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Orally Self-Administered Cocaine: Reinforcing Efficacy by the Place Preference Method

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SEIDMAN, M. H., C. E. LAU, R. CHEN AND J. L. FALK. *Orally self-administered cocaine: Reinforcing efficacy by the place preference method.* PHARMACOL BIOCHEM BEHAV 43(1) 235–241, 1992. – In three separate place preference conditioning (PPC) experiments, groups of rats were exposed to different modes of receiving cocaine: IP cocaine doses (7.5 mg/kg), PO cocaine self-administered bolus doses (15 mg/kg), and 1-h schedule-induced cocaine-solution drinking sessions (19.1 mg/kg). Oral cocaine self-administration of PO bolus and schedule induction took place in situations that preceded transfer into an apparatus for PPC sessions. Thus, the reinforcing efficacies of the pharmacological consequences of both oral cocaine self-administration methods were evaluated by a procedure separate from the self-administration behavior itself. The IP cocaine dose imposition and the two oral cocaine self-administration arrangements all resulted in dose-exposure conditions sufficient for the production of PPC. The serum and brain cocaine pharmacokinetics sufficient for the production of reinforcing efficacy were measured and related to previous data.

Place preference conditioning Drug self-administration Schedule induction
Cocaine pharmacokinetics Cocaine

THE place preference conditioning procedure has been used to assess the reinforcing effects of drugs (3). When the physiological effect of a drug is associated with a set of environmental stimuli (e.g., a distinctive compartment), animals given a choice when drug free increase the time spent in the presence of those stimuli if the drug functioned as a reinforcing agent. A variety of drugs, known by IV self-injection procedures to be reinforcing agents, also are classed as reinforcers by the place preference procedure (9). Several studies using rats have demonstrated that cocaine administered by the IP (4,14, 15,19), IV (16,17,20), or ICV route (15) can produce a conditioned place preference.

Schedule-induced polydipsia can be generated by an arrangement in which animals are fed in daily, intermittent, food-delivery sessions (5). Under such conditions, animals have been induced to drink chronic, elevated amounts of solutions from several classes of drugs (18), including cocaine (6–8,23). In a recent study of oral drug self-administration completed in our laboratory (unpublished results), cocaine solution was chosen in a preference arrangement almost to the complete exclusion of the distilled-water vehicle alternative. Specifically, rats developed schedule-induced polydipsia when exposed to a fixed-interval 1-min food schedule (FI 1-min) in daily 3-h sessions. When the FI 1-min condition continued and two fluids, water and 0.16 mg/ml cocaine solution, were available under concurrent fixed-ratio 6 (FR 6) schedules, cocaine solution was chosen repeatedly almost to the complete exclusion of water during the 3-h session, and the polydipsic intake level was maintained. Although a previous study showed that equivalent volumes of water and 0.16 mg/ml cocaine solution were drunk under a schedule-induction condition when each was presented singly in separate sessions, suggesting equal gustatory acceptance (23), it remained a possibility that intermittent fluid availability under the concurrent FR 6 schedules somehow biased choice toward cocaine solution independent of its putative pharmacologically based reinforcing effects by the oral route. To help answer the question of whether the pharmacological consequences of orally self-administered cocaine can function as a reinforcing event, independent of the act of drinking and of gustatory stimulation, the place preference procedure was used. This technique permits an animal to drink and taste the cocaine solution in the schedule-induction situation but to be evaluated for any consequent pharmacologically based reinforcing property in an ensuing place preference procedure.

In the present set of experiments, the aim was first to reproduce the finding that IP-administered cocaine could function as a reinforcer in the place preference procedure. Replication

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would ensure that with the Holtzman strain of rats, and the particular apparatus used, a reinforcing function was demonstrable. If the IP route result were replicable, then it would be legitimate to determine if the PO self-administration of cocaine also could function as a reinforcing event. Adding cocaine to a few milliliters of a highly acceptable glucose–saccharin solution can ensure the rapid oral self-administration of a significant dose of cocaine in a brief period of time (11).

Also of interest was to determine whether oral self-administration of cocaine at a slower rate over a longer time would yield evidence of a reinforcing function. Such a mode of administration may mimic, and be relevant to, the oral self-administration of cocaine by cultural groups that practice coca leaf chewing (1). To accomplish this aim, it was arranged that animals self-administer the relatively dilute solution of cocaine (0.16 mg/ml) over a 1-h period by schedule-induced drinking.

