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Schedule-Induced Cocaine Drinking: Choice Between Cocaine and Vehicle[1]

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FALK, J. L., M. VIGORITO, M. TANG AND C. E. LAU. *Schedule-induced cocaine drinking: Choice between cocaine and vehicle.* PHARMACOL BIOCHEM BEHAV **35**(1) 187–193, 1990.—Rats were exposed to daily 3-hr schedule-induced polydipsia sessions (fixed-time 1-min food-pellet delivery) with two drinking fluids available: cocaine solution and water. Fluid position was alternated daily. Polydipsia occurred mostly from a preferred-side spout (position preference) until cocaine solution concentration was increased to between 0.52 and 1.04 mg/ml and animals drank mostly water. Within a lower concentration range (0.28–0.6 mg/ml) maximum session cocaine intakes ranged from 54.3 to 120.1 mg/kg. Postsession serum cocaine levels were about 200 ng/ml. At individually chosen cocaine solution concentrations, the addition of saccharin to the solution did not increase cocaine intake, but a compound solution (saccharin plus glucose) did. With progressive dilution of the compound vehicle, an almost complete preference for cocaine solution was maintained. But with a return to water as the vehicle, animals reverted to a position preference after a few sessions, although one maintained a clear cocaine preference. Schedule-induced polydipsia produced chronic, oral self-administration of cocaine resulting in pharmacologically significant intakes and serum levels.

Cocaine Self-administration Schedule induction Serum cocaine Cocaine preference

SCHEDULE-INDUCED polydipsia can be produced by an experimental arrangement under which animals fed in daily, intermittent, food-delivery sessions drink concurrent, large volumes of fluid (3). The induction of this polydipsic phenomenon, which is produced by an environmental condition rather than by pathophysiological manipulations (4), has been used to induce chronic, elevated intakes of several classes of drugs (20), including cocaine (5,25). In previous studies on cocaine, we made only one drinking fluid available during a polydipsia session (either cocaine solution or water) and used cocaine concentrations that allowed the polydipsic intake to be approximately equal to the water intake induced in equivalent 3-hr schedule-induced polydipsia sessions (5,25). In the present studies, a choice between two continuously presented fluids (a cocaine solution and water) was allowed, and a range of cocaine concentrations was explored to determine: (a) the relation between cocaine-solution concentration and intakes of the two fluids, and (b) what serum cocaine levels could be attained with this technique. In additional conditions, two highly acceptable fluids [saccharin solution and a glucose plus saccharin solution (26)] were used as vehicles for cocaine in place of water in order: (c) to determine how large a dose of cocaine animals would orally self-administer during a session, and (d) to ascertain whether a preferential choice for a concentrated cocaine solution could be instituted if animals were exposed first to a cocaine solution which used the glucose plus saccharin vehicle, with the vehicle being slowly reduced in concentration so that these solutes were finally eliminated.

METHOD

Animals

Four male, adult, albino rats of the Holtzman strain (Madison, WI) with a mean initial body weight of 381.8 g (range: 381–383 g) were housed individually in Plexiglas chambers in a temperature-regulated room under continuous illumination. These living chambers also served as the experimental chambers (see below).

Drug

Cocaine hydrochloride was obtained from the National Institute on Drug Abuse (Rockville, MD). Cocaine solution concentrations and intakes were calculated as the salt. Cocaine solutions were prepared by dissolving the drug in distilled water unless otherwise specified.

Apparatus

The individual, Plexiglas chambers ($30 \times 26 \times 23$ cm) were each equipped with a stainless-steel, food-pellet receptacle and two drinking-fluid reservoirs. A reservoir consisted of a stainless-steel, ball-bearing spout attached to a 250-ml Nalgene graduated cylinder. The spouts were located next to one side of the pellet receptacle and were 4 cm apart.

Procedure

Body weights were reduced to 80% of their initial, ad lib

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weights over a 2-week period by limiting daily food rations and animals were maintained at these weights for the duration of the experiment. After weights were stabilized, daily 3-hr schedule-induction sessions were started. Immediately before each daily session, animals were weighed, their overnight water intakes recorded and appropriate fluids placed on each chamber. During the 3-hr schedule-induction session, a 45-mg Noyes Lab Rat food pellet was delivered automatically into each food receptacle every 60 sec (FT 1-min schedule). At the end of each session, fluid intakes were recorded, distilled water was provided as the nonsession drinking fluid, and food rations (Purina Laboratory Chow) for maintaining 80% body weights were given.

