, dose level 1, and dose level 2, respectively. Means were not computed for dose level 3 because several animals failed to perform at all under the highest dose of each drug. For the APO condition, data from the day preceding three saline sessions were taken as the control baseline (no injection) and the data from the three following saline days were averaged for each subject to provide a mean for the vehicle treatment. For both the AMP and HAL conditions, data from 3 days preceding the vehicle injections were averaged to provide a control baseline and those from the 3 days preceding the drug injection were averaged to provide means for the vehicle treatment.

One-way repeated-measure analyses of variance (ANOVAs) were performed for the kinetic, temporal, and sequential measures, using the four levels of treatments: no injection, vehicle, dose level 1, and dose level 2. TPF and BRT were compared for the APO series to see if the lengthening of TPF and BRT was symmetrical, by performing a two-way repeated-measure ANOVA [indices (2) × treatments (4)]. The Duncan test was used as a post hoc method to compare the effects of drugs with those of vehicle treatment. The differences from no injection condition were calculated for vehicle, dose level 1, and dose level 2 for the two sets of measures to plot graphs.

Open Field Locomotion

Sixteen weeks after the operant testing of drug series, the animals were tested in an open field box (38 cm long × 38 cm wide × 25 cm high), housed in the same room as the operant box, to measure open field locomotion. The testing was also performed in the dark part of the lighting cycle. A within-subject design was used in the six animals for the three treatments: saline, APO (0.1 mg/kg, SC), or AMP (1.0 mg/kg, IP). Because APO at 0.1 mg/kg (dose level 2) produced statistically significant changes in operant responses, this dose was selected for open field testing. Dose level 2 (1.0 mg/kg) of AMP was also used in the open field test. Rats were partially habituated to the open field box for 15 min to avoid floor effects, because over-habituation may prevent the animals from manifesting changes in locomotor activity, especially the decreases in locomotion (18). Following the habituation period, rats were injected with either AMP, APO, or saline and they were placed into the open field box immediately. Their behaviors were videotaped for 90 min. This procedure was run every other day, and the order of the three treatments was counterbalanced across subjects. The animals' performance in this open field was later scored by a research assistant, who had no knowledge about this experiment, but had been trained in scoring locomotor activity. The number of times the animals moved from one quadrant of the box to another during a 45-min period, starting 15 min after injections, were taken to index locomotor activities. Because it was predicted that the effects of small doses of APO on locomotion would be suppressive, and that of AMP would be stimulating, one-tailed dependent sample t-tests were used to examine statistical differences in locomotion between AMP or APO and saline.

RESULTS

Open Field Locomotion

The effects of AMP, APO, and saline on open field locomotor activity, in terms of the numbers of crossovers, are compared in Fig. 2. After saline injection, the mean number of crossovers within 45 min was 121. AMP (1.0 mg/kg) greatly increased locomotor activity (mean crossovers = 485); APO (0.1 mg/kg), on the other hand, significantly decreased the animal's locomotion (mean crossovers = 55). t-Tests, performed on 45-min crossovers for AMP or APO and saline, provided statistical support for these observations [$t(5) = 10.01, p < 0.01$; $t(5) = -2.11, p < 0.05$].

Drug Effects on Response Kinetics

The kinetic session means obtained from operant responses were very stable in the highly trained rats. Baseline control values of kinetics are provided in Table 1. As expected, one-way ANOVA revealed no differences between the baseline control values recorded for these kinetic measures in the different drug series. It should be noted that although the force criterion was arbitrarily set at the very low value of 1 g, animals responded with a force of approximately 5–7 g, which presumably is the default value for this variable.

Figure 3 compares the kinetic effects of three drugs. APO at 0.1 mg/kg (dose level 2) produced decreases in PF, $F(3, 15) = 4.47, p < 0.05$, and post hoc (Duncan test) comparisons showed the PF at this dose was significantly lower than those of other conditions. This effect can be attributed primarily to

TABLE 1

KINETIC AND TEMPORAL MEASURES FOR BASELINE (NO INJECTION) CONDITIONS PRIOR TO DRUG ADMINISTRATIONS

Measures	AMP	APO	HAL
PF (g)	5.98 (0.97)	6.56 (1.72)	5.76 (1.40)
dF/dT (g/s)	108 (19)	128 (29)	118 (29)
TPF (ms)	82 (12)	82 (17)	76 (15)
BRT (ms)	93 (14)	84 (14)	91 (21)
B2T2 interval (s)	0.152 (0.040)	0.155 (0.072)	0.154 (0.031)
T2B2 interval (s)	0.490 (0.178)	0.468 (0.138)	0.552 (0.166)
IRT (s)	1.203 (0.129)	1.111 (0.249)	1.104 (0.142)

Values are means with SD in parentheses.

