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Oral Cocaine Self-Administration: Relation of Locomotor Activity to Pharmacokinetics

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LAU, C. E., J. L. FALK AND G. R. KING. *Oral cocaine self-administration: Relation of locomotor activity to pharmacokinetics.* PHARMACOL BIOCHEM BEHAV **43**(1) 45-51, 1992. – Rats were exposed to daily schedule-induced polydipsia sessions in which solutions of cocaine HCl were available. Both cocaine solution concentration (0.08–0.32 mg/ml) and session duration (0.25–3 h) were varied to determine their effects on locomotor activity rate. Additional animals were used to determine the effect of session length on serum cocaine and metabolite levels when drinking 0.32 mg/ml cocaine solution. Changes in locomotor activity rate were related to serum cocaine concentration by a linear concentration-effect model. By estimation from the linear model, the serum cocaine concentration threshold for increasing locomotor activity was about 0.01 μg/ml. Under these schedule-induction conditions, there was no evidence for the development of acute tolerance to the locomotor-stimulating activity of cocaine.

Schedule induction Cocaine Cocaine pharmacokinetics Drug self-administration Locomotor activity

ALTHOUGH a few studies have explored whether the oral self-administration of cocaine can function as a reinforcing event in primates (15,18) and rodents (6,20), there is little information available on the behavioral consequences of oral cocaine self-administration (7,21). This information mainly has addressed the relation of serum cocaine levels to subjective effects. However, the popularity of oral cocaine in elixirs and tonics at the turn of the century, and the social and religious values associated with the "chewing" of coca leaves by native peoples in Peru, Bolivia, and Columbia (1,17), attest to its probable efficacy for producing changes in behavior in addition to its subjective effects. A general aim of the present study, then, was to clarify the bioavailability of cocaine by this route and investigate the behavioral consequences of oral cocaine self-administration in relation to its serum pharmacokinetics.

Cocaine administration can produce dose-related increases in locomotor activity in animals, as well as sensitization to the effects of repeated doses (8,16,19). Previous studies with rats using schedule-induced oral cocaine self-administration in daily 3-h sessions demonstrated marked, dose-related increases in locomotor activity rate during ensuing 2-h activity sessions and the development of sensitization (5). One aim of the present studies was to explore the effect of progressively shortening the duration of the oral cocaine self-administration sessions on the ensuing locomotor activity rate in 4-h sessions. This progression not only decreases the dose of cocaine, but also starts the locomotor activity sessions after shorter durations of exposure to cocaine. Thus, a second aim was to relate serum cocaine concentration at the start of activity measurement to the duration of the preceding drinking session. A third aim was to determine the serum cocaine threshold for producing an increase in locomotor activity rate.

EXPERIMENT 1: ORAL COCAINE SELF-ADMINISTRATION AND LOCOMOTOR ACTIVITY

METHOD

Animals

Five male, albino rats of the Holtzman strain (Madison, WI) with a mean initial body weight of 379 g (range: 367–385 g; approximately 80 days old) were housed individually in stainless steel cages in a temperature-regulated room under continuous illumination. They first served as subjects in studies on the effects of acute and chronic cocaine administration on spontaneous activities (5,10); immediately following the completion of these studies, the present experiment was conducted. Animals remained at their reduced weights of 80% ad lib by limiting daily food rations. Water was always available in the home cages. All aspects of this and the following experiment were executed in accordance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication No. 85-23, revised 1985).

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Cocaine Self-Administration by Schedule-Induced Polydipsia

Cocaine HCl was obtained from the National Institute on Drug Abuse (Rockville, MD). Doses were calculated as the salt. Animals were given a daily 3-h experimental session in individual Plexiglas chambers (30 × 26 × 23 cm). Each chamber was equipped with a food-pellet receptacle and a drinking-fluid reservoir that consisted of a stainless steel, ball-bearing spout attached to a Nalgene graduated cylinder. Fluid intakes were recorded to the nearest milliliter. Animals were weighed at the same time each day, a fluid reservoir was attached to the chamber, and for the next 3 h a 45-mg food pellet (Bio Serv, Frenchtown, NJ) was delivered automatically into each food receptacle every 60 s [a fixed time (FT) 1-min schedule]. This food-delivery schedule is one known to induce a marked polydipsia during daily sessions (4). At the end of each session, fluid intakes were recorded.

