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Schedule-Induced Chlordiazepoxide Intake: Differential Effect of Cocaine and Ethanol Histories

JOHN L. FALK AND MAISY TANG

Department of Psychology—Busch, Rutgers University, New Brunswick, NJ 08903

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FALK, J. L. AND M. TANG. *Schedule-induced chlordiazepoxide intake: Differential effect of cocaine and ethanol histories.* PHARMACOL BIOCHEM BEHAV 33(2) 393–396, 1989.—Groups of rats were given differential histories of drinking either water, cocaine (0.15 mg/ml), or ethanol (2.5%) solutions under fixed-time (FT) 1-min schedule-induced polydipsia conditions in daily, 3-hr sessions. The session solution for all groups was then changed to chlordiazepoxide (0.25 mg/ml), and after daily session intakes had stabilized, FT values of 3 and 5 min were probed for single sessions. Probe-session chlordiazepoxide intakes were greater for the Ethanol History Group than for Cocaine History and Water History Groups. Previous research showed that probe conditions elevated intakes for agents with abuse potential (cocaine, ethanol, midazolam), but not for those lacking such potential (water, chlordiazepoxide, flurazepam). The present study demonstrated that a history of ethanol overindulgence yielded elevated probe intakes for chlordiazepoxide, while a history of cocaine or water overindulgence did not. This is consistent with animal and human evidence indicating that a history of either alcohol or sedative abuse increases the probability that benzodiazepines will function as reinforcers and/or be abused.

Benzodiazepine abuse Schedule-induced polydipsia Oral drug Cocaine abuse Ethanol abuse

WHEN animals are maintained under a food-limited condition and receive food pellets intermittently in daily sessions, they concurrently drink excessive amounts of water during such sessions (12,14). This overindulgence phenomenon, usually referred to as schedule-induced polydipsia, can be maintained chronically in daily sessions. The polydipsia is not produced by any pathophysiological condition attributable to the food-limitation state itself. Rather, it is a function of the schedule of food availability (13). The overindulgence is not specific to water and has been used to induce animals to ingest ethanol chronically (15), as well as a variety of other drug solutions [see (26) for a review].

In a previous study (16), the schedule-induced oral intake of drug solutions yielded intake differences across drugs that correlated with their abuse potential. Specifically, paired groups of rats, drinking either water or a particular drug solution, first were induced to drink equal volumes of fluid in daily, 3-hr, schedule-induced polydipsia sessions under fixed-time 1-min (FT 1-min) conditions of food-pellet availability. This was accomplished by adjusting the concentration of a group's drug solution so that the mean, daily, session fluid intake was equal to the intake of its respective water-control group. These conditions continued in effect, but for occasional, single, probe sessions groups were exposed to 3 hr of either FT 3-min or FT 5-min conditions. Probe-session intakes (ml drunk per pellet) were elevated, relative to water-control groups, for groups drinking solutions of drugs with known abuse potential (cocaine, ethanol, midazolam), but not for drugs of uncertain abuse liability (chlordiazepoxide, flurazepam). Thus, for drug solutions with concentrations adjusted to be iso-acceptable with water-control group intakes under FT 1-min conditions, the intake response to FT 3- and 5-min probe sessions correlated with abuse potential.

The above studies used drug-naive animals. However, recent research indicates that the reinforcing efficacy of a drug may be a function of variables in addition to those determining the intrinsic response to the pharmacological properties of the drug. Two examples are germane to the present experiment. In research with humans, benzodiazepines functioned as reinforcers in experiments employing subjects who were former sedative abusers (18–20, 22), but not for subjects lacking such a history (9–11, 24). In intravenous drug self-administration experiments with nonhuman primates, when benzodiazepines were substituted for pentobarbital, they were much more likely to function as reinforcers than when substituted for cocaine (5,23). In both cases, an extensive history of sedative-agent self-administration may have been an important factor determining the reinforcing efficacy of the benzodiazepines. The initial drug-naive status of all groups of animals in our previous study (16) may have minimized the likelihood of either chlordiazepoxide or flurazepam yielding results similar to those revealed by drugs with less equivocal abuse potentials. To evaluate this possibility, three groups of animals were given schedule-induction histories of either ethanol solution, cocaine solution, or water overindulgence, and were then used to assess the effects of these differential drug histories on the abuse potential of chlordiazepoxide.

METHOD

Animals

Twelve male, albino, adult rats of the Holtzman strain with a

mean initial body weight of 385.1 g (range: 380–394 g) were used. They were housed individually in a temperature-regulated room. Body weights were reduced to 80% of their ad lib weights over a 2-week period by limiting daily food rations and animals were maintained at these weights for the duration of the experiment.

