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Apparent Enhancement by SCH 23390 of Apomorphine-Induced Locomotor Activity in Mice

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MATSUMOTO, K., B. CAI, H. OHTA, L. IMAMURA AND H. WATANABE. *Apparent enhancement by SCH 23390 of apomorphine-induced locomotor activity in mice.* PHARMACOL BIOCHEM BEHAV **39**(3) 699–703, 1991.—Effects of the dopamine (DA) D_1 antagonist SCH 23390 and the DA D_2 antagonist (−)-sulpiride on apomorphine-induced characteristic changes in spontaneous motor activity were investigated in mice using the system we have devised for automatically analyzing animal behaviors in mice. Apomorphine (3 mg/kg, SC) markedly increased parameters of spontaneous motor activity such as locomotor activity and rearing time. Apomorphine-induced increase in locomotor activity had peaks at 5–20 and 30–50 min after administration, and its trough was closely related to the marked increase in rearing time induced by this agonist. Apomorphine-induced locomotor activity accumulated over a 40-min period from 5 to 45 min after apomorphine injection, during which apomorphine-induced increase in rearing time peaked, was significantly increased by intraperitoneal administration of 0.03 and 0.1 but not 0.01 mg/kg SCH 23390. Apomorphine-induced increase in rearing time was dose-dependently depressed by this antagonist. In contrast, (−)-sulpiride (10–40 mg/kg, IP) decreased apomorphine-induced increases in rearing time and locomotor activity rather than enhancing the latter parameter. These data suggest that the apparent enhancement by SCH 23390 of apomorphine-induced locomotor activity is mediated through DA D_1 receptors and does not always correlate with depression of apomorphine-induced rearing behavior in mice.

Apomorphine Dopamine D_1 receptors Dopamine D_2 receptors SCH 23390 (−)-Sulpiride
Locomotor activity Rearing behavior Grooming

MEASUREMENTS of spontaneous motor activity have often been used to obtain preliminary information on the behavioral properties of drugs acting on dopaminergic systems. Stimulation of central DA receptors induces characteristic behavioral changes such as sedation, stereotypy, fast and slow locomotion, rearing, grooming, and others (13). Each parameter of behavioral change has been suggested to have different sensitivity to dopaminergic drugs. For example, stereotyped sniffing and locomotion induced by apomorphine, a mixed D_1/D_2 agonist, are each blocked by both D_1- and D_2-receptor antagonists. In contrast, nonstereotyped sniffing induced by the selective D_1 agonist SK&F 38393 is blocked by SCH 23390, a selective D_1 antagonist, but not metoclopramide, a selective D_2 antagonist, whereas rearing and locomotion induced by SK&F 38393 are depressed by both D_1 and D_2 antagonists (6, 10, 16). Starr and Starr (13) have reported that D_2 and D_1 receptors are implicated in the mechanisms of locomotion and rearing, and that D_1 receptors are involved in the expression of grooming behavior. However, parameters of these behavioral changes appear with different time courses depending on the doses used. Moreover, drug-induced behavioral changes in small animals, such as mice, may be difficult to evaluate due to strain differences (11), empirical factors of observers, variability depending on the observation container, and others.

We have devised a new system for automatically analyzing in detail spontaneous motor activity in mice and have found using the system that apomorphine (3 mg/kg)-induced increase in total activity and locomotor activity shows two peaks at 5–15 and 40–50 min after administration and that the increase in apomorphine-induced rearing time peaks at 25–30 min after administration (8,9). In the present study, the effects of DA antagonists on the characteristic time courses of behavioral changes induced by apomorphine were examined by investigating the effects of SCH 23390 and (−)-sulpiride on apomorphine-induced changes in parameters of spontaneous motor activity using the same system as previously reported (8,9).

METHOD

Animals

Male ddY mice (28–36 g) were obtained from SLC Co., Shizuoka. Animals were housed for at least one week in a labo-

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ratory animal room before the experiments. Housing conditions were maintained thermostatically at 23±2°C with 60% humidity and a 12 h light/dark cycle.