Cocaine preference: First ascending series. To establish a baseline of polydipsic intake behavior, all animals had distilled water as the fluid available from both drinking spouts during the first 18 daily 3-hr sessions. On day 19, cocaine solution was substituted for water on one side, while the other spout continued to provide distilled water. The left-right position of the water and cocaine solution spouts was reversed daily throughout the series of experiments. The cocaine solution concentration was varied in an ascending order: The initial concentration was 0.02 mg/ml. When session fluid intakes had stabilized, the concentration was increased to 0.04 mg/ml. Subsequent increments were in steps of 0.04 mg/ml, each increment occurring after session fluid intakes had stabilized. At each concentration, animals were exposed to a minimum of 6 sessions (range: 6–20 sessions, except animals F1 and F2 were exposed to 56 sessions at 0.68 mg/ml). Increments in cocaine solution concentration continued until a concentration was attained at which a consistent preference for water over the cocaine solution occurred.

Presession cocaine injection: Effect on polydipsic intake. Toward the end of the ascending series, F1 and F2 were injected IP with either 7.5 or 15 mg/kg cocaine hydrochloride immediately before the start of a session. Both animals had a choice between water and 0.68 mg/ml cocaine solution at that point in the experiment, and water was on the preferred side on each of the injection days. There was a 1-month period between the two dose-level injections for both animals.

Cocaine preference: Second ascending series. After completion of the ascending series of cocaine concentrations, two rats (F1 and F4) were exposed to a second ascending series. The series began with 0.04 mg/ml and increased in 0.08 mg/ml steps. One rat (F11) died before the second series was started. The fourth animal (F2) was given only the first series.

Alteration of cocaine vehicle: Saccharin. When the ascending-series studies were completed, the vehicle for the cocaine solution was altered systematically to determine its effect on session cocaine intake; as before, the alternative fluid in the second reservoir was distilled water and its left-right position was changed each session. First, saccharin solution (rather than water) was used as the vehicle for cocaine and the effect of saccharin concentration on session cocaine intake was explored. The saccharin concentration was varied from 0.04 to 0.16% in ascending steps of 0.04, with animals exposed to each concentration step for 3–7 sessions. (F1 did not receive the 0.04% saccharin vehicle concentration.) The initial cocaine solution concentration and the subsequent values chosen in this series varied for each rat; details are presented in the Results section.

Alteration of cocaine vehicle: Compound solution (saccharin plus glucose). Second, a compound solution was used as the vehicle for the cocaine solution. It was composed of 0.16% saccharin and 3% glucose. The alternative fluid remained distilled water. Again, the initial cocaine concentration in this solution was different for each animal and was subsequently decreased from the initial value by 2–4 steps (step size = 0.08 mg/ml), with the initial value and each transition step maintained for 3–5 sessions and the final cocaine concentration maintained for 27–30 sessions. (Details are presented in the Results section.)

In the next sequence of solution presentations, the final cocaine concentration from the above series for each rat was held constant and the compound vehicle solution was diluted by 10% steps from 90 to 10% of the original vehicle concentration, with 2–6 sessions given at each dilution value. However, the last two steps were to 5% of the original vehicle concentration (i.e., a 95% dilution) for 4 days, and finally a return to distilled water as the vehicle for 10 days.

For the next 10 days, the vehicle remained distilled water, but the cocaine concentration for each animal was reduced by 50% and remained at this level until the last experimental manipulation (during which cocaine was no longer presented). The vehicle was then changed to the original compound solution (no dilution) for 2 days, followed by a return to distilled water as the vehicle for 6 days. Finally, water was presented at both spouts for 6 days.

Serum levels of cocaine and metabolites. At certain points during the initial ascending-concentration series, tail-tip blood samples (100 μl) were obtained from the animals immediately after a session and 1 hr postsession. (In one case a third sample was taken at 2 hr postsession.) Serum cocaine and its metabolites were determined using a method modified from the one described by Garrett and Seyda (9).

RESULTS

During the initial 18 sessions, in which distilled water was available from both spouts, all animals developed session polydipsia. The session water intakes for each animal (mean of last 6 sessions) were as follows: F1 = 99.5 ml; F2 = 120.5 ml; F4 = 130.0 ml; F11 = 121.5 ml. All animals showed a distinct side preference, drinking virtually all of their water from the spout closest to the pellet receptacle.

Figures 1–4 show the mean intakes and fluid preference results for each animal during the initial ascending series of cocaine solution concentrations. For each concentration, points are plotted based on the last 6 sessions given at that concentration. Inasmuch as each animal continued to demonstrate a strong side preference throughout most of the ascending series, points are shown separately for drinking on the preferred and nonpreferred sides. (Each point is based on data from 3 sessions.) For all animals, as the concentration of the cocaine solution presented was increased, the amount of it drunk decreased systematically when it was on the preferred side (filled circles). When water was on the preferred side, the amount of water drunk (filled squares) varied less systematically as cocaine concentration was increased. However, polydipsic intake levels were maintained. As cocaine concentration was increased, finally a point was reached at which the side preference no longer determined from which spout animals drank virtually all of their session fluid. Animals began to prefer water over cocaine solution even when water was located on the nonpreferred side (open squares on right-hand portion of each figure). When cocaine solution intake on the preferred side became zero, or very low, the ascending series of concentrations was terminated for an animal. These concentration points differed among animals: F1 = 0.8 mg/ml; F2 = 1.04 mg/ml; F4 = 0.52 mg/ml; F11 = 0.52 mg/ml (cf. Figs. 1–4).

