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Comparison of the Effects of Prototypical Behavioral Stimulants on Locomotor Activity and Rotational Behavior in Rats

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GARRETT, B. E. AND S. G. HOLTZMAN. *Comparison of the effects of prototypical behavioral stimulants on locomotor activity and rotational behavior in rats.* PHARMACOL BIOCHEM BEHAV **54**(2) 469–477, 1996. – The present study was performed to characterize on rotational behavior the dose- and time-effect relationship of four prototypical behavioral stimulants that interact with dopamine systems via different mechanisms of action. Drug effects on rotational behavior was compared with effects on locomotor activity. The drugs examined were apomorphine (0.03–1.0 mg/kg), *d*-amphetamine (0.1–3.0 mg/kg), cocaine (3.0–56 mg/kg), and caffeine (10–100 mg/kg). SKF-38393 (0.3–10 mg/kg), a dopamine receptor agonist that has only modest effects on locomotor activity, was tested as a comparison. In rats with unilateral 6-hydroxydopamine (6-OHDA)-induced lesions of the nigrostriatal tract, *d*-amphetamine and cocaine dose dependently increased both the duration and the maximum number of turns/10 min, whereas apomorphine and caffeine increased only the duration of turning. There was a significant correlation of the effects of the four drugs on rotational behavior with effects on locomotor activity, but effects across drugs were not identical. Dose-response curves revealed potency differences among drugs in their effects on the two behaviors (e.g., apomorphine stimulated rotational behavior at a lower dose than it stimulated locomotor activity, whereas the converse was true with caffeine). Different mechanisms of action of these drugs might account for the differences in their effects on these behaviors.

Rotational behavior Locomotor activity 6-Hydroxydopamine (6-OHDA) Apomorphine *d*-Amphetamine Cocaine Caffeine SKF-38393

ROTATIONAL behavior is a model that is useful for studying the interaction of drugs with the nigrostriatal dopamine system. Psychomotor stimulant drugs and related directly and indirectly acting dopamine receptor agonists have been studied often by this method. When the nigrostriatal tract on one side of the brain is lesioned with 6-hydroxydopamine (6-OHDA), the presynaptic nerve terminals are destroyed and the postsynaptic membrane becomes supersensitive over a period of weeks as a result of upregulation of dopamine receptors and other compensatory changes. Drugs that act directly on postsynaptic dopamine receptors (e.g., apomorphine) produce contralateral turning in these rats (25). Drugs that release dopamine from and/or prevent its reuptake into presynaptic nerve terminals (e.g., cocaine and *d*-amphetamine) produce turning ipsilateral to the lesion (20,24,28).

Dopamine also mediates locomotor activity, but it is the mesolimbic dopamine system that appears to have the predominant role in the control of this behavior (13). Apparent differences in the underlying neural circuitry that governs locomotor activity and the direction of rotational behavior suggests that these two behaviors will be influenced differently by drugs under certain conditions. Indeed, bilateral destruction of the nucleus accumbens with 6-OHDA prevents stimulation of locomotor activity by amphetamine and cocaine, whereas bilateral destruction of the caudate nucleus does not (14,23). Furthermore, amphetamine and apomorphine do not cause rotational behavior in rats that have unilateral destruction of mesolimbic dopamine neurons (15).

There have been few direct comparisons of drug effects on locomotor activity and rotational behavior in a single laboratory where many key independent variables can be held constant between the two measures. The purpose of this study,

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therefore, was to compare the effects of four prototypical behavioral stimulants that interact with brain dopamine systems via different mechanisms of action on these two types of motor behaviors: apomorphine (direct dopamine receptor agonist), *d*-amphetamine (releases dopamine from presynaptic stores), cocaine (dopamine reuptake inhibitor), and caffeine [proposed to enhance dopamine-mediated neurotransmission secondarily to competitive blockade of adenosine receptors; (8)]. Dose–response relationships were determined for each drug; time–effect relationships also were determined for rotational behavior. The selective partial D_1 dopamine receptor agonist SKF-38393, which produces very modest effects on locomotor activity (6), was tested for purposes of comparison to the other prototypical behavioral stimulants. It was of interest to see if drug effects on the two behaviors would differ in ways that might reflect the underlying neural systems, and if one behavioral paradigm might be more appropriate than the other for studying interactions of a particular type of drug with these dopamine systems.

METHOD

Subjects

Male rats of Sprague–Dawley descent (Sasco Inc., Omaha, NE), weighing between 290–320 g after arriving from the supplier, were used. All rats were grouped housed in polycarbonate cages and maintained in a temperature-controlled colony room with a 12 L : 12 D cycle. Food (Purina Rodent Chow, Purina Mills, St. Louis, MO) and water were available ad lib.

Stereotaxic Surgical Procedure

Rats weighing 300–350 g were given unilateral lesions of the right nigrostriatal pathway by injection of 6-OHDA. Rats were anesthetized with 50 mg/kg, IP, pentobarbital (Nembutal solution) and placed in a stereotaxic frame. Stereotaxic coordinates relative to bregma were AP = −4.8, ML = −2.2, DV = −8.0, according to the atlas of Paxinos and Watson (1986). Using a 10 μl Hamilton syringe, 8 μg/4 μl of 6-OHDA in a solution of 0.02% ascorbic acid and 0.9% saline was injected into the right substantia nigra. The solution was injected at a rate of 1 μl/min for 4 min. Upon completion, the injection needle was kept in place for an additional minute to minimize back flow.