Locomotor Activity

Spontaneous activity was measured in a room isolated from other activities and noise. Animals were placed individually into stainless steel cages (38.0 × 25.5 × 17.5 cm) resting on accelerometer platforms, each of which rode on four ball bearings located at the corners (E45-01, Coulborn Instruments, Allentown, PA). Only horizontal platform movements were detected by the coupling of the accelerometer to the ball-bearing-mounted platform. The platforms were connected to individual activity monitors (E52-01) located in an adjacent room. Each monitor was threshold adjusted to record a platform movement activated only by a movement constituting locomotion, but not by smaller sniffing or head movements.

Procedure

Immediately after the daily 3-h schedule-induced oral self-administration session, animals were transferred to a 4-h locomotor activity evaluation session. At the end of this session, animals remained in the activity cages for an additional 2 h and were then returned to their home cages and given food rations (Purina Lab Chow) sufficient to maintain their criterion weights.

Manipulation of cocaine dose by varying cocaine solution concentration. The fluid available during the schedule-induction session was distilled water for 20 days, followed by a compound solution (3% glucose and 0.16% sodium saccharin) for 3 days. Then, the following sequence of cocaine concentrations in compound solution was made available: 0.08 mg/ml (15 days); 0.16 mg/ml (11 days); 0.24 mg/ml (7 days); 0.32 mg/ml (41 days). For the first 14 days under the 0.32-mg/ml cocaine concentration, animals were exposed to the usual drinking session duration of 3 h.

Manipulation of cocaine dose by varying cocaine session duration. To determine whether a 3-h cocaine drinking session was necessary to produce an ensuing increase in locomotor activity, animals were transferred to the locomotor evaluation session after cocaine drinking sessions of progressively shorter duration in the following order: 2 h (7 days), 1 h (7 days), 0.5 h (7 days), and 0.25 h (2 days). Inasmuch as animals drank a fairly large amount of cocaine even in a 0.25-h session, locomotor activity also was evaluated after allowing only a small, controlled amount of cocaine during a 0.25-h session (4 days). This was done by providing only a volume of the 0.32 mg/ml cocaine in compound solution that equalled one quarter of the mean cocaine dose self-administered in the 1-h drinking sessions (cocaine ration condition). Under this condition, a concurrent second fluid reservoir permitted distilled water to be drunk when animals had exhausted the cocaine solution reservoir.

Animals were then withdrawn from cocaine (9 days) by maintaining the same fluid arrangement (concurrent rationed amount of compound solution in one reservoir and distilled water in the other) in 0.25-h sessions, but cocaine was no longer added to the compound solution (a vehicle control condition).

RESULTS

Animals self-administered increasing doses of cocaine as a function of their exposure to increasing cocaine solution concentrations (0.08–0.32 mg/ml) under the inducing condition (FT 1-min food presentation schedule). The effect of the 3-h schedule-induced oral self-administration of vehicle (compound solution) (B) and of the increasing series of ingested cocaine doses on locomotor activity rates in the subsequent 4-h session is shown in Fig. 1. All animals exhibited a marked, dose-related increase in locomotor activity rate. For all figures, the plotted means are calculated from data for all sessions under a given condition.

Figure 2 shows the locomotor activity data as mean 4-h rate profiles resulting from each of the self-administered cocaine dose levels. [When compound solution vehicle was the fluid self-administered, sessions were 2 h, rather than 4 h, but the ensuing locomotor activity remained quite low across the entire session (○).] With the least concentrated cocaine solution (0.08 mg/ml, ●), animals showed a small, short-lived locomotor activity rate increase. At the next levels of cocaine self-administration (0.16 mg/ml, □; 0.24 mg/ml, ■), the mean activity-rate profiles increased markedly. At the largest self-administered dose level (0.32 mg/ml, ×), the activity rate profile scarcely differed from that of the preceding dose level (0.24 mg/ml). For all cocaine doses, the stimulatory effect of cocaine on locomotor activity rates decreased during the course of each 4-h session.