The fluid-preference aspect of these data is clarified by Fig. 5. Inasmuch as a strong side preference occurred, the intakes of water and of cocaine solution were each averaged for 2-day blocks over the last 6 sessions at each concentration and the results (mean cocaine intake/mean cocaine intake + mean water intake, i.e., percent cocaine solution intake) plotted as a function of concen-

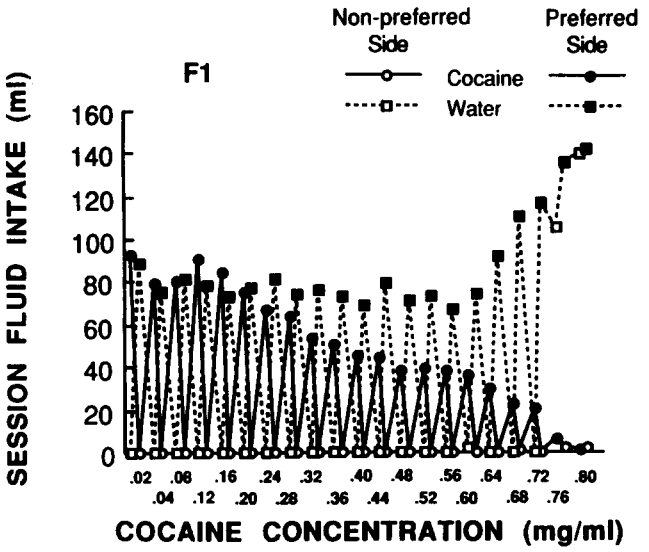

FIG. 1. Mean fluid intakes (ml) of rat F1 for concurrently presented water and cocaine solution during FT 1-min food schedule sessions (3 hr) as a function of increasing cocaine solution concentration (mg/ml). Data based on last 6 sessions given at each concentration.

tration for each rat. Figure 5 shows no evidence that cocaine solution is preferred over water. As cocaine solution concentration was increased, the percent cocaine solution intakes decreased for all animals. For 2 rats the change was graded (F1, F11), but was abrupt for the other 2 rats (F2, F4).

Although the percent of total session polydipsic fluid taken as cocaine solution decreased as a function of increasing concentration (Fig. 5), when presented on the preferred side (3 of the last 6 days at each concentration), session cocaine intake (mg/kg) first

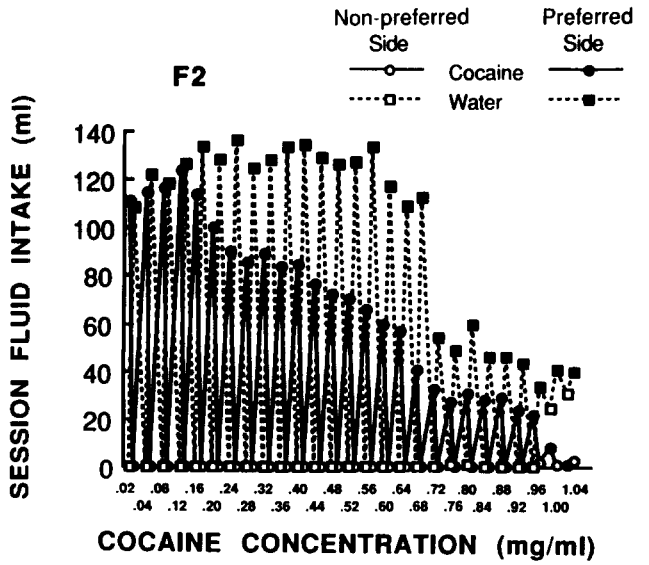

FIG. 2. Mean fluid intakes (ml) of rat F2 for concurrently presented water and cocaine solution during FT 1-min food schedule sessions (3 hr) as a function of increasing cocaine solution concentration (mg/ml). Data based on last 6 sessions given at each concentration.