Rotational Behavior

Rotational behavior was measured using a four-station stainless steel rotometer (MED Associates, East Fairfield, VT) in two separate groups of rats (n = 8). Each rat was placed inside of a round stainless steel bowl (16″ diameter and 10″ high) with a transparent Plexiglas cover. The rat had a cloth belt around its midsection that was attached by velcro to a spring tether, which, in turn, was connected to a direction-sensitive rotation sensor mounted above the bowl. The rotometer detected direction changes (i.e., movement from left to right or vice versa through an arc of at least 5.625°), full rotations (movement through 360° in one direction, without any change in direction during the turn), and partial rotations (movement through 90° in one direction, without any change in direction during the turn) in the clockwise or counterclockwise direction. Rats were allowed to recover from surgery for 7 days and to habituate to the rotometers for at least 5 days before behavioral testing began. Thereafter, rats received 0.3 mg/kg apomorphine SC twice weekly for 2 weeks. Rats showing at least 50 full contralateral turns/10 min for 1 h were used for further testing. Rats satisfying this screening criterion have more than a 90% reduction in striatal dopamine levels (8,18). Rotational behavior testing was carried out two times per week, 3–4 days apart, for all drugs except caffeine, which was tested once a week.

Locomotor Activity

Locomotor activity was measured with six two-channel Electronic Activity Monitors (31404, Stoelting Co., Chicago, IL) in four separate groups of rats (n = 9). Each rat was placed in a polycarbonate rat cage (51 × 41 × 22 cm), which was centered on a sensor platform placed in a ventilated, sound-attenuating chamber that was illuminated by a fluorescent light bulb. The counting threshold of each sensor was calibrated with a swinging pendulum so that one channel of each sensor measured gross movements in the horizontal plane, corresponding to locomotion, and the other channel measured total movements; the difference between the two channels represented the fine movements, such as grooming and sniffing (4,6). Gross and fine movements could also be detected visually through peep holes in each door of the chambers. Rats were allowed to habituate to the activity chambers on 5 days before testing commenced. Activity testing was conducted twice weekly (Tuesday and Friday). Rats received a 30-min pretreatment before being placed in the activity chambers. The last 15 min of the pretreatment interval consisted of an acclimation period, during which activity was not recorded. Locomotor activity was then measured for 30 min.

Drug Administration

In the rotational behavior experiments, one group of rats received doses of caffeine (10–100 mg/kg) or apomorphine (0.03–1.0 mg/kg) and another group received doses of *d*-amphetamine (0.1–3.0 mg/kg), cocaine (3.0–56 mg/kg), or SKF-38393 (0.3–10 mg/kg). All drugs were administered as a 5-min pretreatment and doses of each drug were administered in a random sequence.

In the locomotor activity experiments, doses of caffeine (3.0–100 mg/kg), apomorphine (0.03–1.0 mg/kg), *d*-amphetamine (0.1–3.0 mg/kg), cocaine (3.0–56 mg/kg) or SKF-38393 (0.3–10 mg/kg) were administered in random sequences, each drug to a different group of rats. All drugs were administered as a 30-min pretreatment.

Data Analysis

Drug effects on duration of turning were analyzed using a two-factor repeated measures analysis of variance (ANOVA) with repeated measures on both factors (within-subject design). Drug effects on the maximum number of turns/10 min were analyzed using a one-factor repeated measures ANOVA.

Dose–response curves for locomotor activity and rotational behavior were compared using a linear correlation regression analysis. Each dose of all four test drugs was used to determine the Pearson correlation coefficient (r), the p-value, and the 95% confidence limits.

Drugs

Caffeine sodium-benzoate, *d*-amphetamine sulfate, cocaine hydrochloride, and 6-hydroxydopamine (6-OHDA) hydrobromide were obtained from Sigma Chemical Co. (St. Louis, MO). Apomorphine hydrochloride and SKF-38393 hydrochloride were obtained from Research Biochemicals, Inc. (Natick, MA). All drugs were dissolved in 0.9% saline, with the exception of apomorphine, 6-OHDA and SKF-38393.