Apparatus for Measurement of Spontaneous Motor Activity

The apparatus used for measurement of spontaneous motor activity in mice was the same as described in detail in previous reports (8,9). In brief, the system consisted of a doughnut-shaped cage (inner and outer diameters, 16 and 32 cm, respectively; height, 13 cm) with 36 detector units, which were radially arranged from the center of the cage. Each unit consisted of four pairs of photosensors (higher-, lower-, inner-, and outer-position sensors); the former two were horizontally and the latter two vertically arranged. Each pair of photosensors contained a phototransistor ($\lambda_p = 800$ nm) and light emitting diode (infrared with $\lambda_p = 950$ nm). Scanning of each detector unit (vertical scanning; 10 times/1 ms) was controlled by a one-chip microcomputer to check which pair of photosensors was detecting an animal body. A scan of all units required 36 ms (1 ms/unit × 36 units) and was controlled by a main CPU (Z-80), to which 36 vertical scanning data were sent and analyzed as changes in parameters of spontaneous motor activity. From scanning data, motion distance in each interval period was calculated and defined as locomotor activity. When the higher-position sensors, which were set at a height of 65 mm from the cage floor, turned on, the flag for rearing was set up. The number of times this flag was set was counted as number of rearings. During the time the flag was set up, the number of scanning times was accumulated and converted to duration of rearing time.

Visual Evaluation of Grooming Behavior

Time course of drug-induced grooming behavior in the doughnut-shaped cage was also compared. Briefly, after habituating animals to the cage for 30 min, time spent for grooming was directly recorded every 5 min by one experimenter, using a hand-held digital timer. In some experiments, the behavior of the animal was videorecorded (s-VHS movie camera, HQ AG-410, National, Osaka, Japan) for later analysis.

Drug Administration and Data Collection

Experiments were carried out from 9 a.m. to 4 p.m. To habituate a mouse to a new context, the animal was placed in the doughnut-shaped cage 10 min before starting the experiments, and data were collected every 5 min for more than 120 min. Apomorphine was subcutaneously injected 20 min after starting the experiment. SCH 23390 and (−)-sulpiride were intraperitoneally injected 30 and 60 min before apomorphine administration, respectively. All drug solutions were prepared immediately prior to the experiments. SCH 23390 maleate (Shearing Co., NJ) and apomorphine hydrochloride (Sigma) were dissolved in saline alone and saline containing 0.05% ascorbic acid, respectively. Sulpiride (Fujisawa Pharm. Co. Ltd., Japan) was dissolved in 0.1 N HCl, before dilution with saline.

Statistical Analysis

One-way analysis of variance (ANOVA) followed by Duncan's multiple comparison test was used to evaluate the results obtained. A difference was considered statistically significant at $p<0.05$.

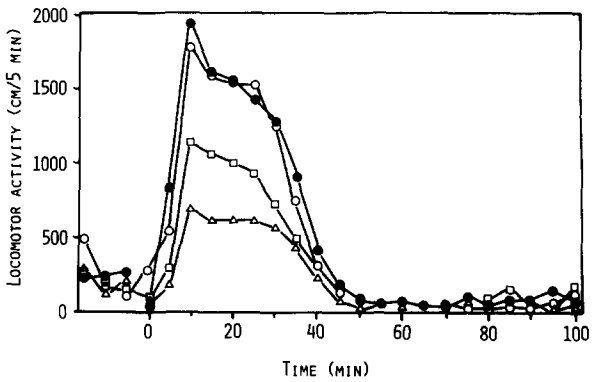

FIG. 1. Effects of SCH 23390 on 1 mg/kg apomorphine-induced increase in locomotor activity. Time course of changes in locomotor activity. Apomorphine (1 mg/kg, SC) was injected at time 0. SCH 23390 [0.003 (○), 0.01 (□) and 0.03 mg/kg (△)] or saline (●) was intraperitoneally injected 30 min before apomorphine. Each point is the mean value of 14 experiments.

RESULTS

Apomorphine markedly and dose-dependently increased locomotor activity. At a dosage of 1 mg/kg, apomorphine-induced increase in locomotor activity peaked 10-20 min after administration (Fig. 1), while at 3 mg/kg, it peaked approximately 5–15 and 35–45 min after apomorphine administration (Fig. 2). Rearing time accumulated for 40 min after 1 mg/kg apomorphine administration slightly but not significantly increased [saline: 126.2±38.1 s; 1 mg/kg apomorphine: 262.6±95.7 s (mean± S.E.M.), n=10–14]. This parameter was markedly increased by 3 mg/kg apomorphine and peaked approximately 20–30 min after administration (Figs. 2 and 3).