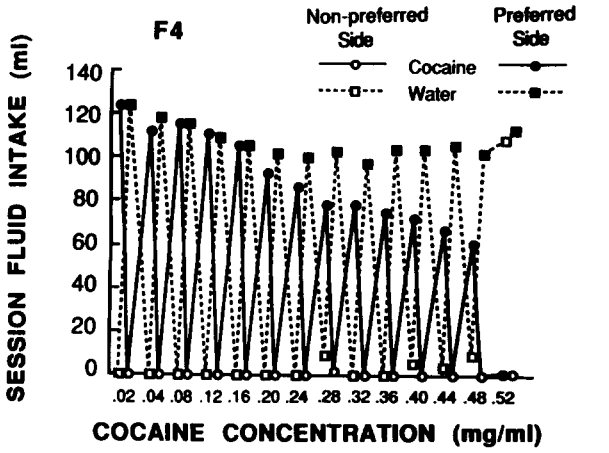

FIG. 3. Mean fluid intakes (ml) of rat F4 for concurrently presented water and cocaine solution during FT 1-min food schedule sessions (3 hr) as a function of increasing cocaine solution concentration (mg/ml). Data based on last 6 sessions given at each concentration.

increased as a function of concentration and then decreased (Fig. 6). The concentration points yielding maximal session intake differed among animals as did the intakes themselves, F1 = 71.1 mg/kg at 0.6 mg/ml; F2 = 120.1 mg/kg at 0.56 mg/ml; F4 = 97.2 mg/kg at 0.44 mg/ml; F11 = 54.3 mg/kg at 0.28 mg/ml.

Table 1 shows the serum levels of cocaine and its metabolites for samples taken at or near points on the ascending series of cocaine concentrations that yielded maximal cocaine intakes. Cocaine intakes are also shown for the sessions sampled.

Figure 7 shows a typical cumulative drinking session for water when it was on the preferred side and, by comparison, for a highly concentrated cocaine solution when it was on the preferred side. Neither presession dose level of cocaine (IP) affected water polydipsia.

Figure 8 compares the results of the first (cf. Fig. 5) and second ascending-series determinations. For F1, the second series yielded

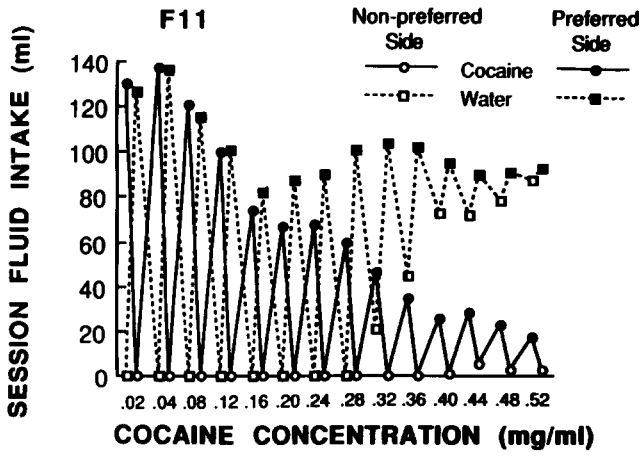

FIG. 4. Mean fluid intakes (ml) of rat F11 for concurrently presented water and cocaine solution during FT 1-min food schedule sessions (3 hr) as a function of increasing cocaine solution concentration (mg/ml). Data based on last 6 sessions given at each concentration.

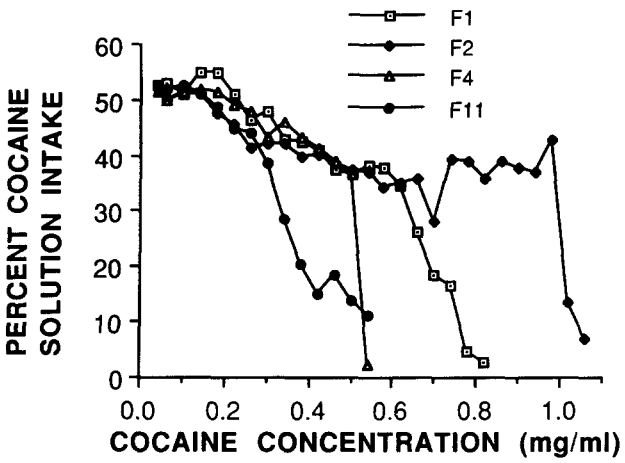

FIG. 5. Percent cocaine solution preference for concurrently presented water and cocaine solution during FT 1-min food schedule sessions (3 hr) for 4 rats as a function of increasing cocaine solution concentration (mg/ml). Points are means of last 6 sessions at each concentration.

lower relative preferences for cocaine solution at all concentrations. For F4, the results of the two series were comparable, although cocaine intakes were sustained for higher concentrations of cocaine in the second series.