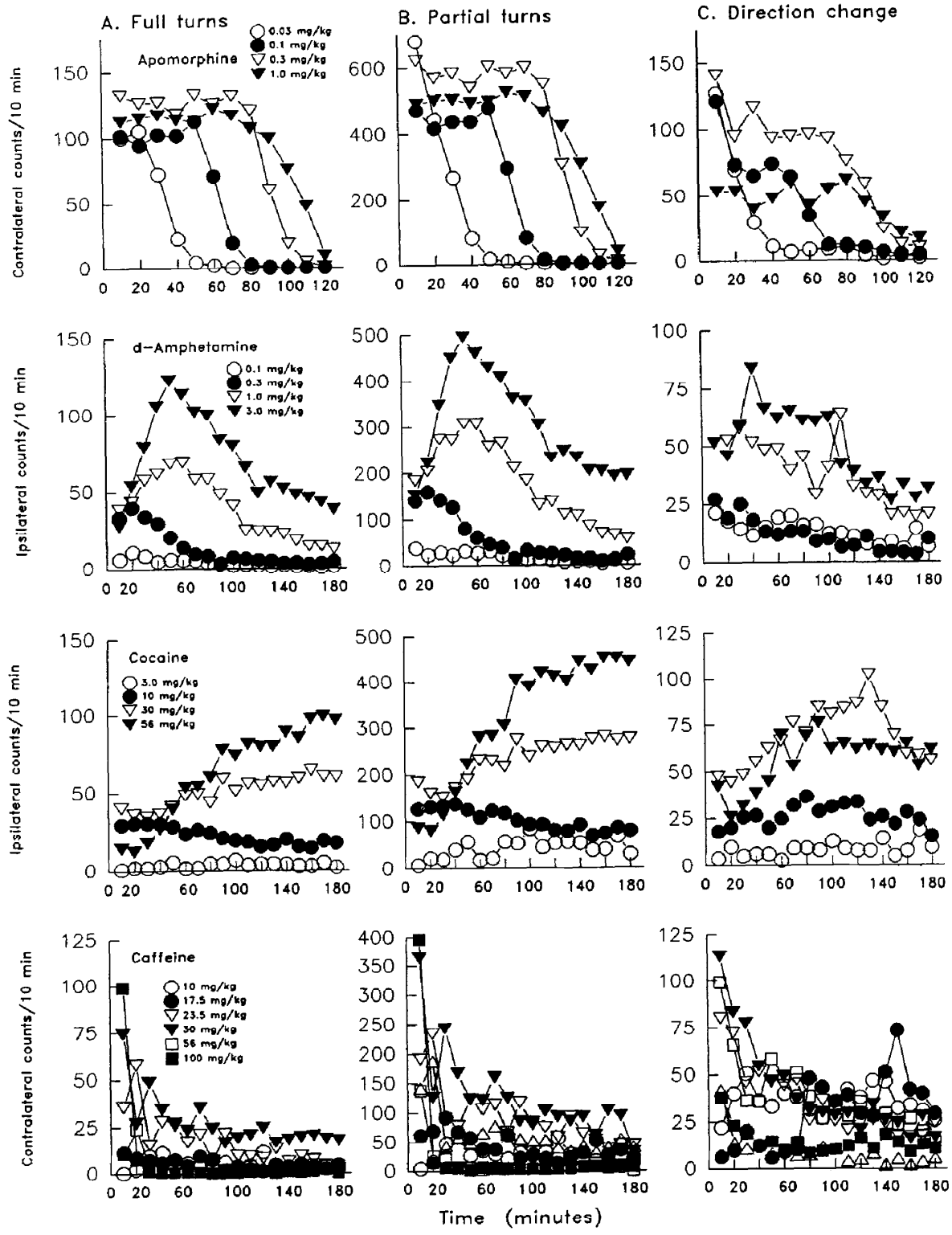

FIG. 1. Dose- and time-effect relationships for apomorphine, *d*-amphetamine, cocaine, and caffeine on rotational behavior. The dose- and time-effects of apomorphine (0.03–1.0 mg/kg), *d*-amphetamine (0.1–3.0 mg/kg), cocaine (3.0–56 mg/kg), and caffeine (10–100 mg/kg) on three measures of rotational behavior (full turns, partial turns, and direction change) were measured in rats with unilateral 6-OHDA-induced lesions of the nigrostriatal pathway. Rotational behavior was measured in 10-min intervals for a 2- or 3-h duration. Apomorphine (0.03–1.0 mg/kg) and caffeine (10–100 mg/kg) produced dose-dependent increases in the duration of full contralateral turns (A), partial turns (B), and direction changes (C). The maximum number of full contralateral turns (A), partial turns (B), and direction changes (C) was unchanged. *d*-Amphetamine (0.1–3.0 mg/kg) and cocaine (3.0–56 mg/kg) produced dose-dependent increases in both the duration and the maximum number of full ipsilateral turns (A), partial turns (B), and direction changes (C). Each point represents the mean number of turns or direction change/10 min.

Apomorphine and 6-OHDA were dissolved in a solution of 0.02% ascorbic acid in 0.9% saline. Apomorphine solutions were freshly prepared prior to use. Aliquots of 6-OHDA solution were stored in light-resistant vials at −20°C. An aliquot was thawed prior to use; any unused portions were disposed of after 2 h. SKF-38393 was dissolved in distilled water. Drugs were administered in a volume of 1.0 ml/kg body weight, with all doses expressed as the free base.

