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# Cocaine-Induced Locomotor Activity in Rats[1]

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YEH, S. Y. AND C. A. HAERTZEN. *Cocaine-induced locomotor activity in rats.* PHARMACOL BIOCHEM BEHAV **39**(3) 723–727, 1991.—Rats were injected SC or IP with a dose of cocaine at 20 mg/kg twice daily or saline (2 ml/kg) for 15 consecutive doses. Horizontal (including ambulatory and repetitive activity) and ambulatory locomotor activities were assessed following the first (acute) and the 15th (chronic) injections. Total locomotor activity (area under curve, AUC) following the acute and the chronic administration of cocaine were comparable, regardless of the route of drug administration. However, the temporal patterns of activity were significantly different; the peak of locomotor activity occurred earlier (chronic vs. acute, 20 vs. 40 min after IP; 130 vs. 180 min after SC) following chronic cocaine administration. Furthermore, the peak activity was significantly higher (3-fold after IP and 50% after SC) in chronically than in acutely treated rats, providing evidence for sensitization. In contrast, activity in the late session (240–280 min after SC) was significantly lower following the chronic SC cocaine administration, providing evidence for desensitization. The absolute slope values of the ascending phase and the descending phase were significantly larger following chronic administration of cocaine than that following the acute dosing. The possibility of changes in locomotor activity with alteration of pharmacokinetics on chronic cocaine treatment is discussed.

Cocaine Locomotor activity

COCAINE-INDUCED sensitization of locomotor activity (4, 6–8, 15–18), of stereotyped behavior (1, 4, 5, 9, 10, 15), of convulsions and seizures (5) and of lethality (5) have been observed in animals as well as in humans. Sensitization of cocaine-induced locomotor activity and stereotypy has been observed after a single cocaine injection, and the sensitization was shown to persist for up to 4 months after withdrawal of the drug from mice chronically injected IP with cocaine at a dose of 20 mg/kg for 4 days (19). This suggests a long-lasting physiological change following chronic cocaine administration. Sudden death in cocaine abusers may be due to sensitization induced by chronic cocaine administration.

Mechanisms underlying the sensitization of cocaine-induced locomotor activity and stereotypy following chronic administration of the drug are not clear. Most previous studies on cocaine-induced locomotor activity utilized IP administration and total activity monitored from 0 to 40 min. Since cocaine-induced locomotor activity quickly returned to the control level after IP administration (4, 6–8, 15–18), the present study was designed to compare the effect of cocaine-induced locomotor activity after SC administration with that after IP administration.

## METHOD

Male Sprague-Dawley rats weighing 200–225 g were maintained on Purina chow and water available ad lib in groups of 3 per polypropylene cage with corn chips as bedding upon their arrival. The rats were kept in an air-conditioned vivarium (22 ± 1°C) with 12-h light-dark cycle (light on at 0700 h) for one week before being used for an experiment at 0800 h on weekends. Rats were transferred from the vivarium to a quiet laboratory, weighed, and placed individually in an activity monitor (40 × 40 × 30 cm; Digiscan Optical Animal Activity Monitor, model RXY, Omnitech Electronics, Inc., Columbus, OH). After an exploratory period of about 30 min, the rats were taken out of the monitor, injected IP or SC with a dose of cocaine at 20 mg/kg (as free base) dissolved in saline at a volume of 2 ml/kg, or saline, and placed back in the monitor. Horizontal (including ambulatory and repetitive movements) and ambulatory activities were monitored immediately in 10-min intervals for a period of 120 min after an IP dosing or 300 min following an SC dosing. Horizontal and ambulatory activity were registered every 10 min by a "dataloger." No one entered the lab during the experimental period. The rats were returned to the vivarium after the experiment and injected IP or SC with 20 mg/kg of cocaine or saline twice daily (0800 and 1800 h) for 7 days. On the 8th day, the rats were transferred to a quiet laboratory, injected with the same dose of cocaine or saline and activities monitored as that described after the first injection. Areas under curve (AUC) of horizontal and ambulatory activity were calculated according to the trapezoidal rule. The mean slope of the ascending phase of the activity curves was calculated from 10 to 180 min (the peak activity point), and 10 to 130 min following the acute and chronic SC cocaine administration, respectively. After the acute and chronic SC cocaine administration, the mean slope of the descending phase of the activity curve was calculated from 180 (the peak activity point) to 300 min, and 130 to 300 min, respectively. Following the acute and chronic IP cocaine administration, the mean slope of the ascending phase of the curves was calculated from 10 to 40 min (the apparent peak activity point) and 10 to 20 min, respectively. The mean slope of the descending phase of the activity curve was calculated from 40 (the peak

[1]A preliminary report of these experiments appeared in FASEB J. A680; 1990.