Figure 3 shows that as the length of the drinking session was decreased from 3 h to 0.25 h decreasing doses of cocaine

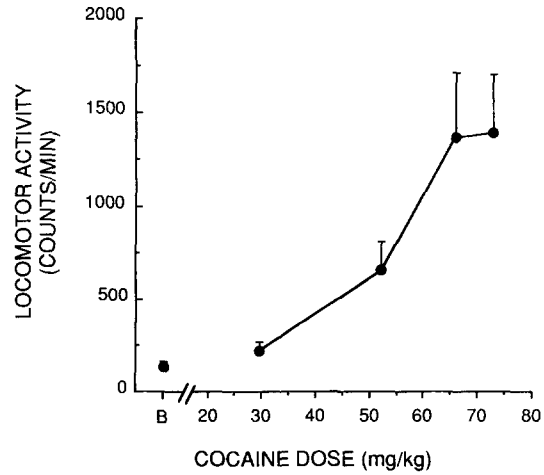

FIG. 1. Mean (SE) locomotor activity rates of five rats during 4-h sessions immediately following 3-h sessions of schedule-induced oral cocaine self-administration. *X*-axis points = mean self-administered dose under increasing cocaine drinking solution concentrations (0–0.32 mg/ml). B, vehicle.

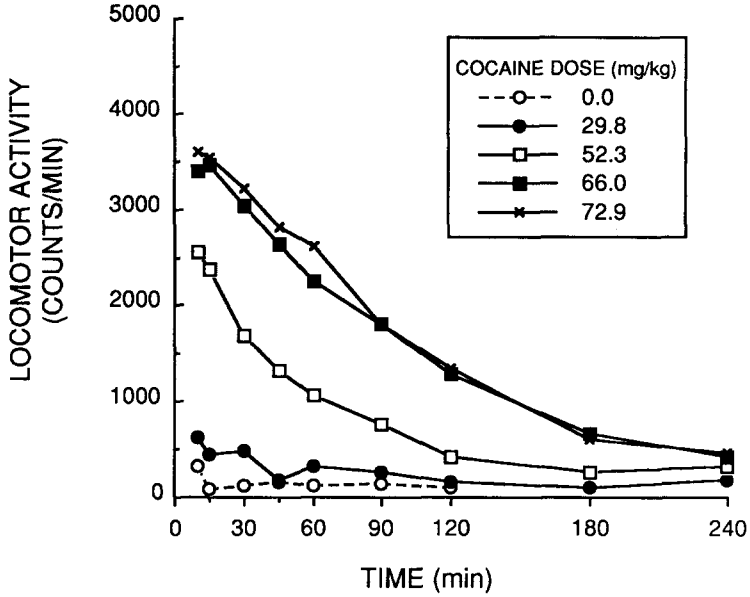

FIG. 2. Mean locomotor activity rate profiles of five rats immediately following 3-h sessions of schedule-induced oral cocaine self-administration.

(0.32 mg/ml) were self-administered. Decreasing doses resulted in decreasing rates in the corresponding locomotor activity sessions that followed. However, the function indicates that overall activity rate for a session reaches a plateau at the cocaine dose consumed in a 1-h drinking session (41.2 mg/kg); the longer sessions, which allowed self-administration of greater doses, did not lead to higher rates of activity. Paired-comparison *t*-tests for the leftmost points in Fig. 3 showed that providing a limited cocaine ration (10.8 mg/kg) in a 0.25 h session produced significantly greater locomotor activity than did vehicle consumption ($p < 0.03$), and the activity resulting from freely available cocaine solution consumed in the 0.25-h drinking session (20.9 mg/kg) was greater than activity after either the vehicle or cocaine-ration conditions ($p < 0.01$).

Figure 4 shows that the locomotor-activity rate profile produced by cocaine self-administration sessions of different lengths increased in a dose-related fashion up to 41.2 mg/kg.