When saccharin was used to alter the vehicle for the cocaine solution and increased in concentration steps, cocaine concentration was also varied idiosyncratically for each animal in an attempt to maximize cocaine intake and choice. At the final saccharin concentration (0.16%) the cocaine solution concentration for each animal was: F1 (0.56 mg/ml); F2 (0.24 mg/ml); F4 (0.64 mg/ml). Considering these animals as a group, and comparing their mean cocaine intake the last time these animals drank these concentrations under water-vehicle conditions with the present saccharin-vehicle results, reveals quite comparable intakes (water vehicle = 51.8 mg/kg; saccharin vehicle = 51.7 mg/kg). Thus, although animals only drank cocaine when it was on the preferred side in the previous water-vehicle condition, and either split their drinking between the two spouts (F1, F4) or followed the cocaine-saccharin solution from side to side (F2), nonetheless, cocaine intakes were equivalent under the two conditions. Hence, altering cocaine solution by adding saccharin did not produce elevated session cocaine intakes.

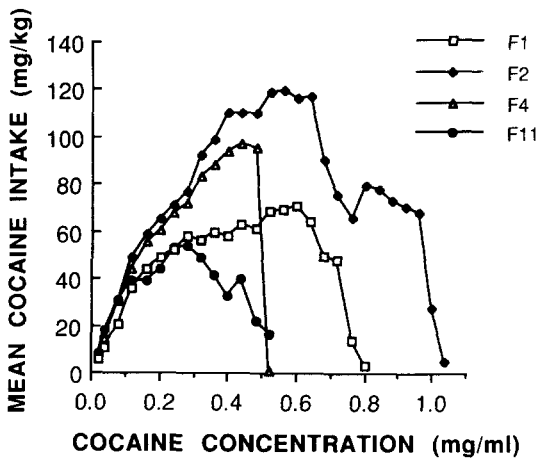

FIG. 6. Mean cocaine intake (mg/kg) when cocaine solution was presented on the preferred side (concurrent presentation of water and cocaine solution) during FT 1-min food schedule sessions (3 hr) for 4 rats as a function of increasing cocaine solution concentration (mg/ml). Points at each concentration are means of last 3 sessions in which cocaine solution was presented on the preferred side.

When the compound solution was used as the cocaine vehicle, cocaine concentrations were progressively decreased for each animal until the final concentrations were attained: F1 (0.24 mg/ml), F2 (0.32 mg/ml), F4 (0.32 mg/ml). The mean of the final six days of session drinking is shown in Fig. 9 (left side). Animals followed the solution from side to side and drank no water from the other spout. Comparing the group mean cocaine intake the last time these animals drank these concentrations under water-vehicle conditions with the present compound-solution results reveals that altering the vehicle produced a marked increase in cocaine intake (water vehicle = 61.5 mg/kg; compound solution vehicle = 89.4 mg/kg).

Figure 9 also shows the effect of progressive dilutions of the compound solution (from 100% to 5%) on session intakes. Little or no drinking occurred from the water spout over the entire range of dilutions, so that even when the compound solution concentration was reduced to 5% of its starting value animals still followed the compound-cocaine solution from side to side. As the dilution of the vehicle solution was increased cocaine intake decreased systematically for all animals.

Figure 10 shows the result of finally returning the vehicle for cocaine to distilled water. On the first session in which animals were offered their cocaine solution on the nonpreferred side they continued to drink exclusively from the cocaine solution spout and self-administer appreciable amounts of cocaine (F1 = 39.5 mg/kg; F2 = 31.4 mg/kg; F4 = 79.7 mg/kg). However, by sessions 3 and 4, F1 reverted to a position preference, as did F4 by sessions 5 and 6. With the exception of the third session, F2 continued to drink exclusively from the cocaine spout, following it from side to side. Upon changing to the lower concentration (Fig. 10, second panel), F1 and F4 displayed a transient preference for cocaine solution followed by a return to a position preference, while F2 continued to drink only cocaine solution. The return to compound solution as the vehicle for 2 days resulted in all animals drinking almost exclusively from the compound-cocaine solution. When distilled water replaced the compound solution as the vehicle for cocaine (Fig. 10, right side), F2 continued to drink only cocaine solution, while F1 and F4 reverted mainly to a position preference.

As a final control manipulation (not shown in Fig. 10), water was made available from both spouts in order to confirm that F2 was following the cocaine solution from side to side rather than perhaps following a particular spout. Under this condition, all animals drank mainly from the water spout on their preferred side.

