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BRIEF COMMUNICATION

Oral Self-Administration of Cocaine: Chronic Excessive Intake by Schedule Induction[1]

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TANG, M. AND J. L. FALK. *Oral self-administration of cocaine: Chronic excessive intake by schedule induction.* PHARMACOL BICOHEM BEHAV **28**(4) 517–519, 1987.—Rats were exposed to daily 3-hr schedule-induced polydipsia sessions (fixed-time 1 min food-pellet delivery) with a cocaine hydrochloride solution as the available session fluid. Cocaine intake level (mg/kg) was a direct function of solution concentration (0.02–0.2 mg/ml). In a second experiment with 0.15 mg/ml cocaine solution available, mean daily session cocaine intake remained constant at about 40 mg/kg over the 5-week period of the experiment. Post-session serum samples of animals drinking either 0.15 or 0.2 mg/ml cocaine solution yielded serum cocaine values that were similar to those producing subjective "highs" in coca-leaf chewers and experienced users of cocaine. The schedule-induction technique can be used to induce the intake of drug solutions, including those which perhaps taste bitter, so that chronic and pharmacologically significant consequences ensue.

Cocaine Self-administration Schedule induction Serum cocaine

MOST of the research on cocaine as a reinforcing agent employs the intravenous route [14], and intravenous cocaine is often used as a baseline reference point in drug substitution procedures to evaluate the reinforcing efficacy of other agents [23]. While intravenous cocaine is clearly a powerful reinforcing agent [9], the routes preferred by the majority of self-administering human users are intranasal, inhalation of free-base smoke, and oral. The oral route has received little research attention. Early research on dogs indicated poor bioavailability of oral (gastrically intubated) cocaine compared to the subcutaneous or intravenous routes of administration [28]. The prevailing assumption through the middle 1970's was that when "given orally, cocaine is largely hydrolyzed in the gastrointestinal tract and rendered ineffective" ([18], p. 387). This picture, coupled with the bitter taste of cocaine hydrochloride, provided little encouragement to investigators who might have been interested in exploring the oral self-administration of cocaine. An attempt to assess the reinforcing efficacy of cocaine gum in rhesus monkeys led to equivocal results, with the animals perhaps choosing the sweeter plain gum in preference to the cocaine-containing gum on the basis of taste rather than pharmacological effects [24]. Nevertheless, classic observations by Freud on cocaine, and the widespread acceptance in the 1890's and early 1900's of cocaine-containing "restoratives" such as Coca-Cola, indicated the effectiveness of cocaine by the oral route [6]. Furthermore, the millions of native coca-leaf chewers in Peru, Bolivia, and Columbia, and archeological evidence of coca chewing in the Valdivia area of southwestern Ecuador in 3000 BC, is further testimony to its tradition of oral effectiveness [15].

In the mid-1970's, the efficacy of oral-route cocaine was the subject of several studies, so that by 1980 the standard Goodman and Gilman textbook of pharmacology was amended to read: "Cocaine is absorbed from all sites of application, including mucous membranes and the gastrointestinal mucosa" ([19], p. 307). Orally-administered cocaine was found to alter the total time and quality of sleep in depressed patients [16,17]. The first study to report plasma cocaine levels in humans following oral administration found similar peak plasma cocaine values after oral and intranasal application of the same dosage, with the subjective drug "high" rated as significantly greater after oral, compared to intranasal, administration [26]. Studies followed that investigated plasma cocaine concentrations in Peruvian Indian or Eurasian coca chewers [7,13]. In the traditional use pattern, there is prolonged chewing of the material with absorption from both buccal mucosa and gastrointestinal tract. Measurable plasma cocaine levels occurred 5 minutes after chewing started, indicating quite rapid absorption [7]. Peak levels of coca-chewers were comparable to those reported in the human experimental literature employing oral or intranasal administration [8, 26, 27]. These studies indicated that the efficacy and bioavailability of cocaine are comparable by the

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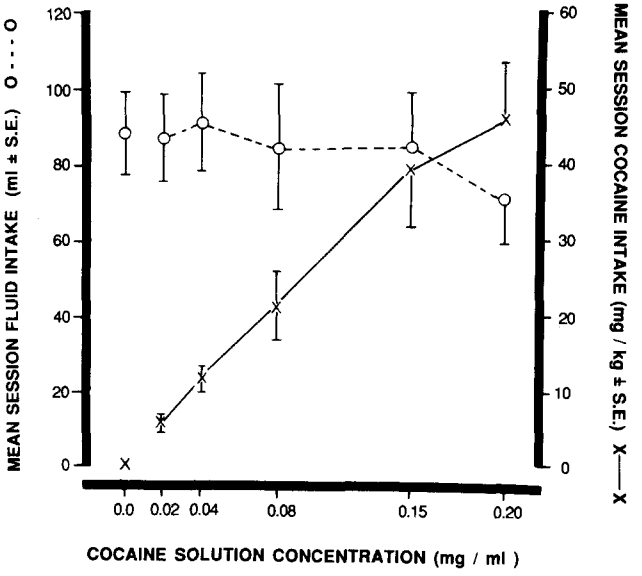

FIG. 1. Mean 3-hr session fluid (ml) and cocaine (mg/kg) intakes for different drinking-fluid cocaine concentrations (N=4).

oral and intranasal routes of administration.