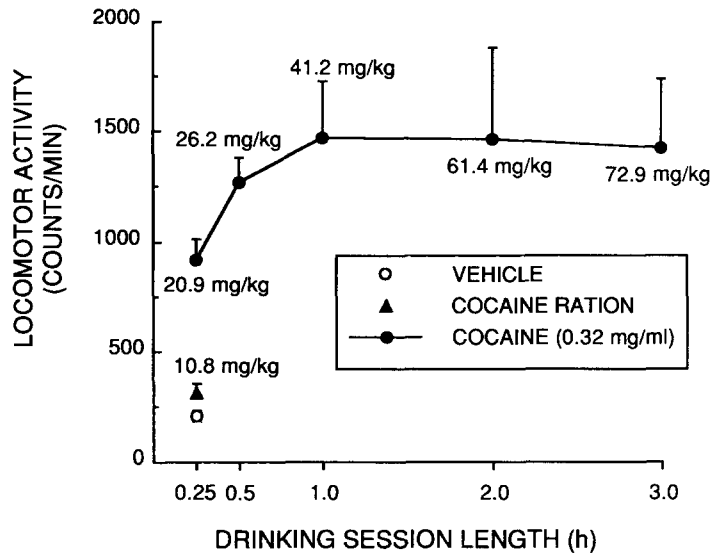

FIG. 3. Mean (SE) locomotor activity rates for 4-h sessions immediately following schedule-induced oral cocaine (0.32 mg/ml) self-administration sessions as a function of drinking session length (n = 5 rats). Self-administered doses indicated near plotted points.

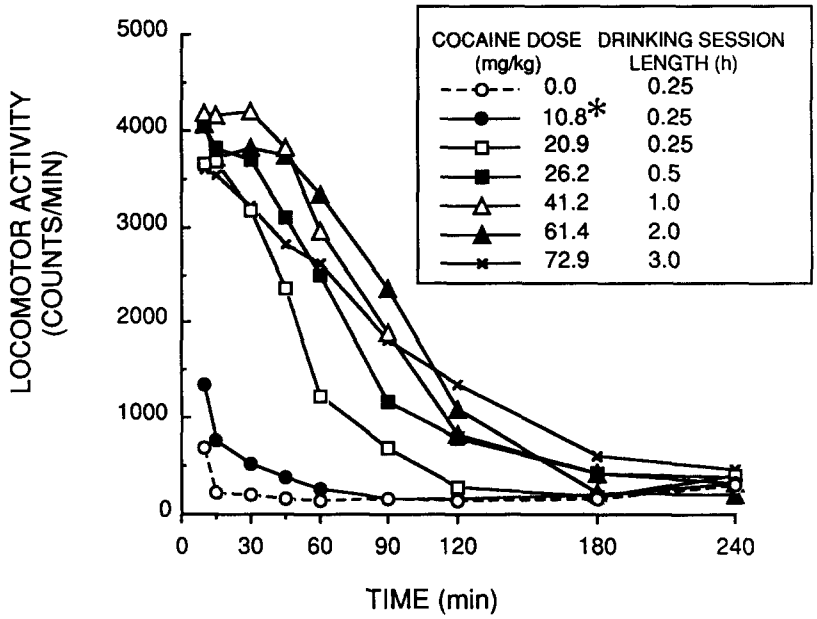

FIG. 4. Mean locomotor activity rate profiles immediately following sessions of schedule-induced oral cocaine (0.32 mg/ml) self-administration that varied in length (n = 5 rats). *Cocaine ration condition.

Compared to this dose, the two higher dose profiles were relatively suppressed in a dose-related fashion during the first hour, but became higher than the 41.2-mg/kg dose profile at the second and third hour points.

EXPERIMENT 2: SERUM LEVELS OF COCAINE AND ITS METABOLITES

METHOD

Animals

Five male, albino rats of the Holtzman strain with a mean initial body weight of 386 g (range: 383–388 g) were used. The maintenance conditions and feeding regimen were the same as those for animals used in Experiment 1.

Procedure

Animals were exposed to daily 3-h sessions of schedule-induced oral cocaine self-administration in which the cocaine solution concentration was increased as in Experiment 1. At the final cocaine concentration (0.32 mg/ml), hourly intakes were recorded for each session. Blood samples (tail tip, 100 μl) were obtained at the following time points during a polydipsia session: 0.25 h (cocaine ration condition), and at 0.25, 0.5, 1, 2, and 3 h (standard 3-h session), providing cocaine intakes remained as usual at the later time points (i.e., not disrupted by the sampling procedure); otherwise, samples at some time points were obtained during sessions on different days. The blood-sampling procedure and high-performance liquid chromatography (HPLC) method for analyzing serum cocaine and its metabolites have been described previously (9–11).