SCH 23390 (0.003, 0.01 and 0.03 mg/kg) dose-dependently decreased the effect of 1 mg/kg apomorphine on locomotor activity in mice (Fig. 1). On the other hand, 0.03 mg/kg SCH 23390 significantly enhanced 3 mg/kg apomorphine-induced increase in locomotor activity which was detected from 5 to 45

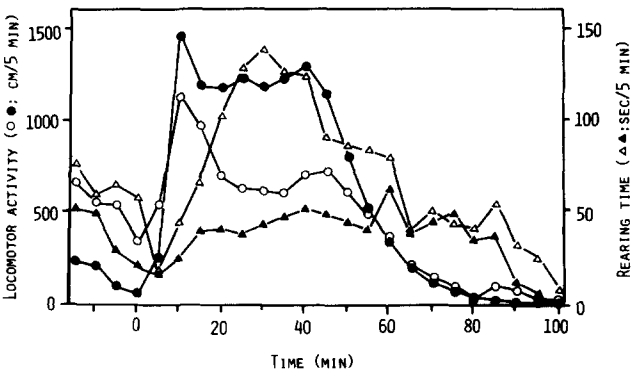

FIG. 2. Time courses of 3 mg/kg apomorphine-induced changes in locomotor activity and rearing time after SCH 23390 administration. Apomorphine (3 mg/kg, SC) was injected at time 0. SCH 23390 (0.03 mg/kg, closed symbols) or saline (open symbols) was intraperitoneally injected 30 min before apomorphine administration. Each point is the mean value of 10 experiments.

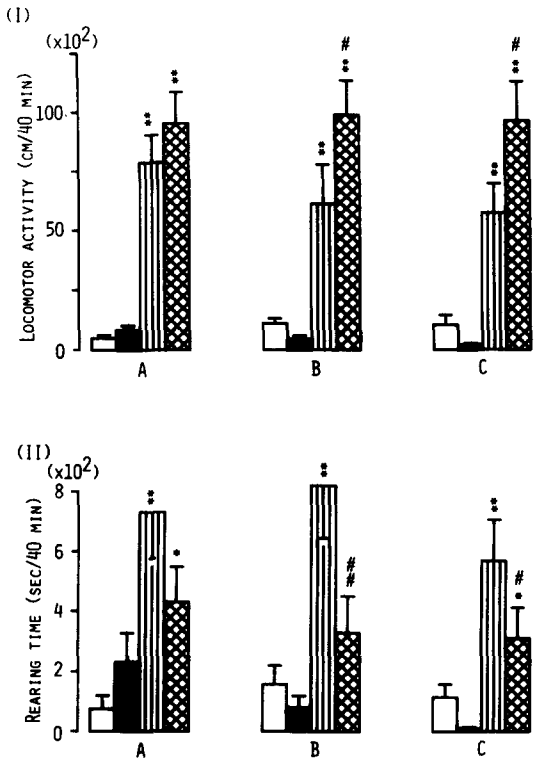

FIG. 3. Effects of SCH 23390 on 3 mg/kg apomorphine-induced increase in locomotor activity and rearing time. SCH 23390 [0.01 (A), 0.03 (B) and 0.1 mg/kg (C)] was intraperitoneally injected 30 min before apomorphine administration. Apomorphine (3 mg/kg, SC) was injected at time 0. Apomorphine-induced increase in locomotor activity (I) and rearing time (II) was accumulated over a 40 min period from 5 to 45 min after apomorphine administration. Open, closed, striped and crossed columns represent control, SCH 23390 alone, 3 mg/kg apomorphine alone and SCH 23390 plus apomorphine administration. Each datum represents the mean of 10–15 experiments, with the S.E.M. indicated. $*p<0.05$ and $**p<0.01$ compared to saline. $\#p<0.05$ and $\#\#p<0.01$ compared to apomorphine alone.