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TABLE 1

COMPARISON OF THE COCAINE-INDUCED LOCOMOTOR ACTIVITY IN THE ACUTE AND CHRONIC COCAINE-TREATED RATS AFTER IP DRUG ADMINISTRATION[1]

| Intervals | Treatment | Horizontal Activity | Ambulatory Activity | AUC of Horizontal Activity | AUC of Ambulatory Activity |
|---|---|---|---|---|---|
| | | Counts, Mean ± S.D. | | Minute-Counts, Mean ± S.D. | |
| 0 to 30 min | | | | | |
| | Acute[2] | 3470 ± 227 | 1582 ± 175 | 25595 ± 2593 | 11462 ± 2188 |
| | Chronic[3] | 6748‡ ± 670 | 3607‡ ± 546 | 54446‡ ± 3330 | 29483‡ ± 2601 |
| 0 to 40 min | | | | | |
| | Acute | 5765 ± 625 | 2705 ± 250 | 46178 ± 3322 | 21433 ± 1133 |
| | Chronic | 9440† ± 874 | 4910† ± 617 | 80911‡ ± 7025 | 42584‡ ± 5522 |
| 0 to 50 min | | | | | |
| | Acute | 7901 ± 1296 | 3712 ± 599 | 68332 ± 9514 | 32085 ± 4205 |
| | Chronic | 11353* ± 1313 | 5684* ± 747 | 103965† ± 10484 | 52969† ± 6407 |
| 0 to 60 min | | | | | |
| | Acute | 10092 ± 2246 | 4794 ± 1099 | 89967 ± 17704 | 42528 ± 8488 |
| | Chronic | 13177 ± 1546 | 6389 ± 897 | 122653* ± 14260 | 60363* ± 8188 |
| 0 to 120 min | | | | | |
| | Acute | 17206 ± 5449 | 8048 ± 2803 | 166967 ± 52234 | 78190 ± 26776 |
| | Chronic | 19717 ± 8433 | 9442 ± 4230 | 192198 ± 76024 | 91963 ± 38169 |

[1]Rats were IP injected with cocaine at 20 mg/kg (as free base), twice daily. [2]After the first injection. [3]After the 15th injection. (N=4 for each group.) *$p<0.05$; †$p<0.01$; ‡$p<0.001$.

activity point) to 100 min and 20 to 120 min after the acute and chronic IP cocaine administration, respectively. Rats were weighed once daily. Data were analyzed for statistical significance by a two-way analysis of variance (ANOVA) followed by Duncan's multiple-range test. The significance level was set at $p<0.05$ (two tails).

## RESULTS

The horizontal and ambulatory activities were increased significantly from 20 to 120 min after an acute IP administration of cocaine as compared to that of saline controls. Peak activity appeared between 40 to 60 min for acute IP cocaine (Fig. 1). Following administration of a challenge dose of cocaine in the chronic IP cocaine-treated rats, the peaks of horizontal and ambulatory activity were shifted from 40 to 20 min and were significantly greater (approximately three times) than that after an acute cocaine administration (Fig. 1). The AUC of the horizontal and ambulatory activities in the chronic cocaine-treated rats from 0 to 30, 0 to 40, 0 to 50 and 0 to 60 min were significantly increased over the acute dose; from 0 to 120 min, a trend toward increase (approximately 15%) as compared to that of the rats treated with cocaine acutely was evident (Table 1). In the chronic cocaine-treated rats, the horizontal and ambulatory activity, from 50 min on, showed a trend toward a decrease as compared to that after an acute cocaine injection. The slope of the ascending phase of these activity curves in the chronic cocaine-treated rats was significantly larger than that after the acute cocaine-treated group (Table 3).