RESULTS

Figure 5 shows that these animals, which were exposed to the same cocaine self-administration conditions as those in Experiment 1, ingested almost the same doses as those animals when session time was varied (cf., ● with the doses shown in Fig. 3). The serum cocaine concentration reached after 15 min of schedule-induced cocaine solution drinking was not in-

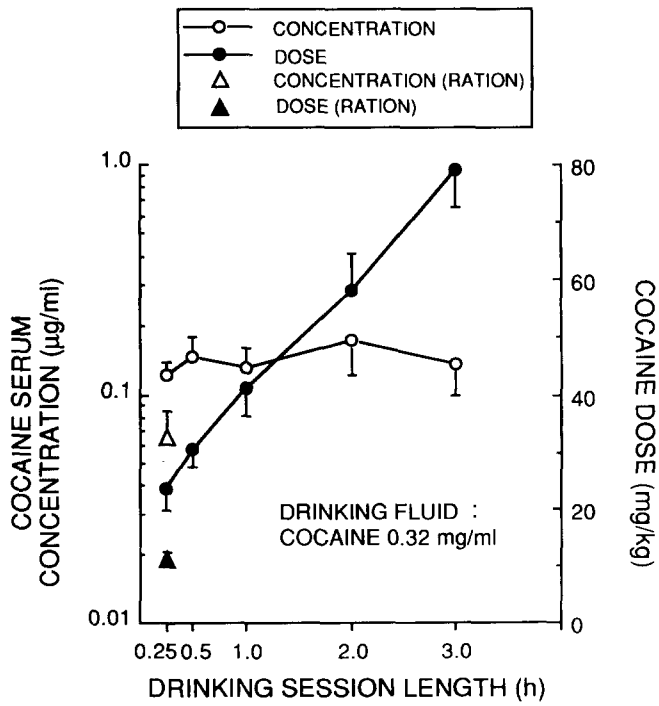

FIG. 5. Mean (SE) schedule-induced oral cocaine self-administered dose and resulting serum cocaine concentration as a function of drinking-session length (n = 5 rats).

increased by longer sessions even though they led to the self-administration of larger total cocaine doses. The cocaine-ration dose (11.0 mg/kg), which was close to the dose allowed animals in Fig. 3 (10.8 mg/kg), produced a serum cocaine concentration of 0.064 μg/ml (△). Under these conditions, these values define the oral dose and serum concentration of cocaine that produce an approximate threshold increase in locomotor activity.

The cocaine metabolites norcocaine and benzoylnorecgonine maintained steady states after 30 min of drinking, while benzoylecgonine reached a plateau by 1 h (Fig. 6).

EXPERIMENT 3: CORRELATION OF ACTIVITY-RATE AND COCAINE-CONCENTRATION PROFILES AND THE ESTIMATION OF STIMULATORY THRESHOLD

METHOD

Animals

Three locomotor-activity animals from Experiment 1 were matched to a group (n = 4) from a previous study of serum cocaine pharmacokinetics (5) with respect to their intakes of cocaine in the daily, 3-h schedule-induction sessions under two cocaine-concentration conditions (0.16 and 0.24 mg/ml). All were male, Holtzman animals maintained under the same laboratory and food-deprivation conditions.

Procedure

The relation between locomotor activity and serum cocaine concentration was ascertained by matching three locomotor-activity animals from Experiment 1 with the group (n = 4) from a study of serum cocaine pharmacokinetics [Fig. 7 of (5)] so that intakes were almost identical for the two groups in their response to two cocaine concentration levels (0.16 and 0.24 mg/ml) in 3-h schedule-induction sessions. The locomotor-activity and pharmacokinetic groups drank similar doses of cocaine solution: 42.1 vs. 39.6 mg/kg when 0.16 mg/ml was available and 61.7 vs. 62.1 mg/kg when 0.24 mg/ml was available. Data from the two mean locomotor-activity rate profiles (0.25–4 h) are plotted against serum cocaine concentrations for the same time period. However, in the previous study (5) only serum cocaine concentrations at the 0, 1, 2, 3, and 4 h postdrinking time points were measured; the points at 0.25, 0.5, 0.75, and 1.5 h were not measured and therefore were determined from the serum concentration–time profile. They were calculated from an equation appropriate for a one-compartment model assuming first-order elimination after 3 h of oral self-administration of cocaine solution: $C = C_0e^{-}kt$.

RESULTS

Figure 7 shows a linear relation and high correlation between locomotor activity and serum cocaine concentration (r = 0.95, $p < 0.0001$). Under this condition, the threshold serum cocaine value that maintained an increase in locomotor activity was about 0.01 μg/ml.