DISCUSSION

These studies extended previous research (5,25) on the schedule-induced drinking of cocaine solutions by demonstrating chronic session ingestion of concentrated solutions which resulted in elevated serum levels of cocaine and it metabolites similar to levels observed not only in coca-leaf chewers, but also in nasal-inhalation cocaine abusers. On the first series, in which the animals were exposed to a choice between water and a cocaine solution of ascending concentration, postsession serum samples were analyzed for cocaine and metabolites at or near the cocaine solution concentration producing the greatest cocaine intake (Table 1). The animal (F11) with the lowest mg/kg cocaine intake

TABLE 1

SERUM COCAINE AND METABOLITES (ng/ml) PRESENT AT 0 AND 1 HR POSTSESSION AFTER SCHEDULE-INDUCED SESSION (3 HR) DRINKING VARIOUS COCAINE SOLUTION CONCENTRATIONS (mg/ml)

	Cocaine		Serum Concentration (ng/ml)							
	Conc.	Intake	Cocaine		Norcocaine		BE*		BNE†	
Rat No.	(mg/ml)	(mg/kg)	0 hr	1 hr	0 hr	1 hr	0 hr	1 hr	0 hr	1 hr
F1	0.48	60.2	201.6	114.2	97.1	34.6	103.6	97.6	144.4	123.7
	0.60	64.7	182.2	199.6	54.5	0	207.3	162.1	93.0	162.8
F2	0.48	100.4	133.4	49.6	99.6	0	9137.1	5251.1	777.1	494.9
	0.60	115.3	94.0	373.4	50.5	53.0	8679.4	8461.8	627.8	767.0
	0.80	79.7	148.7	538.7	0	0	8077.7	6324.0	512.7	445.2
	0.80‡	95.4	198.2	320.6	83.4	35.7	9736.8	4917.3	502.3	301.0
F4	0.48	101.4	159.8	114.8	181.9	66.1	3427.8	2834.5	397.3	349.3
F11	0.48	40.4	32.3	32.2	55.8	0	1306.3	665.1	77.1	69.6

*Benzoylecgonine; †benzoylnorecgonine; ‡2nd hr measures: cocaine = 38.9; norcocaine = 17.1; BE = 3103.8; BNE = 215.5.

yielded low serum levels, while animals drinking greater amounts, particularly if these were gained from ingesting the two higher concentrations (0.60 and 0.80 mg/ml), yielded much higher levels. In all cases, ingestion of the two higher concentrations yielded greater serum cocaine levels 1 hour postsession than immediately after the session.

It is of interest to compare the serum cocaine levels in Table 1 with those reported for humans taking cocaine by oral, buccal, and nasal routes. Subjects given an oral dose of cocaine (by capsule) containing 2 mg/kg had peak plasma cocaine levels of about 200 ng/ml, a level which approximates the values observed in the present experiment (27). Upon attaining that level, and for the next 45 minutes, subjects reported the "high" as equivalent to that obtained from their usual experience with street cocaine. Coca leaves or powder chewed in the traditional fashion yielded a plasma cocaine maximum of 150 ng/ml and reports of feeling stimulated (13). Chewing larger amounts of coca leaves produced correspondingly higher plasma cocaine levels (17). By comparison, peak plasma cocaine levels equivalent to those in the present experiment (about 200 ng/ml) were produced in humans by the nasal inhalation of 96 mg of cocaine hydrochloride (14). Maximal reported "highs" in these subjects occurred before plasma values had reached their peaks. In subsequent studies using the same 96 mg nasal dose, subjects also yielded a comparable peak plasma

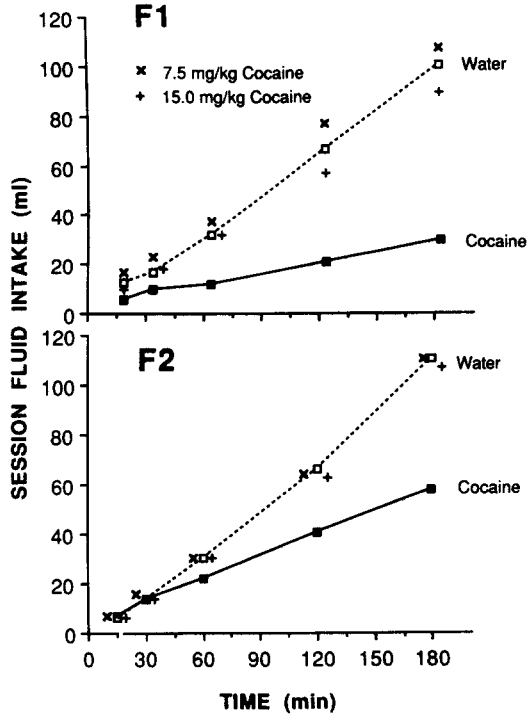

FIG. 7. Cumulative water intake (open squares) for representative FT 1-min session when water was presented on the preferred side for rats F1 and F2 and the effect of presession doses of cocaine (IP) on water intake for similar sessions. Cumulative cocaine solution (0.68 mg/ml) intakes when cocaine solution was presented on the preferred side are shown for comparison.