Following an acute SC injection of cocaine, the horizontal and ambulatory activities were increased significantly from 40 to 300 min as compared with the saline controls. The peaks of horizontal and ambulatory activity were observed at 180 min and then decreased after the acute dose (Fig. 2). Following chronic SC cocaine injection, the horizontal and ambulatory activities were increased significantly from 20 to 250 min as compared with the saline controls. After chronic cocaine administration, the peaks of horizontal and ambulatory activity were shifted from 180 min to 130 min as compared with the acute dosing, and the activities were significantly increased (approximately 50%). Furthermore, the horizontal and ambulatory activities at 30 and 40 min and from 90 to 130 min were significantly increased compared to those after an acute cocaine administration (Fig. 2). The AUC of these activities from 0 to 180 min was significantly larger than that after the acute cocaine administration, whereas the AUC of these activities from 0 to 240 or from 0 to 300 min showed a trend toward an increase (approximately 10–15%) (Table 2). On the other hand, the horizontal and ambulatory activity from 240 to 300 min and the AUC of these curves from 240 to 300 min were significantly decreased as compared to that induced by an acute cocaine dose.

The absolute slope values of the ascending and descending phases of these curves obtained from chronic cocaine-treated rats were significantly larger than that after an acute drug administration, which may suggest an increased rate of absorption and elimination of cocaine (Tables 3, 4) (see the Discussion section).

Cocaine did not significantly change body weight as compared with the saline control groups. One day after the drug treatment, the weight gained by the saline control rats was significantly larger than that by the cocaine-treated rats (Fig. 3).

## DISCUSSION

Most previous investigators have used the peak of the locomotor activity at certain time intervals (40 to 60 min) after an acute IP cocaine dosing as the cut-off point to compare the effect of acute and chronic cocaine-induced locomotor activity and ignored the whole spectrum of the activity over time. We used the peak of the locomotor activity, 30 to 60 min after an acute IP cocaine dosing, as the cut-off time for the chronic cocaine administration. The AUC of the horizontal and ambulatory activity in the chronic cocaine-treated rats from 0 to 30, 0 to 40, 0

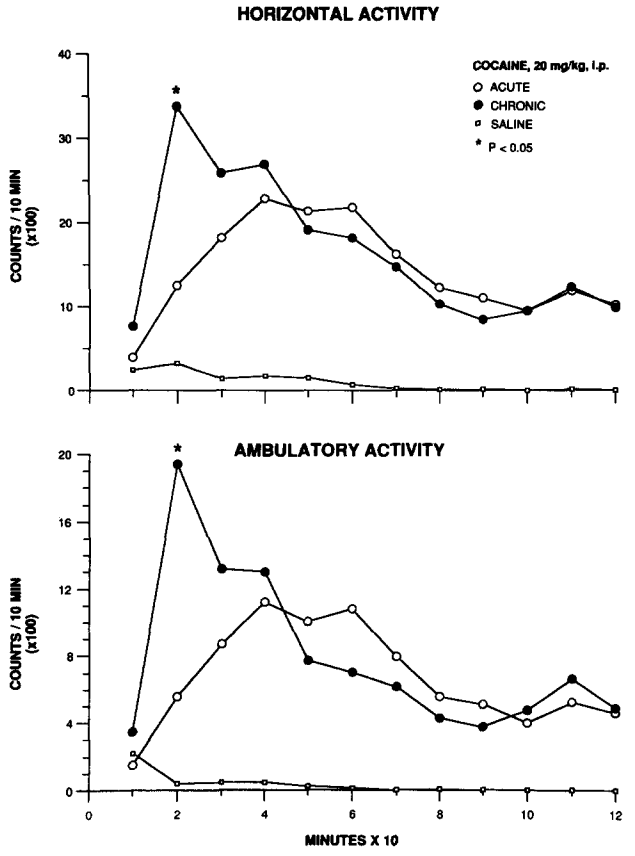


FIG. 1. The effect of cocaine on horizontal (including ambulatory and repetitive movement) and ambulatory activity in rats following the first (acute) and 15th (chronic) IP injection of cocaine HCl (20 mg/kg as free base) or saline. Rats were IP administered with cocaine HCl (20 mg/kg as free base) twice daily. Horizontal (including ambulatory and repetitive movement) and ambulatory activity were monitored by photocells every 10 min for a period of 120 min. (N = 4 for each group.)