GENERAL DISCUSSION

The dose-related increase in locomotor activity (Figs. 1 and 2) resulting from schedule-induced oral cocaine self-administration confirmed previous results with these animals (5), but tracked the effect for 4 h rather than limiting activity-session

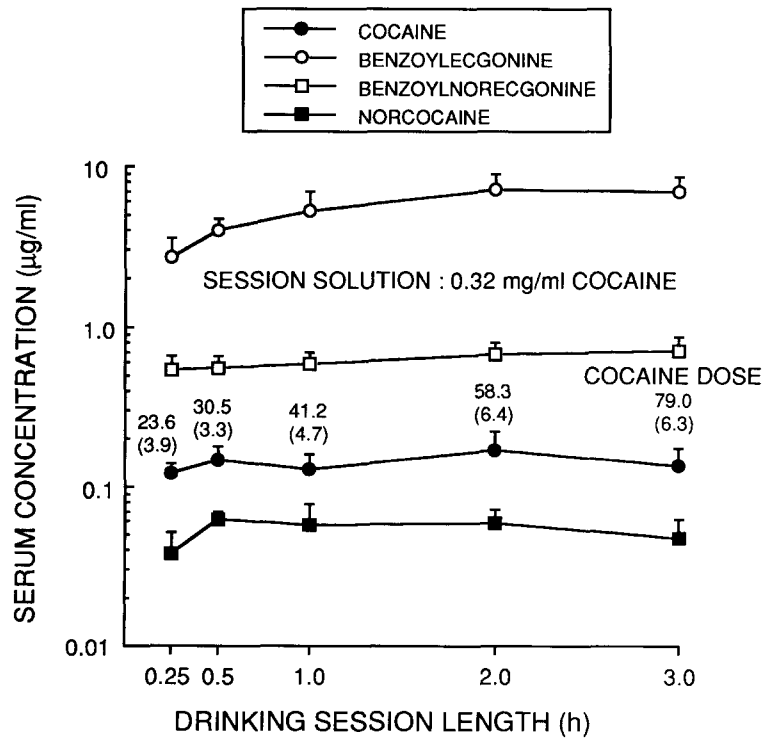

FIG. 6. Mean (SE) serum concentrations for cocaine and its metabolites as a function of drinking-session length (n = 5 rats). Cocaine dose [mg/kg (SE)] self-administered indicated above points for serum cocaine concentration.

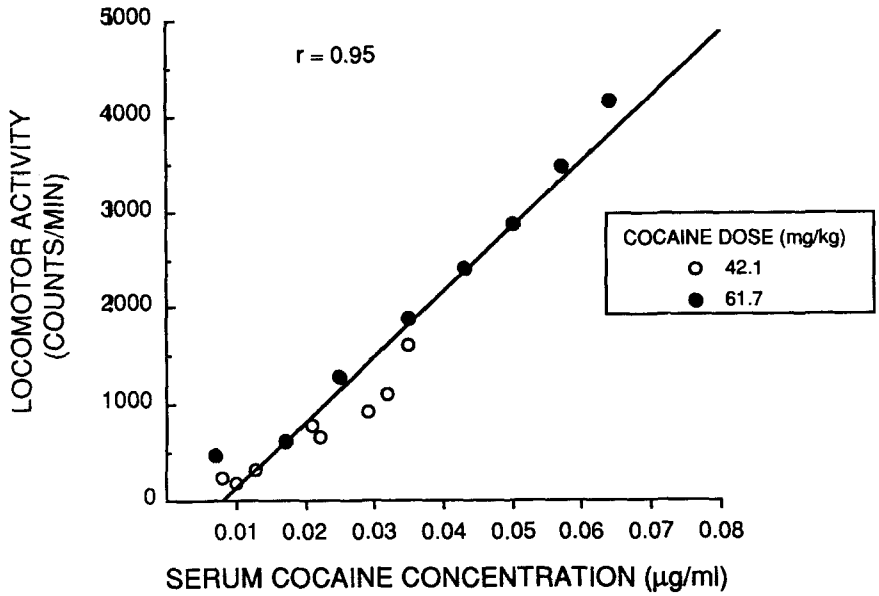

FIG. 7. Mean locomotor activity rates during 4-h sessions as a function of serum cocaine levels during sessions. Serum cocaine levels were produced by presession 3-h schedule-induced oral cocaine self-administration at two cocaine solution concentrations: 0.16 and 0.24 mg/ml.