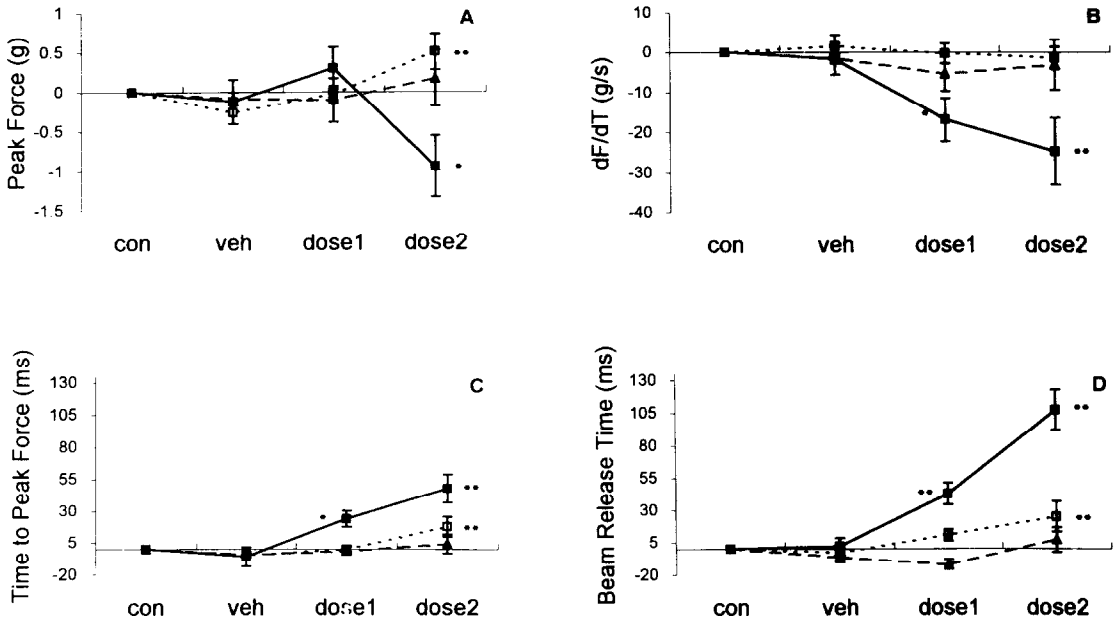

FIG. 3. Comparisons of effects of three drugs (AMP, APO, and HAL) on the kinetics as a function of the following four treatment conditions: control baseline (con), vehicle injection (veh), dose level 1 (dose1) (AMP: 0.3 mg/kg; APO: 0.03 mg/kg; HAL: 0.03 mg/kg), and dose level 2 (dose2) (AMP: 1.0 mg/kg; APO: 0.1 mg/kg; HAL: 0.1 mg/kg). The difference scores for PF, dF/dT, TPF, and BRT were computed by subtracting the mean values during the control period from the mean values recorded in each of the other treatments, and are illustrated in (A), (B), (C), and (D), respectively. The drug series of AMP, APO, and HAL are expressed as dotted line with open squares, solid line with filled squares, and dashed line with open triangles, respectively. Levels of significance: $*p < 0.05$ and $**p < 0.01$ compared with the respective vehicle conditions (Duncan test). Brackets show SEM.

the dose-dependent decreases in dF/dT, $F(3, 15) = 7.77, p < 0.01$. Although reciprocal increase in TPF, $F(3, 15) = 8.94$, $p < 0.01$, compensated for the decrease of dF/dT at 0.03 mg/kg, adjustments were not sufficient to compensate for the decrease in dF/dT at 0.1 mg/kg and, hence, as mentioned, PF fell at this dose. It will also be seen that BRT was significantly lengthened in a dose-dependent fashion, $F(3, 15) = 31.61$, $p < 0.01$, approximately twice as much as TPF, $F(3, 15) = 25.20, p < 0.01$.