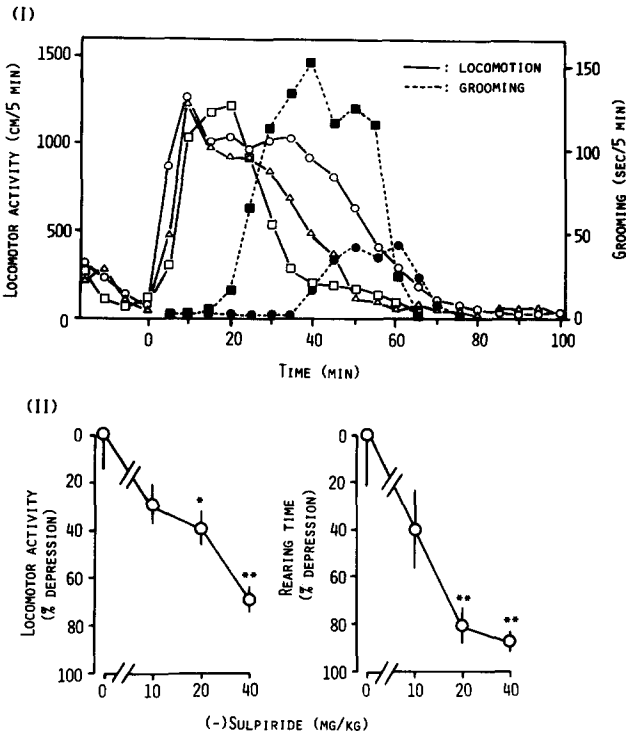

FIG. 4. Effects of (−)-sulpiride on apomorphine-induced increase in locomotor activity, grooming behavior and rearing time. (I) Time course of changes in locomotor activity (open symbols) and grooming behavior (closed symbols). Apomorphine (3 mg/kg, SC) was injected at time 0. (−)-Sulpiride [0 (○, ●), 10 (△) and 20 (□, ■) mg/kg] was intraperitoneally injected 60 min before apomorphine (3 mg/kg). Each datum represents the mean of 15 (for locomotor activity) or 7 (for grooming behavior) experiments. (II) Dose-dependent effect of (−)-sulpiride on the parameters (locomotor activity and rearing time) increased by 3 mg/kg apomorphine was expressed as % depression of apomorphine-induced increase in each parameter. Each datum was accumulated for 60 min after apomorphine administration and represents the mean of 15 experiments with the S.E.M. indicated. $*p<0.05$ and $**p<0.01$ compared to apomorphine alone.

min after administration (Figs. 2 and 3). SCH 23390 enhancement of apomorphine-induced locomotor activity was accompanied by a marked increase in the average speed of movements (data not shown). Apomorphine (3 mg/kg)-induced locomotor activity was enhanced by a higher (0.1 mg/kg) but not a lower (0.01 mg/kg) dosage of SCH 23390 (Fig. 3). In contrast, the total rearing time increased by apomorphine (3 mg/kg) was significantly decreased by SCH 23390 (0.03 and 0.1 mg/kg). As reported previously (8), the increase in number of rearings during the 40 min-period from 5 to 45 min after administration of 3 mg/kg apomorphine was not as marked as the rise in total rearing time (number of rearings in control and apomorphine-treated mice were 67 ± 22 and 134 ± 25 counts/40 min (mean ± S.E.M., $n = 10$), respectively; total rearing time in control and apomorphine-treated mice were 158 ± 55 and 823 ± 176 s/40 min, respectively).

(−)-Sulpiride (10–40 mg/kg, IP) dose-dependently decreased total locomotor activity and rearing time, both of which were accumulated for 60 min after apomorphine (3 mg/kg) injection (Fig. 4-I and 4-II). On the other hand, in the mice treated with apomorphine (3 mg/kg, SC) plus (−)-sulpride (20 mg/kg, IP), enhanced grooming behavior appeared about 20 min postadministration, peaked at 30–40 min after apomorphine administration and continued for more than 30 min (Fig. 4-I).