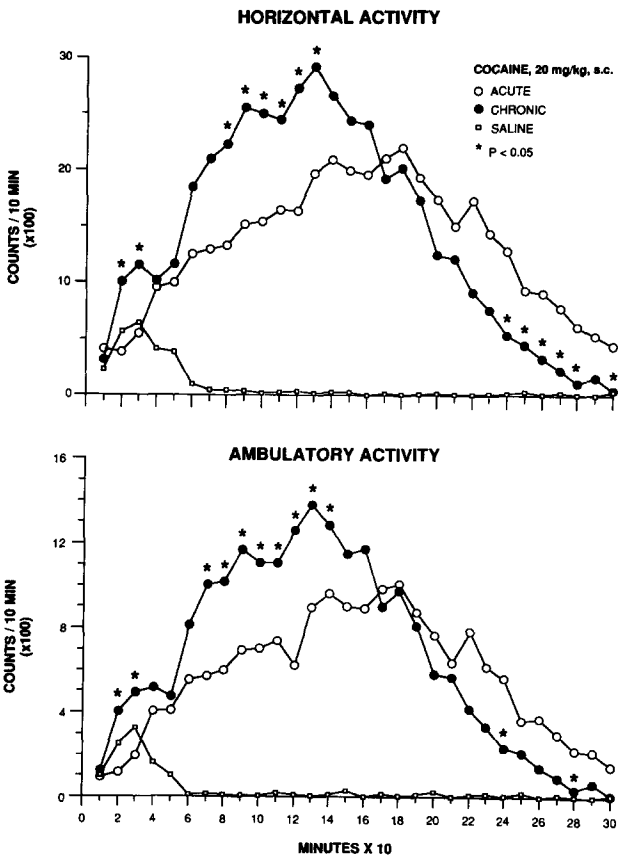


FIG. 2. The effect of cocaine on horizontal (including ambulatory and repetitive movement) and ambulatory activity in rats following the first (acute) and 15th (chronic) SC injection of cocaine HCl (20 mg/kg as free base) or saline. Rats were SC administered with cocaine HCl (20 mg/kg as free base) twice daily. Horizontal and ambulatory activity were monitored by photocells every 10 min for a period of 120 min. (N = 8 for each group.)

to 50 and 0 to 60 min, but not 0 to 120 min, were significantly increased as compared to the rats treated with cocaine acutely (Table 1). Chronic IP cocaine administration increased the peak activity and decreased the latency to the peak activity, which confirmed previous observations (16,19). The locomotor activity and the AUC from 60 to 120 min showed a trend toward decrease which appeared to be due to fast elimination of cocaine from the brain and body, presumably due to changes of cocaine pharmacokinetics (see below). Therefore, we further investigated the effect of cocaine-induced locomotor activity in rats chronically administered cocaine by SC route. After SC administration, the spectrum of cocaine-induced locomotor activity is similar to that after IP route; i.e., chronic SC cocaine administration increased the peak activity and decreased the latency to the peak activity. After an acute SC cocaine dosing, the peak locomotor activity was observed at 180 min. The activity from 180 to 240 min shows a trend toward decrease, and the activity from 240 to 300 min was significantly decreased as compared to the acute cocaine dosing. This suggests repeated cocaine administration induced desensitization on locomotor activity (Fig. 2, Table 2). These results further indicated that chronic SC cocaine administration induced sensitization of locomotor activity in rats at the earlier and desensitization at later time periods. To our knowl-

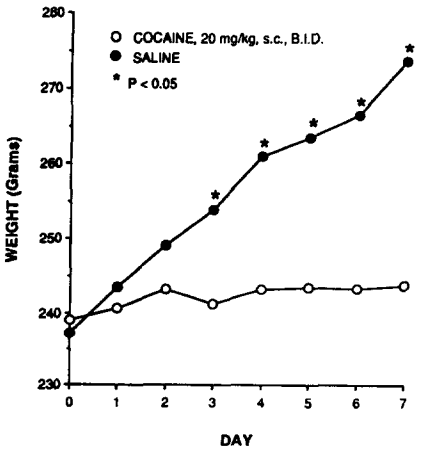


FIG. 3. The effect of cocaine or saline on body weight of rats. Rats were SC or IP administered with cocaine HCl (20 mg/kg as free base) twice daily.