RESULTS

Figure 1 shows the dose- and time-effect relationship of apomorphine, *d*-amphetamine, cocaine, and caffeine for full turns (column A), partial turns (column B), and direction change (column C) over time. Apomorphine (0.03–1.0 mg/kg) produced a dose-dependent increase in the duration of both full and partial contralateral turns. For example, the lowest dose of apomorphine (0.03 mg/kg) increased full turns for a duration of approximately 40 min and the highest dose (1.0 mg/kg) increased full turns for a duration of approximately 110 min. Although apomorphine (0.03–1.0 mg/kg) produced a dose-dependent increase in the duration of full turns and partial turns, the maximum number of turns/10 min was unchanged. For example, each dose of apomorphine produced a maximum number of approximately 110 full turns/10 min. Apomorphine (0.03–1.0 mg/kg) also produced a dose-dependent increase in the duration of direction changes without affecting the maximum number of direction changes. For example, the lowest dose of apomorphine (0.03 mg/kg) increased direction changes for a duration of approximately 30 min, whereas the highest dose (1.0 mg/kg) increased direction changes for a duration of approximately 90 min. Each dose of apomorphine produced a maximum number of approximately 120 direction changes/10 min. As in the case with apomorphine, *d*-amphetamine (0.1–3.0 mg/kg) and cocaine (3.0–56 mg/kg) produced a dose-dependent increase in the duration of both full and partial ipsilateral turns. For example, the lowest doses of *d*-amphetamine (0.1 mg/kg) and cocaine (3.0 mg/kg) had minimal effects on full turns over the 3 h time course. The highest doses of *d*-amphetamine (3.0 mg/kg) and cocaine (56 mg/kg) increased full turns for a duration of more than 3 h. In contrast to apomorphine, *d*-amphetamine (0.1–3.0 mg/kg) and cocaine (3.0–56 mg/kg) produced a dose-dependent increase in the maximum number of both full and partial turns/10 min with the highest doses producing the peak increases in full turns and partial turns. *d*-Amphetamine (0.1–3.0 mg/kg)- and cocaine (3.0–56 mg/kg)-induced increases in direction changes also increased dose dependently with the highest doses producing the peak increases in direction change. Caffeine (10–100 mg/kg) had very modest effects on rotational behavior. The highest dose of caffeine (100 mg/kg) produced a peak increase in contralateral turning in the first 10 min of the 3-h session. However, this increase in turning diminished thereafter. There were only two doses of caffeine (23.5 and 30 mg/kg) that increased contralateral turning over the 3-h time course. The other doses of caffeine were relatively ineffective in producing turning. Pretreatment with these doses markedly stimulated the animals, as reflected by increases in direction changes (see Table 1 for statistical analysis).

Total locomotor activity is compared with three measures of rotational behavior (full and partial turns and direction change over the entire 2–3-h session) for apomorphine (0.03–1.0 mg/kg), *d*-amphetamine (0.1–3.0 mg/kg), cocaine (3.0–56 mg/kg), and caffeine (10–100 mg/kg) in Fig. 2. Apomorphine (0.03–1.0 mg/kg), *d*-amphetamine (0.1–3.0 mg/kg), and cocaine (3.0–56 mg/kg) produced a dose-dependent increase in total locomotor activity counts and also in full turns, partial turns, and in direction changes. As previously shown (4,9), caffeine (3.0–100 mg/kg) produced a biphasic increase in locomotor activity, the lowest (3.0 mg/kg, not shown) and the highest doses (100 mg/kg) producing little or no effect on locomotor activity and the intermediate doses (10 and 30 mg/kg) producing the peak increases in activity. Caffeine (10–100 mg/kg) also had a biphasic effect on rotational behavior (full turns and partial turns). The peak increase in rotational behavior occurred at the 23.5 and the 30 mg/kg doses. Direc-

TABLE 1

F-VALUES FOR DRUG EFFECTS ON DURATION OF TURNING AND MAXIMUM NUMBER OF TURNS/10 MIN FOR FULL AND PARTIAL TURNS AND DIRECTION CHANGE

Drug (Variable)	Duration of Turns	Max. Number of Turns/10 min
Apomorphine		
(full)	$F(33, 231) = 6.3, p < 0.0001$	$F(3, 7) = 1.34, p = 0.2855$
(partial)	$F(33, 231) = 5.2, p < 0.0001$	$F(3, 7) = 1.49, p = 0.245$
(direction)	$F(33, 231) = 3.18, p < 0.0001$	$F(3, 7) = 2.45, p = 0.09$
d-Amphetamine		
(full)	$F(51, 357) = 12.9, p < 0.0001$	$F(3, 7) = 35.9, p < 0.0001$
(partial)	$F(51, 357) = 7.12, p < 0.0001$	$F(3, 7) = 22.5, p < 0.0001$
(direction)	$F(51, 357) = 8.9, p < 0.0001$	$F(3, 7) = 31.8, p < 0.0001$
Cocaine		
(full)	$F(51, 357) = 5.59, p < 0.0001$	$F(3, 7) = 22.6, p < 0.0001$
(partial)	$F(51, 357) = 6.41, p < 0.0001$	$F(3, 7) = 25.2, p < 0.0001$
(direction)	$F(51, 357) = 1.61, p = 0.0069$	$F(3, 7) = 6.02, p = 0.004$
Caffeine		
(full)	$F(51, 357) = 4.6, p < 0.0001$	$F(3, 7) = 7.08, p = 0.0018$
(partial)	$F(51, 357) = 3.62, p < 0.0001$	$F(3, 7) = 8.23, p = 0.0008$
(direction)	$F(51, 357) = 3.94, p < 0.0001$	$F(3, 7) = 7.74, p = 0.001$