If the schedule-induced oral self-administration of cocaine yielded evidence of a reinforcing effect by the place preference method, then a third aim was to determine the serum and brain levels of cocaine and its metabolites that were operative in producing the reinforcing effect.

EXPERIMENT 1: COMPARISON OF COCAINE AS A REINFORCER BY IP IMPOSITION AND ORAL SELF-ADMINISTRATION

METHOD

Animals

Thirty-eight male, albino rats of the Holtzman strain (Madison, WI) with a mean initial body weight of 384 g (range: 380–396 g) were housed individually in stainless steel cages in a temperature-regulated room under continuous illumination. Animals were experimentally naive.

Drug Administration

Cocaine HCl was obtained from the National Institute on Drug Abuse (Rockville, MD). All solutions were made by dissolving the drug in nano-pure water. Doses were calculated as the salt.

For IP administration, cocaine HCl (7.5 mg/kg) was dissolved in isotonic NaCl solution (0.9%) and injected in a volume of 1 ml/kg body weight. Control injections were the same volume of isotonic saline solution.

For PO self-administration, a compound solution of 3% glucose and 0.16% sodium saccharin was prepared, and cocaine HCl was added to yield a solution of 2.5 mg/ml. Animals were allowed to self-administer 6 ml/kg of the solution (15 mg/kg body weight) by licking the blunted end of a 13-ga needle attached to a syringe. Drinking took about 2 min. For vehicle PO self-administration, animals drank the same volume of compound solution without the addition of cocaine.

Apparatus

The place preference conditioning procedure occurred in a chamber consisting of three compartments: two end compartments (30 × 33 × 36 cm) and a middle compartment (16 × 8 × 13 cm). The middle compartment was separated from the others by removable guillotine doors. Flooring in the compartments was wire mesh with strands 1.3 cm apart. Compartment walls were of different shades: The two end ones were shaded black and white, respectively, and the middle one was grey. Compartment tops consisted of clear Plexiglas. The middle compartment served as a small, neutral region between the black and the white compartments. The location of an animal within the apparatus was monitored by a Panasonic WV-BL200 videocamera, mounted above four identical apparatuses, with videotape playback scored at a later time. The apparatuses were located adjacent to one another in a quiet, isolated room, but animals could not see each other inasmuch as the compartment walls were painted as described.

Procedure

After establishing ad lib weights, animals were reduced to 80% body weight by limiting daily food rations. Weight reduction was a necessary condition in Experiment 2 and was used in Experiment 1 so that the results of all experiments could be compared. These experiments were executed in accordance with the Guide for the Care and Use of Laboratory Animals (NIH Publication 85-23, revised 1985).

Rats were assigned to four groups: IP cocaine (n = 8), IP saline (n = 7), PO cocaine (n = 7), and PO Vehicle (n = 8). Originally, eight rats were assigned to each group, but five were added later to replace rats that did not satisfactorily ingest the solutions presented to them. One IP saline group animal was eliminated for failing to satisfy the compartment preference score criterion by spending too much time in the grey compartment (see below).

All animals were fed 8.1 g food before a place preference session each day. (This food ration was given so that the results from animals in these groups could be compared with those in Experiment 2, which allowed animals to earn food pellets presession.) The IP groups were fed 30 min presession and the PO groups were fed 45 min presession. The additional 15 min for the PO groups occurred owing to a 15-min delay imposed between the end of PO drug self-administration and the start of the place preference conditioning session to allow time for drug absorption. The place preference procedure took place at the same time of day on 12 consecutive days.

Experiments consisted of three phases. The first 3 days comprised the preconditioning phase (Phase 1). The purpose of Phase 1 was to habituate animals to the apparatus and determine the nature and degree of their compartment preferences. No drug was administered on these days. Each rat was placed in the grey, middle compartment. The guillotine doors were in place so the animal could not explore. After 30 s, doors were removed and the animal was allowed to move freely within the compartments for 15 min. It was then returned to its home cage and fed the remainder of its daily ration to maintain the 80% ad lib weight. The amount of time spent in each compartment was used to determine compartment preference scores, and the mean of the scores for days 2 and 3 defined each rat's preferred (P) and lesser-preferred (LP) compartment. A rat was considered to be in a compartment if its snout tip was in this compartment. If a rat spent more time in the grey compartment than in either of the other compartments on days 2 or 3, then it was eliminated from the study. One rat from the IP saline group was eliminated for failing to satisfy this criterion.