Although solutions of cocaine hydrochloride are known to have a somewhat bitter taste, the success of the schedule-induced polydipsia method in producing elevated intakes of bitter drug solutions [3, 10–12, 20, 21, 25] encouraged us to assess cocaine solution drinking with this technique. The schedule-induced polydipsia method is an experimental arrangement under which food-limited animals fed in daily, intermittent food-delivery sessions concurrently drink large volumes of fluid [2]. The method has been applied to the production of chronic, elevated intakes of several classes of drugs [22].

EXPERIMENT 1: SCHEDULE-INDUCED COCAINE INTAKE AS A FUNCTION OF SOLUTION CONCENTRATION

METHOD

Animals

Four male, albino rats of the Holtzman strain were used. Their initial mean body weight was 380.5 g (range: 375–386 g). They were first housed in standard Acme stainless-steel, individual cages in a temperature-regulated room.

Procedure

Animals were slowly reduced to 80% of their ad lib body weights by limiting their food rations over a 2-week period. When weights were stabilized at 80%, they were moved into individual Plexiglas chambers and housed under continuous-illumination conditions. Each chamber (30×26×23 cm) was equipped with a stainless-steel food pellet receptacle mounted on one wall. Water was available from stainless-steel, ball-bearing spouts attached to Nalgene graduated cylinders mounted on the same wall as the pellet receptacle. At 1000 hr each day, all animals were weighed and their overnight water intakes were recorded. They were returned to their chambers and a 3-hr food-schedule-induced session was begun: A 45-mg Noyes food pellet was automatically delivered into the food receptacle every 60 sec (FT 1 min) for a total of 180 pellets. At the end of the session, water intakes were recorded. Any food rations necessary for maintaining the 80% body weight were given at that time. Following the establishment of chronic, daily schedule-induced water polydipsia, the fluid available during selected sessions (2–7 day interval) was changed to a cocaine hydrochloride solution: An ascending-concentration series of solutions was presented starting at 0.02 and proceeding through 0.04, 0.08, 0.15 and 0.20 mg/ml.

Tail-tip blood samples (100 μl) were obtained immediately after completion of a session during which 0.20 mg/ml cocaine solution was ingested and were analyzed for cocaine by the method of Garrett and Seyda [4].

RESULTS

Session polydipsic intakes are shown in Fig. 1, along with the cocaine intakes (calculated as the salt). It appears that 0.20 mg/ml is the threshold at which the bitter quality of the solution begins to produce a rejection relative to the intakes for water and the lower concentrations of cocaine. The post-session serum cocaine values ranged from 30 to 119 ng/ml.

EXPERIMENT 2: SCHEDULE-INDUCED CHRONIC COCAINE INTAKE

METHOD

Animals

Six male, albino rats of the Holtzman strain were used. Their initial mean body weight was 378.7 g (range: 370–387 g). Housing conditions were as in experiment 1.

Procedure

Weight reduction, experimental chambers, and session food schedule (FT 1 min) were as in experiment 1. Following stabilization of session water polydipsic intakes, animals were given one session with 0.10 mg/ml cocaine solution; then the solution was increased to 0.15 mg/ml for the remainder of the experiment. After 2 weeks of daily cocaine polydipsia sessions, post-session blood samples were taken and analyzed as in experiment 1. Cocaine polydipsia sessions continued for another 3 weeks, at which time the experiment was terminated.

RESULTS

Table 1 shows the group mean intake of 0.15 mg/ml cocaine solution for the first and last 5-day periods of its 5-week ingestion in terms of both ml and mg/kg. Intake data at these two times were quite comparable. On occasional, selected days, hourly session intakes were measured. These indicated that approximately equal amounts were drunk during each of the 3 hours. For example, on day 13 the mean hourly intakes were, 27.3, 26.2 and 27.7 ml, respectively. Post-session serum cocaine values ranged from 0 to 110 ng/ml. The animal that yielded the zero serum cocaine value was the one having the poorest polydipsic response of the group, and drank only 34 ml during the session on the serum-sampling day.

DISCUSSION

High, chronic levels of oral cocaine intake are readily attained by utilizing the schedule-induced polydipsia technique. Neither the bitter taste nor the possible local anaesthetic effect of cocaine solution suppressed session intake at the concentration offered chronically (0.15 mg/ml), nor did

TABLE 1

GROUP (N=6) MEAN (±S.E.) INTAKE OF 0.15 mg/ml COCAINE SOLUTION INGESTION FOR 3-HR SCHEDULE-INDUCTION (FT 1 MIN) SESSIONS

	ml	mg/kg
Mean of 1st 5 days	81.2 ±16.56	40.0 ±8.46
Mean of last 5 days	81.8 ±17.30	39.6 ±9.0

they produce any unusual spillage problems.

The post-session serum cocaine levels measured in both experiments were similar to the peak values measured in coca-chewers (11–149 ng/ml) by Holmstedt *et al.* [7] and in experimental subjects (53 ng/ml) given 16 mg of cocaine hydrochloride intranasally [8]. At these levels, subjects in both studies reported feeling "high," "stimulated," "amphetamine-like," "full of energy," etc. Given these parallels between serum cocaine levels and subjective effects, it is reasonable to suppose that the schedule-induction technique resulted in the self-administration of cocaine doses with reinforcing efficacy. Studies in animals have demonstrated that various drugs [1, 5, 30], including cocaine [29], can function as reinforcers when available intragastrically. These studies are consistent with evidence that the orally-consumed cocaine available in nostrums and coca-leaf preparations also appear to act as reinforcers.

Animals can be induced to orally self-administer pharmacologically significant levels of cocaine solution chronically. Daily sessions produce serum cocaine concentrations that are similar to those producing subjective "highs" in coca-leaf chewers and experienced users of cocaine.

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