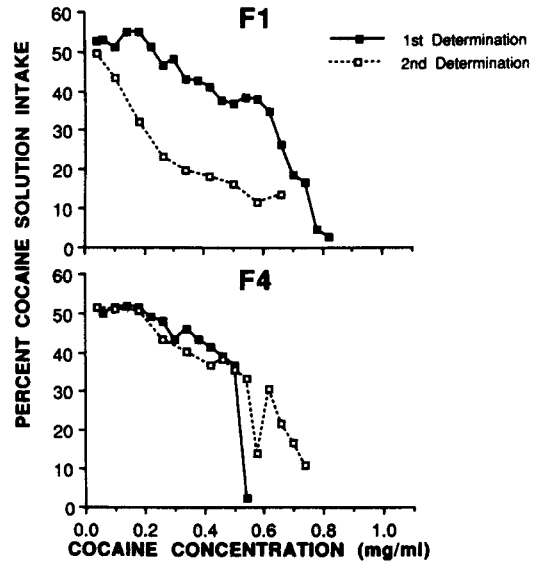

FIG. 8. Comparison of the first (cf. Fig. 5) and a second determination of the cocaine solution preference series for 2 rats.

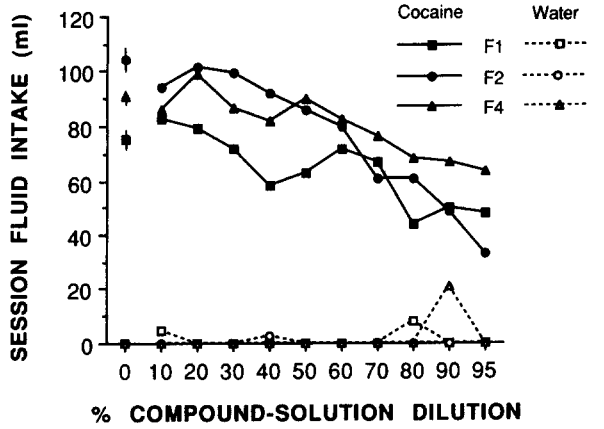

FIG. 9. Session fluid intakes (ml) for concurrently presented cocaine dissolved in a compound vehicle solution (0.16% saccharin + 3% glucose) and water as a function of increasing dilution of the vehicle. Points at left (0% dilution) are means (± SE) of last 6 sessions for cocaine in compound solution and for water. Other points are means of last 2 sessions under each dilution condition. Cocaine concentration in vehicle was 0.24 mg/ml (rat F1) and 0.32 mg/ml (rats F2, F4).

cocaine level (6) and reported being highly stimulated (7).

Inasmuch as the serum levels of cocaine attained in the present experiment were equivalent to those produced in humans when cocaine was administered by oral or nasal routes, and which were described as producing stimulation or a typical street-cocaine high, it is reasonable to assume that these levels would reinforce behavior which preceded them. The claim that orally administered cocaine "is largely hydrolyzed in the gastrointestinal tract and rendered ineffective" (18), has been revised in light of the effectiveness of the intragastric route in humans (27), rhesus monkeys (1, 2, 28) and rats (8). Further, there is evidence that the buccal route is more effective than the intragastric (2). In most studies utilizing the oral route for cocaine administration (including the present study), administration probably occurs by some combination of the buccal and gastrointestinal routes.

In spite of evidence (serum cocaine levels, subjective and behavioral effects) from research on both humans and animals that

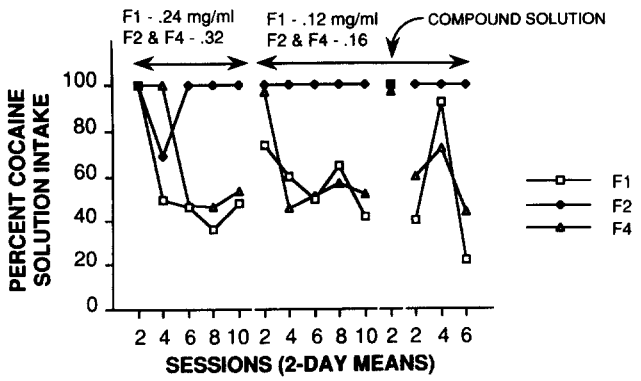

FIG. 10. Percent cocaine solution preference for concurrently presented water and cocaine solution during FT 1-min food schedule sessions (3 hr) after return to water as the cocaine vehicle (left panel) following progressive dilution of compound solution vehicle (cf. Fig. 9). Second panel: reduction in cocaine solution concentrations. Third panel: return to compound solution (saccharin + glucose) as the vehicle for cocaine. Right panel: return to conditions in second panel.