DISCUSSION

The present results demonstrate that the locomotor activity induced by a high dose of apomorphine (3 mg/kg) is apparently enhanced by the DA D_1 antagonist SCH 23390 but not the DA D_2 antagonist (−)-sulpiride. Apomorphine (3 mg/kg)-induced locomotor activity had two peaks, and its trough was closely related to apomorphine-induced marked increases in rearing time. These data agree well with our previous reports (8,9). Similar behavioral characteristics induced by dopaminergic agents have been reported by other groups using stereotyped behavior in rats (1) and rotational behavior in rats and mice (7,14). Characteristic and different time courses of changes in behavioral parameters (i.e., locomotor activity and rearing time) may be due to behavioral competition as described by Mandel et al. (7); i.e., one type of behavior (e.g., locomotor activity) decreases due to a large increase in other types of behavioral responses (e.g., rearing and/or stereotypy).

When administered alone, SCH 23390 has been shown to produce sedation by antagonizing at postsynaptic D_1 receptor sites against endogenous DA. At a similar range of dosages, SCH 23390 produced different effects on apomorphine-induced increase in locomotor activity depending on the dose of apomorphine used; i.e., this antagonist depressed 1 mg/kg apomorphine-induced locomotor activity but apparently enhanced 3 mg/kg apomorphine-induced locomotor activity and the average speed of locomotion. The former depressive effect of SCH 23390 is consistent with the data reported by Vaccheri et al. (15) that SCH 23390 antagonized apomorphine (300 μg/kg, SC)-induced hypermotility. On the other hand, (−)-sulpiride, a selective D_2 antagonist, dose-dependently decreased rather than enhanced locomotor activity induced by a mixed D_1/D_2 agonist, apomorphine (3,12). Thus, these results suggest that DA D_1 receptor sites may be involved in SCH 23390 enhancement of apomorphine (3 mg/kg)-induced locomotor activity.

Many reports have shown that DA D_1 receptor stimulation is required for full expression of pharmacological effects of DA agonists primarily in nonlesioned preparations (5, 17, 18). Therefore, the apparent enhancement of apomorphine (a mixed type of D_1/D_2 agonist)-induced locomotor activity by the D_1 antagonist SCH 23390 presents a clear contradiction to these reports. The reason for this discrepancy remains unclear, but species and/or strain differences of animals used or difficulty in visual evaluation of apomorphine-induced behavioral responses in mice may be contributing factors (11).

There is a possibility that the stimulatory effects of SCH 23390 on apomorphine-induced locomotor activity may be due to selective blocking of apomorphine-induced sedation which is mediated through presynaptic DA autoreceptors (2). However, this does not seem to be the case as SCH 23390 has been reported to intensify the depressive effects of apomorphine on locomotor activity in mice rather than to counteract the effects of this agonist. Furthermore, presynaptic DA autoreceptors have been shown to be of the DA D_2 type (4).

Rearing behavior is generally measured as the incidence of rearing. This behavior is not only mediated by DA D_2 receptor stimulation but can also be modified by DA D_1 receptor agents (10,13). Using a newly devised system for measurement of animal movement, our present and previous studies demonstrate that a high dose of apomorphine (3 mg/kg) markedly increases rearing time rather than the number of rearings. Furthermore, the present study indicates that SCH 23390 enhancement of apomorphine-induced locomotor activity appears in parallel with blocking of apomorphine-induced increase in rearing time. Therefore, the depressive and apparent stimulatory effects of SCH 23390 (0.03 mg/kg) on apomorphine-induced locomotor activity seem closely dependent on the appearance of significant stimulatory effect of apomorphine on rearing time. Moreover, the present results suggest that SCH 23390 could simply shift apomorphine-induced behavioral responses from rearing behavior to locomotion, resulting in an apparent increase in locomotor activity. Such a behavioral competition shift by SCH 23390 appears to be not the only factor relating to SCH 23390 enhancement of 3 mg/kg apomorphine-induced locomotor activity in mice, since (−)-sulpiride, a selective D_2 antagonist, dose-dependently decreased apomorphine-induced increase in rearing time without enhancing locomotor activity. The mechanisms underlying the apparent enhancement by SCH 23390 of apomorphine-induced locomotor activity remain to be elucidated.

In summary, this is the first report, to our knowledge, to show the apparent enhancement of apomorphine-induced locomotor activity by the D_1 antagonist SCH 23390. The exact mechanisms involved remain to be clarified, but the present results suggest that the blocking of apomorphine-induced rearing behavior by SCH 23390 may be only one of many factors involved in these phenomena.

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