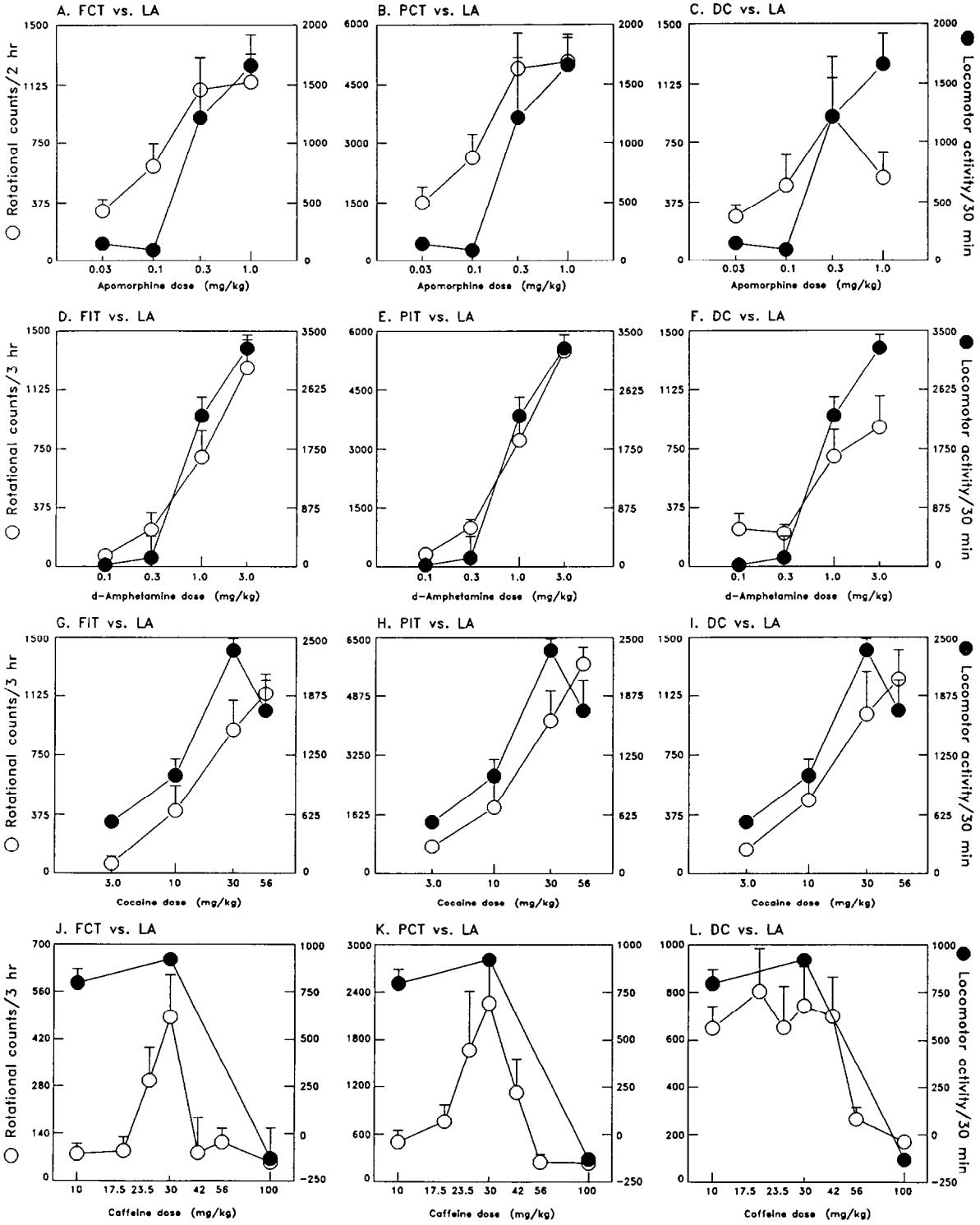

FIG. 2. Comparison of the effects of apomorphine, *d*-amphetamine, cocaine, and caffeine on rotational behavior and locomotor activity. The effects of apomorphine (0.03–1.0 mg/kg), *d*-amphetamine (0.1–3.0 mg/kg), cocaine (3.0–56 mg/kg), and caffeine (10–100 mg/kg) on three measures of rotational behavior (full turns, partial turns, and direction change) were compared to effects on locomotor activity. Rotational behavior was measured for 2 or 3 h and locomotor activity was measured for 30 min. Apomorphine (0.03–1.0 mg/kg), *d*-amphetamine (0.1–3.0 mg/kg), and cocaine (3.0–56 mg/kg) produced dose-dependent increases in total locomotor activity counts and all three measures of rotational behavior (full turns, partial turns, and direction change). Caffeine (10–100 mg/kg) produced biphasic increases on two measures of rotational behavior (full turns and partial turns). Locomotor activity was elevated at all doses except at the highest doses (56 and 100 mg/kg), which produced decreases in these measures. Each point represents the mean activity counts ±SEM or the mean number of turns ±SEM. FT = full turns (C = contralateral; I = ipsilateral), PT = partial turns (C = contralateral; I = ipsilateral), DC = direction change, LA = locomotor activity.

tion changes were elevated at each dose of caffeine tested except the 56 and the 100 mg/kg doses, which produced decreases in these measures. Direction changes and locomotor activity were virtually superimposable.