In the AMP series, PF was elevated significantly at 1.0 mg/kg (dose level 2), $F(3, 15) = 6.33, p < 0.01$. Because dF/dT was not influenced by AMP, the elevation of peak force must have been caused by lengthening of TPF, $F(3, 15) = 5.30, p < 0.05$. This inference was confirmed by the post hoc comparison, which showed TPF was longer at 1.0 mg/kg than in the other conditions. BRT was also lenghened at 1.0 mg/kg of AMP, $F(3, 15) = 4.47, p < 0.05$.

Haloperidol did not change any of the kinetic measures significantly at 0.03 (dose level 1) and 0.1 mg/kg (dose level 2), whereas at 0.3 mg/kg HAL greatly disrupted performance, essentially blocking performance in five of the six rats.

Drug Effects on the Temporal Features of Response Sequences

Temporal and sequential measures were derived from an analysis of the behavioral sequence the rats performed. These temporal and sequential measures did not vary significantly during baseline (control) sessions over the course of the experiment (Table 1). Apomorphine had a significant influence on these temporal measures. One-way ANOVAs showed that the B2T2 interval, $F(3, 15) = 6.21, p < 0.01$, and the T2B2 interval, $F(3, 15) = 19.28, p < 0.01$, were both greatly lengthened at 0.1 mg/kg (dose level 2) (see T2B2 interval graph in Fig. 4A). This accounts for the significant lengthening of IRT (Fig. 4B) at this dose of APO, $F(3, 15) = 18.72, p < 0.01$.Although IRT showed a tendency to increase at 0.1 mg/kg (dose level 2) of HAL, neither HAL nor AMP significantly influenced any of the temporal measures.

Diagrammatic representations of the effects of APO and AMP on force-time envelopes are shown in Fig. 5. APO at 0.1 mg/kg lowered the default peak force, primarily through decreasing the rate of rise of force. In addition, APO lengthened both force rise time and force fall time, but lengthened the latter more. These changes resulted in the response envelope being flattened and asymmetrical with an elongated tail. The effects of AMP were to increase peak force, by increasing time to peak force without changes in the rate of rise of force. Force fall time was also lengthened by AMP. Therefore, the overall effect of AMP on the force-time envelope was an amplification.

DISCUSSION

Low doses of APO decrease DA tone due to a preferential action at DA autoreceptors. This results in a decreased release of DA at forebrain areas such as the caudate-putamen (5). The depression in operant motor performance caused by the

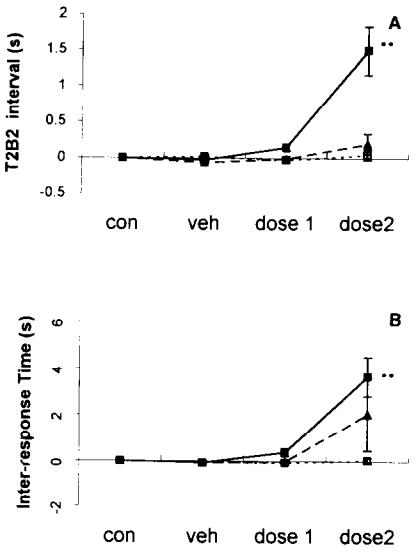

FIG. 4. Temporal and characteristics of beam presses. (A) The T2B2 interval was measured as the time from exiting tray 2 to pressing beam 2. (B) IRT was measured from the onset of the preceding beam press to the onset of the current beam press. The difference scores illustrated in both panels were computed by subtracting the mean interval during the control period from the mean interval recorded in each of the other treatments. The drug series of AMP, APO, and HAL are expressed as dotted line with open squares, solid line with filled squares, and dashed line with open triangles, respectively. Levels of significance: $*p < 0.05$ and $**p < 0.01$ compared with the respective vehicle conditions (Duncan test). Brackets show SEM.

low doses of APO may be mediated by this mechanism. The functional impairment of motor behaviors after injecting APO observed in the rats might be analogous to the motor deficits observed in Parkinson's disease, a neurological movement disorder characterized by the permanent loss of DA neurons.

The suppression of motor performance by APO was expressed through both the temporal features of responding and the force-time topography of individual responses. To get food in our paradigm, subjects had to chain a press of the central beam (B2) with a visit to the central tray (T2). Apomorphine (0.1 mg/kg) lengthened the B2T2 interval and the T2B2 interval. In other words, APO slowed down switching from one component of the sequence to the other. These results are paralell to that obtained in Parkinson's patients by Benecke et al. (3). In their study, patients were required to perform an isometric (ball squeeze) or an isotonic task (elbow flexion), and to chain the two components together. Parkinson's patients were slow when each single movement was performed seperately and even slower when two movements were executed sequentially. The duration of each of the component movements increased and so too did the pause between the first and the second movements.