The next 8 days (days 4–11) constituted the conditioning phase (Phase 2). On even-numbered days, all rats were administered vehicle. For IP groups, this was an isotonic saline injection. For PO groups, this was compound solution ingestion. After vehicle administration, an IP group animal was immediately placed into its preferred compartment with the guillotine door blocking its access to the other compartments. A PO

group animal remained in its home cage for 15 min after ingesting its ration of compound solution and was then placed in its preferred compartment with access to the rest of the apparatus blocked. An animal remained confined in its preferred compartment for 30 min on these Phase 2 days and was then returned to its home cage and fed the remainder of its daily food ration.

On the odd-numbered days of Phase 2 (days 5, 7, 9, and 11), the two control groups (IP saline and PO vehicle) continued to receive the same vehicle treatments they did on the even-numbered days, but the two cocaine groups received cocaine solutions. IP cocaine animals were injected with 7.5 mg/kg cocaine and PO cocaine animals ingested 15 mg/kg in the compound solution. All rats, regardless of group, were placed into their LP compartments, the PO groups again waiting 15 min before being transferred to the apparatus. After 30 min of confinement to their LP compartments, all rats were returned to their home cages and fed the remainder of their daily food rations.

On day 12, the postconditioning phase test was given (Phase 3). The procedure on this day was the same as on Phase 1 days: No drug or vehicle was given and free choice of chambers was allowed. Thus, after the appropriate postfeeding delay each rat was placed in the middle, grey compartment for 30 s, guillotine doors were removed, and an animal was free to move within the three chambers for 15 min. For all groups, the Phase 3 preference scores were compared to those of Phase 1 to determine if a change in compartment preference had occurred. Table 1 outlines the place preference conditioning schedule.

RESULTS

For all experiments, compartment preference scores were calculated for days 2 and 3 of the preconditioning phase and for day 12, the postconditioning phase. For these sessions, the total seconds spent in each compartment was tabulated. The total time spent in each of the two end compartments (the black and the white) on days 2 and 3 was used to define a rat's initial compartment preference. (Day 1 was treated as an exploration and adaptation day and was not tabulated.) The number of seconds spent in the preferred compartment, black or white, was designated P, the number of sec spent in the lesser-preferred compartment as LP, and in the grey compartment as G. The place preference score for each animal on these days was calculated by the formula:

$$\text{preference score} = [\text{LP} + (\text{G}/2)]/900.$$

This formula yields a value between 0 and 1. A value of 0.5 would result if there were no difference between times spent in the black and white compartments. Inasmuch as the score is calculated in terms of time spent in the LP compartment, the mean value for the two preconditioning days cannot be greater than 0.5.

The preference score for the postconditioning test day was calculated by the same formula, with P and LP designated in accordance with each animal's preconditioning preference. If an animal showed an increase in time spent in its LP compartment on the test day, then its preference score would increase.

The results of the place preference conditioning procedure for the four groups are shown in Figs. 1 and 2.

Figure 1 shows a significant within-group change in place preference for the IP cocaine group, $t(7) = 7.22, p < 0.0005$, and this increase was significantly greater than that of the IP saline group, $t(13) = 5.07, p < 0.0005$. The within-group change for the IP saline group was not significant, $t(6) = 0.13, p < 0.5$.

In Fig. 2, the PO cocaine group shows a significant within-group change in place preference, $t(6) = 2.64, p < 0.04$, and this increase was significantly greater than that of the PO vehicle group, $t(13) = 2.56, p < 0.05$. The within-group change for the PO vehicle group was not significant, $t(7) = 0.68, p < 0.5$.