Figure 3 shows the correlation regression analyses for apomorphine (0.03–1.0 mg/kg)-*d*-amphetamine (0.1–3.0 mg/kg)-, cocaine (3.0–56 mg/kg)-, and caffeine (10–100 mg/kg)-induced rotational behavior (full turns, partial turns, and direction change) and locomotor activity (total, gross, and fine activity counts). Based on the regression analyses, drug effects on all three measures of rotational behavior correlated significantly with all three measures of locomotor activity for each drug. Although a significant correlation was shown in every measure of locomotor activity and rotational counts, some

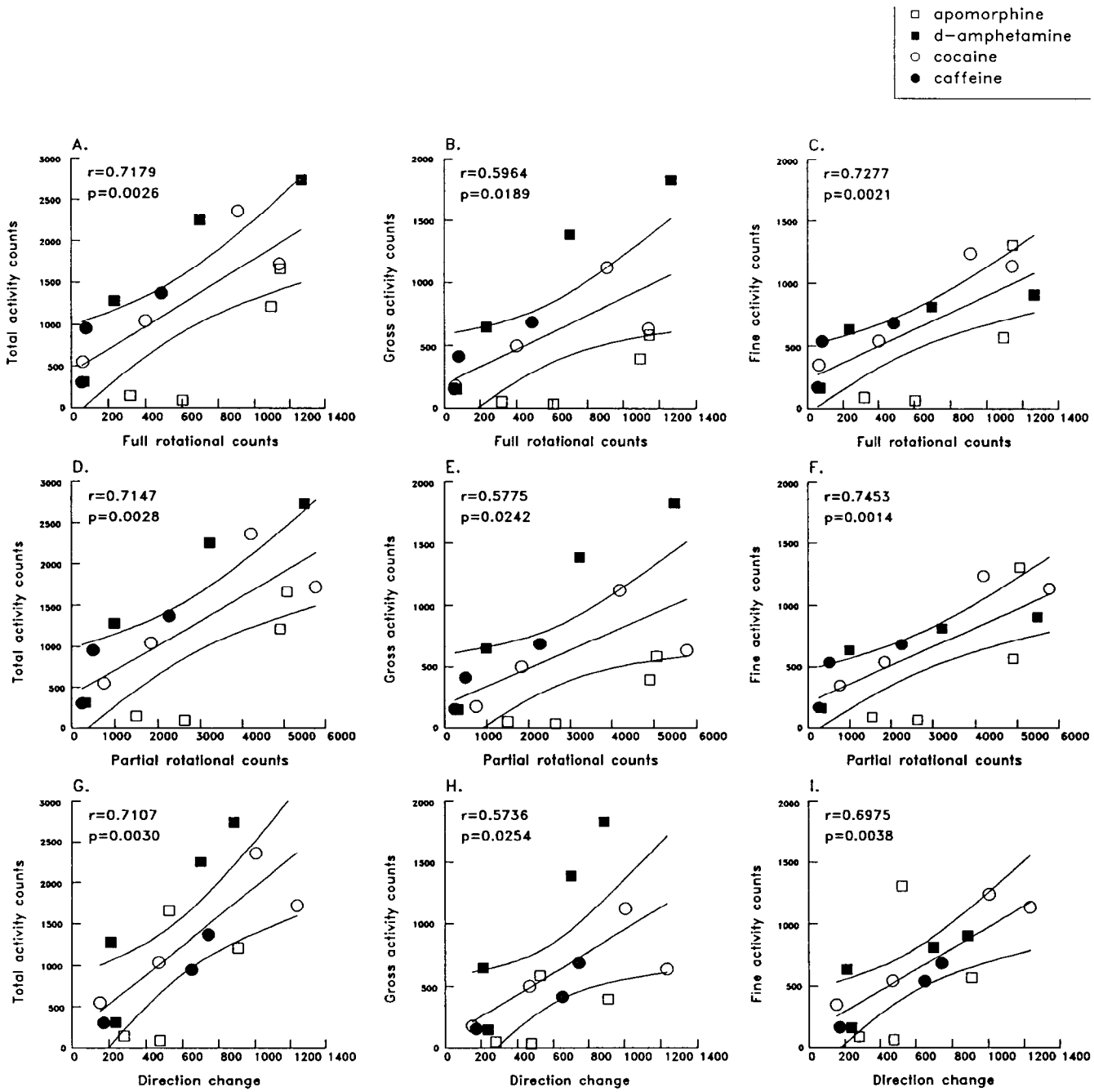

FIG. 3. Correlation regression analysis for locomotor activity and rotational behavior for each drug. The effects of apomorphine (0.03–1.0 mg/kg), *d*-amphetamine (0.1–3.0 mg/kg), cocaine (3.0–56 mg/kg), and caffeine (10–100 mg/kg) on three measures of locomotor activity (total, gross, and fine) were compared with their effects on three measures of rotational behavior (full turns, partial turns, and direction change). Drug effects on all three measures of rotational behavior correlated significantly with all three measures of locomotor activity for each drug dose.