length to 2 h. The effects on activity of the larger doses of cocaine were still evident 4 h after oral self-administration (Fig. 2). The lowest dose level ingested over the 3-h period led to a modest, but definite, increase in the ensuing locomotor activity session (Fig. 2). It was of interest to determine whether small, oral doses self-administered more rapidly also would be effective. Initial study of these animals (5) demonstrated that the rapid ingestion of a 15-mg/kg cocaine ration reliably increased locomotor activity, and the related pharmacokinetics showed rapid onset and appreciable levels of serum cocaine (10). But, schedule-induced oral cocaine intakes at that approximate dose level were not effective in increasing ensuing locomotor activity when the dose was self-administered over a 3-h session (5). Figure 3 demonstrates that when 20.9 mg/kg cocaine was ingested over a 0.25-h session it was quite effective, as was a 10.8-mg/kg cocaine ration. The latter dose level produced a serum cocaine concentration of 0.064 μg/ml (Fig. 5). This value defines, for these animals, the approximate threshold stimulus for producing an increase in locomotor activity if the increase is measured as the mean activity rate across the entire 4-h session. However, if the threshold is estimated not from the mean activity change for the 4-h period but in terms of relating the profiles for serum cocaine concentration and locomotor activity then the threshold is about 0.01 μg/ml (Fig. 7).

A log-linear concentration–effect model has been proposed by Levy (13) and was used to correlate subjective "high" ratings with log plasma cocaine concentration (14). However, fitting the log-linear model to the data set from Fig. 7 yielded a lower correlation (r = 0.76) than did the linear model (r = 0.95). Linear models have been used to relate the analgesic activity of paracetamol to its blood and brain concentration in rats (12) and eye movements to blood ethanol concentration in humans (2). Neither model applies beyond a point where a pharmacologic effect no longer increases with an increase in drug concentration. Hence, data from the rightmost point in Fig. 1 could not be used in Fig. 7.

The locomotor-activity animals began sessions in Experiment 1 immediately after completing their participation in previous studies of the effect of cocaine on activity using the same apparatus and general procedures (5,10). Therefore, they began with a history of exposure to cocaine and at a more advanced age (approximately 12 months) than usual. Schedule-induced oral self-administration of cocaine had sensitized these animals to cocaine (10), and older rats yield evidence of greater responsiveness to the effects of psychomotor stimulants compared to young animals (3). These factors may have decreased the thresholds for cocaine effectiveness compared to those that might be determined from young, drug-naive animals. However, the present threshold estimations may model the situation of the human cocaine user who is older and uses chronically.

In previous studies with these animals, the area under the curve (AUC) for the locomotor-activity rate profile was related to the serum cocaine-concentration profile AUC for a range of cocaine doses with different routes of administration (IP, PO, and schedule-induced drinking) (5,10). These data indicated that schedule-induced cocaine ingestion was more effective in stimulating activity than were either IP or PO routes at given serum cocaine AUC values. However, animals became sensitized to cocaine during schedule-induced cocaine intake, which was the last of the functions determined. Thus, it is difficult to infer whether the greater effectiveness of this mode of administration was due to: a) sensitization or b) the length of time prior to activity measurement that serum cocaine had been elevated that day (3 h or schedule-induced intake followed by a locomotor-activity session). Comparing Figs. 3 and 5 helps clarify this question. At all session lengths, schedule-induced drinking led to about the same postsession serum cocaine concentration (Fig. 5). But, the associated locomotor activity rates were lower when this serum cocaine level was produced by drinking sessions less than 1 h in duration (Fig. 3). Apparently, not just the level of serum cocaine was important in determining activity rate but also how long the

serum had been at that level. Both the AUC functions and the present data indicate that schedule-induced oral cocaine intake possesses marked potency and efficacy for elevating locomotor activity rate. The AUC functions, linear-model fit (Fig. 7), and above comparison of Figs. 3 and 5 all indicate that no acute tolerance develops to the locomotor-stimulating effect of oral cocaine. Figure 3 shows, in agreement with previous PO studies (5) that brief, schedule-induced cocaine intake sessions were effective in elevating the ensuing locomotor activity rate.

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