Comparing the magnitude of the change in preference score between a drug group and its corresponding control group shows that the IP cocaine group had a significantly

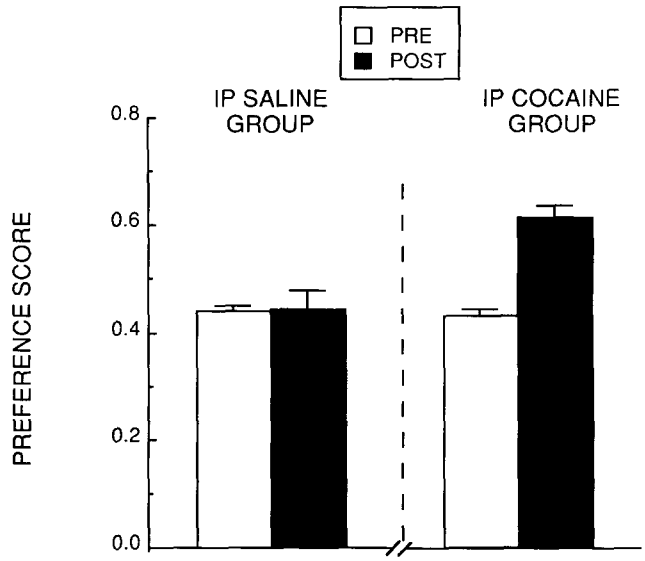

FIG. 1. Mean (SE) preference scores for the pre- and postconditioning phases of place preference conditioning. Dose level = 7.5 mg/kg cocaine.

TABLE 1

PLACE PREFERENCE CONDITIONING SCHEDULE

Day	Phase	Drug Treatment	Place Preference Apparatus Exposure
1	Pre	None	Choice 15 min
2	Pre	None	Choice 15 min*
3	Pre	None	Choice 15 min*
4	Cond	Vehicle	P 30 min
5	Cond	Cocaine+	LP 30 min
6	Cond	Vehicle	P 30 min
7	Cond	Cocaine+	LP 30 min
8	Cond	Vehicle	P 30 min
9	Cond	Cocaine+	LP 30 min
10	Cond	Vehicle	P 30 min
11	Cond	Cocaine+	LP 30 min
12	Post	None	Choice 15 min*

Pre, preconditioning; cond, conditioning; post, postconditioning; P, preferred compartment; LP, lesser-preferred compartment; choice, choice of compartments.

*Compartment preference assessed.

+For vehicle groups, vehicle given rather than cocaine.

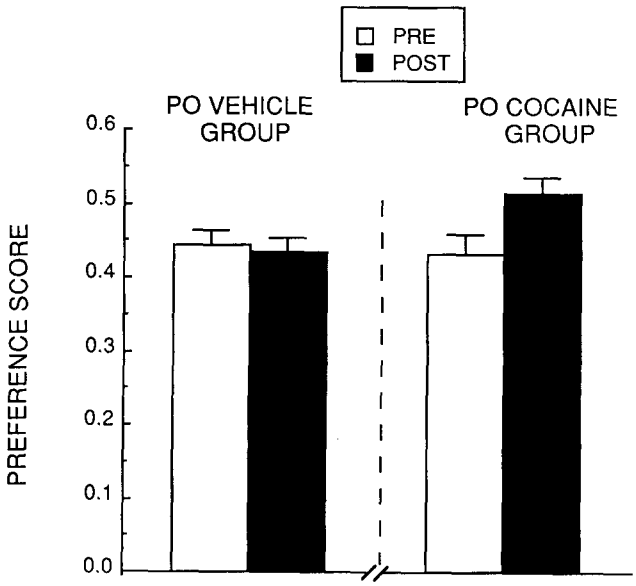

FIG. 2. Mean (SE) preference scores for the pre- and postconditioning phases of place preference conditioning. Dose level = 15 mg/kg cocaine.

greater change in place preference than did the PO cocaine group, $t(13) = 2.37, p < 0.05$.

EXPERIMENT 2: SCHEDULE-INDUED ORAL SELF-ADMINISTRATION OF COCAINE–REINFORCING CONSEQUENCES AS MEASURED BY PLACE PREFERENCE METHOD

METHOD

Animals

Thirty male, albino rats (Holtzman), experimentally naive, with a mean, initial body weight of 384 g (range: 380–393 g) were housed under the conditions described in Experiment 1.

Apparatus

Schedule-induced polydipsia sessions occurred in individual, Plexiglas chambers (30 × 26 × 23 cm). A stainless steel food pellet receptacle was mounted within each chamber into which 45-mg food pellets (Bio Serv, Frenchtown, NJ) were delivered. A stainless steel, ball-bearing spout protruded into the chamber. The spout was attached to a Nalgene graduated cylinder, which served as a fluid reservoir for solutions to be self-administered.