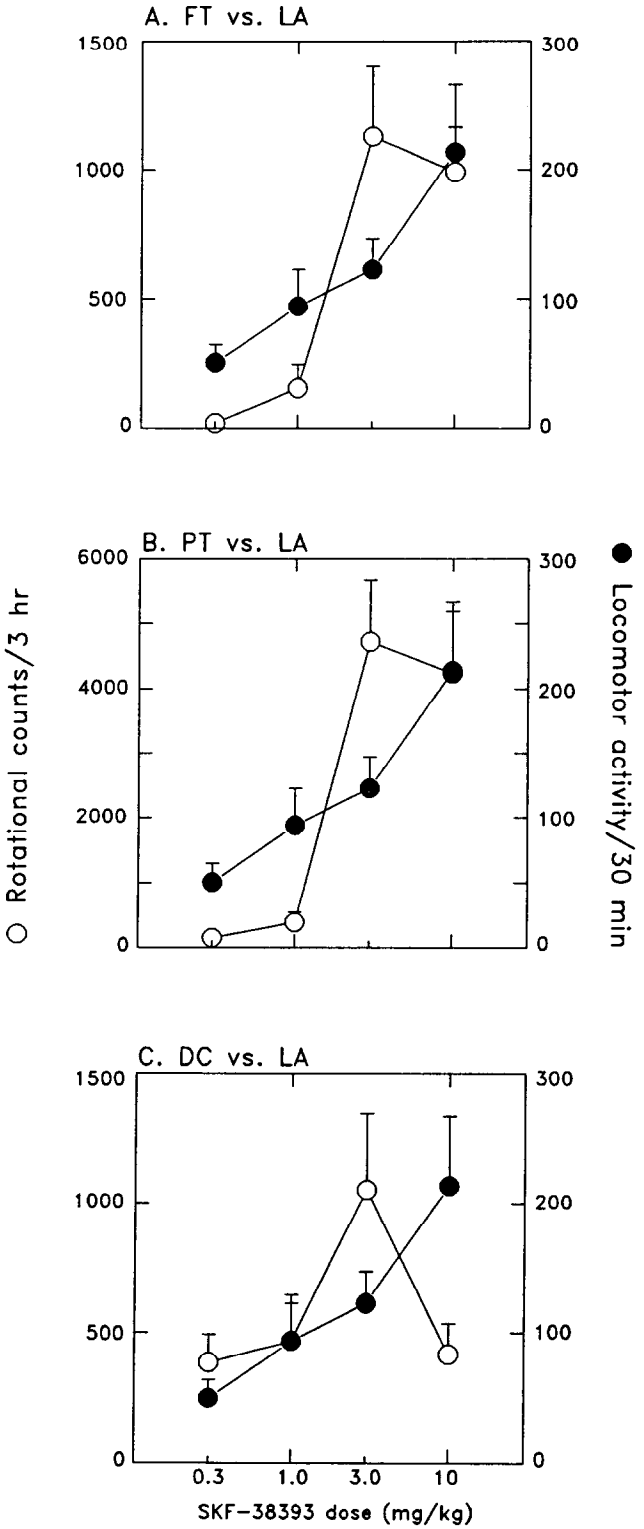

FIG. 4. Comparison of the effects of SKF-38393 on rotational behavior and locomotor activity. The effects of SKF-38393 (0.3–10 mg/kg) on three measures of rotational behavior (full turns, partial turns, and direction change) were compared to effects on locomotor activity. Rotational behavior was measured for 3 h and locomotor activity was measured for 30 min. SKF-38393 (0.3–10 mg/kg) produced moderate increases in total locomotor activity counts. These same doses of SKF-38393 produced profound increases in all three measures of rotational behavior (full turns, partial turns, and direction change). Each point represents the mean activity counts ±SEM or the mean number of turns ±SEM. FT = full turns, PT = partial turns, DC = direction change, LA = locomotor activity.

points fell outside the 95% confidence limits, notably the open and filled squares (apomorphine and *d*-amphetamine). In fact, in some instances there was not a significant correlation for a particular drug, for instance, apomorphine, panel I, open squares ($r = 0.3220$).

SKF-38393 (0.3–10 mg/kg)-induced rotational behavior (full turns, partial turns, and direction change/3 h) and total locomotor activity are compared in Fig. 4. In agreement with previous findings (1,2,6,27), SKF-38393 (0.3–10 mg/kg) produced very modest increases in locomotor activity counts. These same doses of SKF-38393 produced intense dose-dependent increases in full turns and partial turns. SKF-38393 produced a biphasic increase in direction changes with the peak increase occurring at the 3.0 mg/kg dose.

DISCUSSION

Despite sometimes large differences among the four prototypical behavioral stimulants in their dose- and time-effect relationships for rotational behavior, as others also have shown (24,29), their effects on rotational behavior and locomotor activity usually correlated significantly. For example, *d*-amphetamine and cocaine increased both locomotor activity and ipsilateral turning dose dependently, and apomorphine did the same for locomotor activity and contralateral turning. Both motor behaviors were affected in a biphasic manner by caffeine. However, the effects of the drugs on rotational behavior and locomotor activity were by no means identical. There were potency or efficacy differences between the two procedures for a given drug and the direction of those differences varied from one drug to another. For example, apomorphine stimulated turning at a 3–10-fold lower dose than it stimulated locomotor activity. In contrast, caffeine produced near-peak increases in locomotor activity at a dose, 10 mg/kg, that had essentially no effect on turning.