oral administration of cocaine is an effective route, indications in animals that the oral self-administration of cocaine can function as a reinforcer are scant. Rhesus monkeys were reinforced under a multiple fixed-ratio 20, fixed-interval 1-min schedule by the delivery of 1-gram packages of coca leaves or placebo packages (21). Many more packages were earned and chewed when coca packages were available than was the case on days when placebo packages were available. The animals self-administered about 9 mg/kg of cocaine base per day. Rhesus monkeys also self-administered cocaine solutions intragastrically (28). In a study by Meisch and his associates (R. A. Meisch, personal communication, July 10, 1989), rhesus monkeys first trained on fixed-ratio schedules with ethanol as the reinforcing agent had cocaine solution gradually substituted for ethanol. The animals sustained fixed-ratio behavior and drank approximately 5 mg/kg cocaine in 3-hr sessions. C57BL/6J mice with a similar ethanol history self-administered about 6 mg/kg doses of cocaine in fixed-ratio sessions lasting 30 min (11). Lewis rats drinking a cocaine solution self-administered about 8 mg/kg cocaine in 1-hr sessions, but Fischer 344 rats took lesser amounts which did not differ from vehicle intakes (10). In the present experiment, although animals without prior histories of ethanol or other drug self-administration ingested large doses of cocaine chronically, only a history of exposure to cocaine in the compound saccharin plus glucose solution vehicle produced evidence for the later differential selection of cocaine solution in preference to distilled water. Even in this case, it is possible that the development of cocaine-solution preference was due to the association of the taste of cocaine with the highly acceptable compound solution rather than a learned appreciation of the pharmacological effects of cocaine.

The lack of development of a clear preference for cocaine solutions over vehicle under a concurrent-presentation condition contrasts with previous findings for ethanol. Under schedule-induction conditions, rats prefer 5% ethanol to water and to dilute glucose solutions (19,23), although even in ethanol-dependent animals 5% ethanol is not preferred over a concentrated glucose solution (19,23) or isotonic NaCl solution (24). The redetermination of the ascending cocaine-concentration preference function indicated that neither long exposure to cocaine solution drinking, nor the drinking of highly concentrated cocaine solutions, altered the cocaine versus vehicle preference function (Fig. 8).

In order to explore the possibility that cocaine solution polydipsia might be limited by the pharmacological consequences of the accumulating dose of ingested cocaine on drinking behavior, the effect of presession IP doses of cocaine on water polydipsia was determined. Figure 7 indicates that neither dose level of cocaine had a marked effect on polydipsic behavior. Further, even at a rather high concentration (0.68 mg/ml), the rate of cocaine solution intake remained quite linear throughout the session. Finally, the use of the compound (saccharin plus glucose) solution as the vehicle for cocaine induced a somewhat greater intake of cocaine than when water was employed as the vehicle, indicating that the level of cocaine ingestion under the water-vehicle condition had not been limited by the effect of the accumulated dose.

The method of using the relative free-intake levels of two fluids presented in a concurrent choice as indicators of their respective potentials as reinforcing agents may have limited utility. Although intravenous availability of two concurrent solutions typically shows selection of a putative reinforcing agent in clear preference to a vehicle (16,22), in the case of oral consumption procedures, position preferences often limit the sensitivity of the concurrent-choice method. But perhaps of greater import, the reinforcing functions of a drug depend not only upon its intrinsic pharmacological properties, but also upon its schedule of availability. For example, under conditions of continuous availability, it has been difficult to demonstrate the reinforcing efficacy of intravenously

available nicotine. However, with schedules permitting only intermittent availability of nicotine, it quite clearly functions as a potent reinforcing agent [for a review see (12)]. In many concurrent, oral, fluid-choice procedures (including the one used in the present experiment), the fluids are freely, rather than intermittently, available. Such presentation conditions may function to attenuate differences in reinforcing efficacy. Just as the intermittent availability of one commodity (food) can strengthen the reinforcing efficacy of a concurrently available, alternative commodity (e.g., water), as illustrated by schedule-induced polydipsia, an intermittent schedule of availability for the two commodities of a choice may enhance any intrinsic difference in reinforcing efficacy between the two commodities. Recent research on concurrent choices between cocaine and vehicle confirm this suggestion. In rhesus monkeys given a choice between a 0.8 mg/ml cocaine solution and water, there was a preference for cocaine when the schedule of fluid availability was fixed-ratio 8. But as the size of the fixed-ratio schedule was decreased, water-reinforced behavior often exceeded that maintained by cocaine (R. A. Meisch, personal communication, July 10, 1989). Similarly, Fischman and Rachlinski [cited in (15)] "found that human subjects given a choice between 8 mg IV cocaine and IV saline showed no systematic preference for either solution when the requirement for injection was a FR 10. However, when the FR was increased to 200, there was a clear preference for the 8 mg cocaine dose." It remains for future research to clarify whether it is the increased response cost or the schedule of intermittency that enhances such differences in reinforcing efficacy.

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