Procedure

Animals were reduced to 80% of their ad lib weights. For 2 weeks, at the same time each day, animals were weighed, transferred to chambers, and for 3 h received a food pellet every 60 s (FT 1-min schedule). Distilled water was the fluid available in the reservoirs. At the end of the session, animals were returned to their home cages and fed the remainder of their rations required to maintain the 80% body weight levels. Water was always freely available in the home cages. By the end of this 2-week period, session polydipsia had been induced in most of the animals. The 24 rats with the greatest mean daily session fluid intakes were divided randomly into two groups of 12 animals each, a cocaine polydipsia and vehicle polydipsia group.

For the next three sessions, the FT 1-min session length was reduced to 1 h, and after each session animals were returned to their home cages as usual. The next day was day 1 of the preconditioning phase of place preference conditioning (Table 1). The 1-h session length remained in effect, but instead of being transferred back to their home cages after the session animals were placed in place preference apparatuses. Place preference conditioning was executed as described in Experiment 1 (Table 1), with each day's conditioning occurring immediately after the 1-h polydipsia session.

The vehicle polydipsia group had distilled water available in their reservoirs during the daily sessions whereas the cocaine polydipsia group had cocaine solution available on the odd-numbered days of the conditioning phase. For the first of these days (day 5), the cocaine solution concentration was 0.08 mg/ml and for the remaining 3 odd-numbered days in this phase it was 0.16 mg/ml. On day 12, the postconditioning day, both groups had distilled water available in their reservoirs.

The preference scoring procedure was identical to that of Experiment 1. Three rats were eliminated from the study for spending too much time in the grey compartment.

RESULTS

Table 2 shows the mean (SE) fluid intakes for the two groups during 1-h polydipsia sessions. The vehicle polydipsia group drank water on days 1–12 and the mean shown comprises the data from all of these days. The session water intake for the cocaine polydipsia group is based upon all of the days on which this group drank water (days 1–4, 6, 8, 10, and 12). The group means are nearly equal. After one transition day, on which a low concentration of cocaine solution was offered (0.08 mg/ml on day 5), Table 2 shows that the 1-h self-

TABLE 2

MEAN (SE) 1-h POLYDIPSIC INTAKES DURING THE 12-DAY PLACE PREFERENCE CONDITIONING PROCEDURE

	Groups	
Intakes	Cocaine Polydipsia (n = 11)	Vehicle Polydipsia (n = 10)
All water sessions		
ml (SE)	35.0 (1.1)	35.0 (1.0)
Day 5: 0.08 mg/ml cocaine		
ml (SE)	40.0 (3.3)	–
mg/kg (SE)	10.5 (0.9)	–
Day 7: 0.16 mg/ml cocaine		
ml (SE)	37.5 (3.2)	–
mg/kg (SE)	19.8 (1.7)	–
Day 9: 0.16 mg/ml cocaine		
ml (SE)	37.5 (3.1)	–
mg/kg (SE)	19.6 (1.6)	–
Day 11: 0.16 mg/ml cocaine		
ml (SE)	34.7 (4.8)	–
mg/kg (SE)	17.9 (1.3)	–

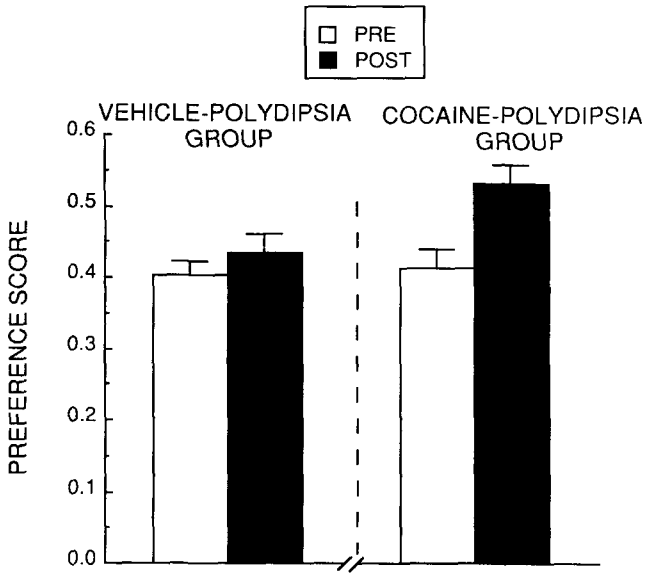

FIG. 3. Mean (SE) preference scores for the pre- and postconditioning phases of place preference conditioning. Mean dose level = 19.1 mg/kg; 1-h schedule-induction sessions drinking cocaine solution (0.16 mg/ml).

administered dose of cocaine remained stable over the three ensuing cocaine sessions.