Turning induced by caffeine occurred over a narrow range of doses, less than twofold, similar to the results of a previous study (5). Locomotor activity, on the other hand, was increased by caffeine over at least a threefold range of doses in this study, and over a 30-fold range in other studies in which more doses were tested [e.g., (4,9)]. The reason for these differences in effects of caffeine on rotational behavior and locomotor activity is not clear but, presumably, is due to the different mechanisms by which caffeine affects the two behaviors. Many of the effects of caffeine on behavior are mediated by competitive blockade of adenosine receptors (22). One subtype of adenosine receptor, A_{2a}, is highly localized to the basal ganglia (16) and appears to have a negative modulatory influence on neurotransmission mediated by the D_2-dopamine receptor (3). The enhancement of dopaminergically mediated neurotransmission subsequent to blockade of the A_{2a}-adenosine receptor appears to be an important element in the mechanism by which caffeine stimulates locomotor activity (3). The importance of adenosine-receptor blockade in caffeine-induced rotational behavior is far from certain (7). CGS 15943, a nonxanthine competitive antagonist at adenosine re-

ceptors, is 25 times more potent than caffeine in stimulating locomotor activity in rats (10); however, it does not produce significant turning in rats with unilateral 6-OHDA-induced lesions of the nigrostriatal tract (7,11), dissociating completely the effects of this drug on the two behaviors.

In contrast to caffeine, SKF-38393 was more potent and efficacious in increasing rotational behavior than it was in increasing locomotor activity. The small increases in locomotor activity induced by SKF-38393 were generally within the range of baseline activity that occurs after an injection of a drug vehicle, such as saline; they were detectable, in part, because the animals had been thoroughly habituated to the testing procedure to ensure a low activity base line (6). Even so, the peak increase in locomotor activity after SKF-38393 was less than one-fourth that occurring after caffeine and less than one-tenth of the peak activity induced by amphetamine or cocaine. On the other hand, as shown here and elsewhere (11,21), SKF-38393 induced intense contralateral turning of a magnitude comparable to that induced by apomorphine, amphetamine, and cocaine.

Differences between drug effects on rotational behavior and locomotor activity may also be due to increased sensitivity of receptors in the denervated striatum. For instance, Herrera-Marschitz et al. (8) showed that caffeine injected unilaterally into the unlesioned striatum does not produce contralateral turning, but does so in rats with 6-OHDA-induced lesions. Subsequently, Josselyn and Beninger (12) reported that intrastriatal caffeine does, in fact, induce contralateral turning in the intact rat; however, caffeine induced much less turning in intact rats than it did in rats with nigrostriatal tract lesions. These findings suggest that dopaminergic denervation and/or postsynaptic supersensitivity is necessary for caffeine to produce a significant amount of rotational behavior. They may also explain why SKF-38393 produces robust contralateral turning at doses that produce only small increases in locomotor activity.

There have been many studies of the neural circuitry underlying the effects of drugs on locomotor activity and rotational behavior [e.g., (14,15,17,26); also, (13,19)]. Results from these studies suggest that the nigrostriatal dopamine system plays a predominant role in mediating the direction of rotational behavior, and that the mesolimbic dopamine system plays a predominant role in mediating the rate of turning and locomotor activity. The results of the present study do not provide any direct evidence about the relationship between rotational behavior vs. locomotor activity and different dopamine systems. Nevertheless, the differences in drug effects on rotational behavior vs. locomotor activity are compatible with the concept that the two behaviors are subserved by different neuronal substrates.

Both rotational behavior and locomotor activity are used widely as models to study drug interactions with dopamine systems. Our results may be useful for determining which behavioral paradigm (i.e., locomotor activity vs. rotational behavior) is more appropriate for studying the interactions of a particular drug with dopamine systems. For example, locomotor activity would be the better procedure for studying caffeine and, by implication, other methylxanthines, whereas SKF-38393 and, perhaps, other partial D_1 dopamine receptor agonists could best be studied using rotational behavior.

Numerous methodological approaches have been used for microanalysis of the locomotor activity response to drugs (13). In this study, for example, total activity was parsed into gross activity (movement in the horizontal plane corresponding to locomotion) and fine activity (small, often repetitive movements, such as grooming and sniffing), as described previously (4,6). In contrast, the number of full ipsilateral or contralateral turns has typically been the sole measure of drug effects on rotational behavior. In this study, we recorded three different measures of rotational behavior: full turns, partial turns, and direction change. These different measures remain to be characterized more completely. Nevertheless, it appears that full and partial turns reflect the same type of drug effect, whereas direction change, which is a measure of side-to-side movements, may reflect hyperactivity of the animal and a different component of drug action. Multiple measures of rotational behavior should allow a more complete characterization of the effects of a drug than only a single measure alone.

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