TABLE 2

COMPARISON OF THE COCAINE-INDUCED LOCOMOTOR ACTIVITY IN THE ACUTE AND CHRONIC COCAINE-TREATED RATS AFTER SC DRUG ADMINISTRATION[1]

| Intervals | Treatment | Horizontal Activity | Ambulatory Activity | AUC of Horizontal Activity | AUC of Ambulatory Activity |
|---|---|---|---|---|---|
| | | Counts, Mean ± S.D. | | Minute-Counts, Mean ± S.D. | |
| 0 to 180 min | | | | | |
| | Acute[2] | 25884 ± 3212 | 10811 ± 1625 | 235981 ± 30443 | 103359 ± 15521 |
| | Chronic[3] | 35470* ± 8529 | 15283* ± 4484 | 335713† ± 81855 | 156761† ± 41634 |
| 0 to 240 min | | | | | |
| | Acute | 35540 ± 6029 | 15283 ± 3299 | 341097 ± 57389 | 150118 ± 31570 |
| | Chronic | 41914 ± 11843 | 19135 ± 6661 | 414156 ± 116379 | 194603 ± 63398 |
| 0 to 300 min | | | | | |
| | Acute | 39778 ± 7723 | 17107 ± 4188 | 329099 ± 74966 | 170396 ± 40963 |
| | Chronic | 43241 ± 12494 | 19807 ± 7068 | 432703 ± 124810 | 202911 ± 68098 |
| 180 to 300 min | | | | | |
| | Acute | 16100 ± 5198 | 6296 ± 2778 | 156118 ± 51978 | 67039 ± 27861 |
| | Chronic | 9792 ± 8045 | 3992 ± 4122 | 96989 ± 84344 | 46150 ± 42554 |
| 240 to 300 min | | | | | |
| | Acute | 5525 ± 4660 | 1824 ± 1019 | 51002 ± 21208 | 20280 ± 10418 |
| | Chronic | 1868* ± 1576 | 672* ± 1080 | 18546* ± 25432 | 8307* ± 11817 |

[1]Rats were SC injected with cocaine at 20 mg/kg twice daily. [2]After the first injection. [3]After the 15th injection. (N = 8 for each group.) *$p<0.05$; †$p<0.01$.

edge, this is the first report of cocaine-induced desensitization on locomotor activity in rats following chronic cocaine administration.

The higher peak locomotor activity and the shorter latency to the peak activity after IP cocaine administration than that after SC dosing appear to be due to increased drug absorption after the IP route than that after SC administration, since it is well known that absorption of a drug administered by the IP route is faster than that by SC route. Chronic cocaine treatment elevated the peak of the locomotor activity, increased the slopes of the ascending and descending phases of the locomotor activity curves and decreased the latency to the peak activity. These phenomena may be due to an increased rate of absorption and elimination of cocaine. A good correlation between locomotor activity and cocaine concentrations in the brains of mice has been reported (2,18).

In regard to the disposition of cocaine vs. cocaine administration, Ho et al. (6) observed that, after IP administration, concentrations of cocaine in the brain of chronic cocaine-treated rats at 5 and 15 min were significantly higher than that after an acute dose, whereas, at 45 and 60 min, the concentrations of cocaine were significantly lower. Pettit et al. (14) observed that cocaine

TABLE 3

REGRESSION ANALYSIS OF THE SLOPES OF THE HORIZONTAL AND AMBULATORY CURVE AND ANALYSIS OF VARIANCE OF REGRESSION COEFFICIENTS OVER GROUPS FOLLOWING IP ADMINISTRATION OF COCAINE[1]

| A: Regression Analysis of the Locomotor Activity Curves | | | | | | | B: Analysis of Variance of Regression Coefficients Over Groups | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Curve | Treatment | Intercept | Coefficient | S.E. | STD REG Coefficient | T | | S. S. × 1000 | *df* | M. S. × 1000 | F | *p*(tail) |
| I. Ascending phase of the curve | | | | | | | | | | | | |
| Horizontal Activity | Acute[2] | −125.6 | 62.68 | 12.03 | .85 | 5.21 | R.O.G[4] | 15396 | 2 | 7698 | 39 | 0.00000 |
| | Chronic[3] | −1863 | 262.4 | 28.28 | .97 | 9.28 | R.W.G[5] | 3131 | 20 | 196 | | |
| Ambulatory activity | Acute | −131.5 | 32.31 | 6.93 | .83 | 4.66 | R.O.G | 6170 | 2 | 3085 | 39.9 | 0.00000 |
| | Chronic | −1247 | 159 | 20.77 | .95 | 7.68 | R.W.G | 1238 | 20 | 77 | | |
| II. Descending phase of the curve | | | | | | | | | | | | |
| Horizontal activity | Acute | 3413 | −25.22 | 8.45 | −.56 | −2.98 | R.O.G | 720 | 2 | 360 | 0.53 | 0.5908 |
| | Chronic | 3674 | −31.86 | 5.48 | −.71 | −5.82 | R.W.G | 35885 | 60 | 677 | | |
| Ambulatory activity | Acute | 1702 | −13.14 | 4.48 | −.56 | −2.93 | R.O.G | 1958 | 2 | 98 | 4.62 | 0.632 |
| | Chronic | 1839 | −16.60 | 3.13 | −.67 | −5.30 | R.W.G | 11197 | 60 | 211 | | |