Figure 3 shows a significant within-group change in place preference for the cocaine polydipsia group, $t(10) = 3.88$, $p < 0.003$, and this increase was significantly greater than that of the vehicle polydipsia group, $t(19) = 2.20$, $p < 0.04$. The within-group change for the vehicle polydipsia group was not significant, $t(9) = 1.22$, $p < 0.25$.

EXPERIMENT 3: SERUM AND BRAIN LEVELS OF COCAINE AND ITS METABOLITES AFTER 1-h COCAINE SOLUTION (0.16 mg/ml)-POLYDIPSIA

METHOD

Animals

Four male, albino rats (Holtzman), experimentally naive, with a mean, initial body weight of 383 g (range: 380–387 g) were housed under constant illumination in the polydipsia chambers described in Experiment 2.

Procedure

Animals were reduced to 80% of their ad lib weights. Then, at the same time each day animals were weighed, their overnight water intakes recorded, and for the next 3 h received a food pellet every 60 s (FT 1-min schedule). Distilled water was the fluid available in the reservoirs for the first seven daily sessions. At the end of a session, animals were fed the remainder of their rations required to maintain the 80% body weight levels. Water was always freely available between sessions. On days 8–10, the session fluid was changed to 0.08 mg/ml cocaine and on day 11 it was increased to 0.16 mg/ml, where it remained for the duration of the experiment. On day 22, the cocaine solution intake was recorded after 1 h of session time, a tail-tip blood sample (100 μl) was drawn, and animals were killed by guillotine. Trunk blood and whole-brain samples were taken and measured as described previously (11,12).

RESULTS

On the sampling day, animals drank a mean of 18.6 ± 2.5 mg/kg cocaine in 1 h, which was comparable to the 19.1 ± 0.9 ingested by animals in Experiment 2.

Figure 4 shows the cocaine and metabolite levels in tail-tip and trunk serum and in whole brain after 1-h polydipsic ingestion of the cocaine solution (0.16 mg/ml).

GENERAL DISCUSSION

IP imposition of 7.5 mg/kg cocaine, or its rapid oral self-administration as a 15-mg/kg bolus, resulted in the conditioning of a preference for the lesser-preferred compartment (Figs. 1 and 2). The IP results confirmed previous findings that IP administration of a similar dose, 5 mg/kg, produced a positive conditioning effect (4,13–15,19). The 5-mg/kg IP dose was reported to produce the maximal conditioning effect (19), with lower doses being either less effective (19) or ineffective (4). The use of the PO bolus self-administration and oral schedule-induced self-administration techniques is unusual. To our knowledge, they are the only place preference studies that have demonstrated effective conditioning by the oral route. Careful attempts to condition place preference with oral ethanol self-administration produced aversion rather than preference (21,22).

There is an interesting relation between the serum cocaine concentration peaks after IP and PO doses (as measured from tail-tip samples) and the conditioning results. In a previous study on animals of the same strain that were also maintained at 80% body weights, the 7.5-mg/kg IP and 15-mg/kg PO doses of cocaine produced the same serum cocaine concentration peaks, 0.130 μg/ml, at 15 and 30 min after administration, respectively (11). Both the IP cocaine and PO cocaine groups showed significant place preference conditioning, but the IP group had a significantly greater change in place preference than did the PO group. This suggests that the greater efficacy of the IP over the PO route was not attributable to any difference in serum cocaine concentration peak, but rather to the rate of increase to the peak. In IV studies of cocaine self-administration in monkeys, the rate of dose infusion had a profound effect on its reinforcing efficacy (2,10).