Apomorphine also influenced the force-time envelopes of individual beam presses (see Fig. 3). Although the rate of rise of force (dF/dT) decreased at 0.03 mg/kg, TPF at this dose increased to maintain PF at baseline level. However, the decrease of dF/dT at 0.1 mg/kg was no longer compensated by the increase of TPF, and then PF fell. This suggests that the primary effect of APO, at least in this test, is to decrease dF/dT. Other studies have reported that patients with Parkinson's disease showed a decrease in the rate of rise of force when they were required to perform rapid isometric movements or a decrease in the speed of arm displacements in isotonic movements (9,12,14,23). It is reasonable to think that the depression in the rate of increase of muscle force is one of the characteristics of Parkinsonian bradykinesia.

Another interesting observation was that APO lenghtened the beam release time twice as much as it lengthened TPF, suggesting an impairment in response termination. Similar effects on response termination due to neuroleptics and 6-hydroxydopamine lesions have been reported by Fowler et al. (11) and by Amalric and Koob (1).

The attempt in the present experiment to generate the effects of dopamine blockade on motor performance by administration of HAL was not successful. At 0.03 and 0.1 mg/kg HAL did not produce significant effects on response topography whereas at 0.3 mg/kg, five out of six rats failed to respond. This may be due first to the range of doses selected. Haloperidol at 0.3 mg/kg seemed too high for operant testing. In Fowler et al.'s study (11), in which a narrower dose range was used (0.04, 0.08, and 0.16 mg/kg), HAL increased peak forces through increasing the rise time of the force-time envelope, while decreasing response rate. In the current experiment, HAL only produced a tendency for response rate to decrease (increase of IRT). Another factor contributing to the failure of the HAL treatment to influence performance may be the interaction between the force requirements and the effects of this drug. In Fowler et al.'s experiment, a force production of 10 g was required for the rats to obtain a reward. This implies that the animals had to learn to produce adequate peak force. In our paradigm, only 1 g of force was required to get a reward. Because the default peak force was about 6 g, achieving the force requirement in our paradigm required no learning. It seems possible that HAL would have more influence on learned force production.

Although comparisons of the effects on motor performance of APO with those of HAL yielded ambiguous results,

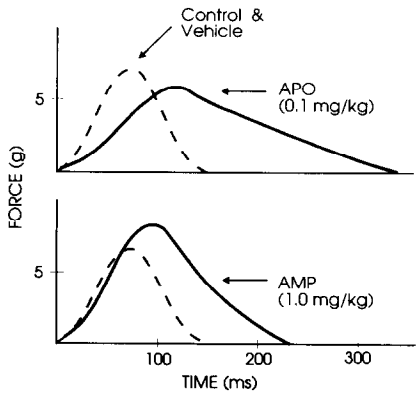

FIG. 5. Diagramatic illustrations of the effects of APO (0.1 mg/kg) and AMP (1.0 mg/kg) on force-time envelopes, which are constructed according to the mean kinetic measures of six rats. Baseline data (dashed curves) were derived by combining data from both the control and vehicle conditions. These conditions did not differ from each other statistically (see Table 1 and Fig. 3). The solid curves are representative force-time envelopes after the treatment of either AMP or APO, which are superimposed onto the control and vehicle curves.

comparisons of the effects of APO with AMP were clear. Unlike APO, AMP (1.0 mg/kg) did not influence response rate and the rats were as active as in the control condition. In contrast to APO, which produced decreases in PF and dF/dT, AMP generated higher PFs with no changes in dF/dT. Similarly, APO produced decreases of locomotor activity in the open field whereas AMP greatly increased rates of locomotion. Therefore, it can be concluded that low doses of APO have opposing effects to AMP on operant motor performance.

In summary, low doses of APO caused motor performance to slow by increasing the duration of each response and lengthening the times between consecutive responses. The treatment also caused decreases in peak force, primarily by decreasing the rate of rise of force. This APO-induced pattern of motor dysfunctions in rats appears to be similar to the bradykinesia seen in human Parkinson's disease.

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