[1]Rats were IP injected with cocaine 20 mg/kg, twice daily. [2]After the first IP injection. [3]After the 15th IP injection. [4]R.O.G means regression over groups. [5]R.W.G means regression with groups. (N = 4 for each group.)

TABLE 4

REGRESSION ANALYSIS OF THE SLOPE OF THE HORIZONTAL AND AMBULATORY CURVE AND ANALYSIS OF VARIANCE OF REGRESSION COEFFICIENTS OVER GROUPS FOLLOWING SC ADMINISTRATION OF COCAINE[1]

| A: Regression Analysis of the Locomotor Activity Curves | | | | | | | B: Analysis of Variance of Regression Coefficients Over Groups | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Curve | Treatment | Intercept | Coefficient | S.E. | STD REG Coefficient | T | | S. S. × 1000 | *df* | M. S. × 1000 | F | *p*(tail) |
| I. Ascending phase of the curve | | | | | | | | | | | | |
| Horizontal activity | Acute[2] | 422.9 | 10.69 | 0.68 | .80 | 15.80 | R.O.G[4] | 41307 | 2 | 20654 | 61.02 | 0.00000 |
| | Chronic[3] | 458.1 | 20.04 | 1.97 | .71 | 10.19 | R.W.G[5] | 82588 | 244 | 338 | | |
| Ambulatory activity | Acute | 129.2 | 5.29 | 0.37 | .77 | 14.17 | R.O.G. | 9694 | 2 | 4847 | 47.80 | 0.00000 |
| | Chronic | 158.9 | 9.69 | 1.07 | .67 | 9.03 | R.W.G | 24745 | 244 | 101 | | |
| II. Descending phase of the curve | | | | | | | | | | | | |
| Horizontal activity | Acute | 4722 | −14.52 | 1.29 | −.74 | −11.26 | R.O.G | 11819 | 2 | 5909 | 11.24 | 0.00000 |
| | Chronic | 5087 | −17.94 | 1.37 | −.74 | −13.08 | R.W.G | — | 244 | 526 | | |
| Ambulatory activity | Acute | 2211 | −7.01 | 0.71 | −.70 | −9.93 | R.O.G | 1691 | 2 | 845 | 5.49 | 0.005 |
| | Chronic | 2436 | −8.65 | 0.74 | −.70 | −11.68 | R.W.G | 37600 | 244 | 154 | | |

[1]Rats were SC injected with cocaine 20 mg/kg, twice daily. [2]After the first SC injection. [3]After the 15th SC injection. [4]R.O.G means regression over groups. [5]R.W.G. means regression with groups. (N = 8 for each group.)

concentrations in the plasma and in the microdialysant of the extracellular fluid in the nucleus accumbens of chronic cocaine-treated (by SC route) rats challenged with the drug (by IP route) were significantly higher than that of the controls. Similar results were observed in the mice treated with cocaine for 2 to 3 days (18). Misra et al. (12,13) reported that, after a challenge SC cocaine dose, peak levels of cocaine in the brain, plasma and most tissues (kidney, lung, spleen and fat) of chronic cocaine-treated rats occurred between 1 and 2 h and were significantly higher than that in the controls, whereas between 3 and 4 h, cocaine levels were significantly lower. It should be pointed out that the peak concentrations of cocaine in the plasma, brain and most tissues of control rats were observed between 3 and 4 h. Similar results were observed in the acute and chronic cocaine-treated dogs (11). Although the cited data support the assumption that chronic cocaine treatment may alter cocaine pharmacokinetics, the relation between locomotor activity, concentrations of monoamines and cocaine in the brain has yet to be established.

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