In Experiment 2, the cocaine polydipsia group showed significant place preference conditioning but the vehicle polydipsia group did not. This confirms that the pharmacological consequences of 1-h polydipsic cocaine solution intake are sufficient to produce a reinforcing effect. The dose of cocaine self-administered in 1-h (Table 2; days at 0.16 mg/ml) elevated serum cocaine to 0.134 μg/ml as measured from tail-tip serum (Fig. 4). This is similar to the concentration (0.130 μl/ml) for the IP and PO groups (Experiment 1) at 15 and 30 min after administration, respectively. After 0.5 h of polydipsic drinking of the same cocaine solution (0.16 mg/ml), the serum concentration of these animals was already at 0.110 μg/ml (unpublished data). This indicates that the rate of serum cocaine concentration increase was almost as high for the cocaine polydipsia group as for the PO cocaine group, and the place preference conditioning result was similar. The relation between rate of serum concentration increase and conditioning outcome would probably be even more convergent had we measured trunk serum levels rather than tail-tip serum. It is evident from Fig. 4 that after 1 h of polydipsic cocaine self-administration tail-tip sampling underestimates the systemic

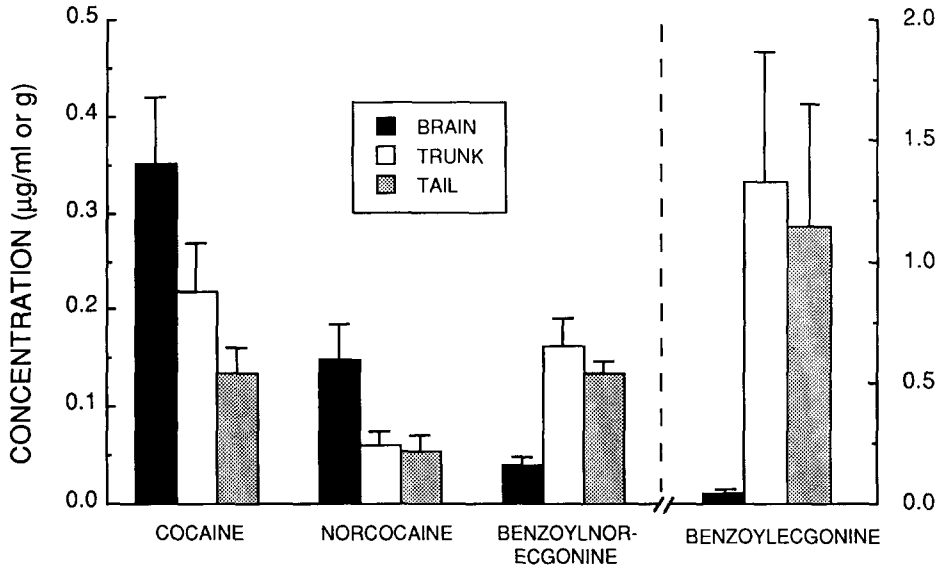

FIG. 4. Mean (SE) cocaine and metabolite values for serum (trunk and tail-tip samples) and brain after 1-h schedule-induced oral cocaine solution (0.16 mg/ml) self-administration session for four animals.

level reflected by trunk serum measures. Previous measures have shown that after 3-h polydipsic sessions the trunk and tail-tip serum values are equivalent because there is sufficient time for the tail-tip site to equilibrate with central circulation values (6).

The whole-brain cocaine concentration value (0.352 µg/g) was considerably greater than the serum values (Fig. 4). This agrees with our previous observations that even after 3 h of schedule-induced cocaine solution intake, when trunk and tail-tip serum values had equilibrated, the brain cocaine concentration still remained about three times higher (6).

To summarize, IP imposition, PO bolus drinking, and oral self-administration of cocaine all produced conditioned place preference. The efficacy of cocaine doses, taken in 1-h schedule-induced polydipsia sessions, to condition a place preference is consistent with the results of a study (unpublished) that found that schedule induction produced an overwhelming preference for cocaine solution available on a FR 6 schedule over water available on a concurrent FR 6 schedule. The conditioning of a place preference by the pharmacological consequences of schedule-induced cocaine drinking suggests that it was these sufficient consequences (e.g., the measured serum and brain cocaine concentration levels), rather than intermittent, gustatory stimulation, that were the initiating factors producing the predominant preference for oral cocaine solution over water.

ACKNOWLEDGEMENTS

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