Drugs

Chlordiazepoxide hydrochloride (generously supplied by Dr. Peter F. Sorter, Hoffmann-La Roche, Inc., Nutley, NJ), cocaine hydrochloride (obtained from National Institute on Drug Abuse, Rockville, MD) and ethanol were used in the present study. Drug solution concentrations and intakes were calculated in terms of the salt, except for ethanol for which the solution concentration is specified by volume (v/v) and the intake as g ethanol/kg.

Procedure

Animals were given daily, schedule-induced polydipsia sessions in individual, Plexiglas chambers (30 × 26 × 23 cm). Each chamber was equipped with a stainless-steel, food-pellet receptacle and a drinking-fluid reservoir, which consisted of a stainless-steel, ball-bearing spout attached to a Nalgene graduated cylinder. Fluid was freely available from the spout. Animals were weighed at the same time each day and an appropriate fluid (see below) was placed on each chamber. For the next 3 hr, 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 weight were provided.

There were three groups of animals (N = 4 each group). A baseline of polydipsic intake behavior was first established by making distilled water available as the session fluid for a period of at least 3 weeks. Then, one of three session fluids was assigned to each of the three groups: distilled water, cocaine (0.15 mg/ml) or ethanol (2.5%). Previous research from our laboratory had determined that the respective concentrations of cocaine and ethanol solutions would yield session fluid intakes equivalent to the session water intake of the distilled-water group. (For the first cocaine session a solution of 0.10 mg/ml was available; a 0.15 mg/ml solution was available thereafter.) The Ethanol Group received 113 consecutive sessions drinking ethanol solution and the Cocaine Group received 68 consecutive sessions drinking cocaine solution. This constituted the differential drug-history treatment for the respective drug groups. The Water Group, which continued to have only water available as the session fluid during this phase of the experiment, was given 3-hr probe sessions in which the usual FT 1-min schedule was changed to FT 3 min (78th session) and FT 5 min (96th session).

Chlordiazepoxide was then substituted as the session drinking solution for all groups. The chlordiazepoxide solution was 0.15 mg/ml for 25 sessions and 0.20 mg/ml for 21 sessions; thereafter, the concentration was maintained at 0.25 mg/ml. After 59 sessions at 0.25 mg/ml, the effect on session polydipsia of changing the session FT value was determined. This was accomplished by instituting single-session probes of FT 3 min (60th session) and FT 5 min (70th session) while maintaining the session length at 3 hr. The sessions between probe days (61–69) remained at the standard FT 1-min value.

RESULTS

Figure 1 shows the mean 3-hr schedule-induced polydipsic intakes for the three groups under their respective differential drug-history conditions in the first phase of the experiment. The groups drank comparable amounts of fluid under these FT 1-min conditions, and for the last 10 sessions the mean (± SE) daily drug intake for the Cocaine Group was 47.9 (± 11.67) mg/kg and for the Ethanol Group was 5.8 (± 0.33) g/kg.

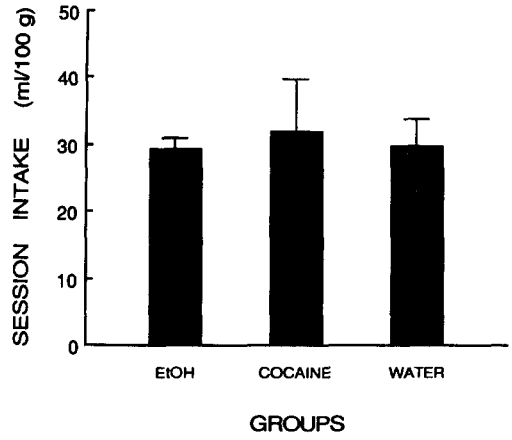

FIG. 1. Mean (+SE) intakes (ml/100 g) for 3 groups of rats drinking either ethanol (2.5%), cocaine solution (0.15 mg/ml), or distilled water during 3-hr, FT 1-min schedule-induced polydipsia sessions.

When the session fluid was changed to chlordiazepoxide for all the groups, they drank comparable amounts of the drug solution during daily sessions under the FT 1-min condition (cf. Fig. 2). Their overall mean (± SE) daily intake of chlordiazepoxide was 50.4 ± 7.30 mg/kg, based on the mean of 6 baseline days (3 sessions prior to each of the 2 probe sessions). Figure 2 reveals that when given FT 3- and 5-min session probes, the groups with remote water- and cocaine-solution overindulgence histories yielded only modest ml/pellet chlordiazepoxide solution intake increases in response to the probes, while the group with the ethanol-solution history had greater intake responses.

The relatively large standard errors in Fig. 2 reflect individual-animal differences in baseline intake levels. The systematic aspect of the group-intake differences is revealed by the distribution of ranks for the FT 5-min minus FT 1-min intake values. Calculating

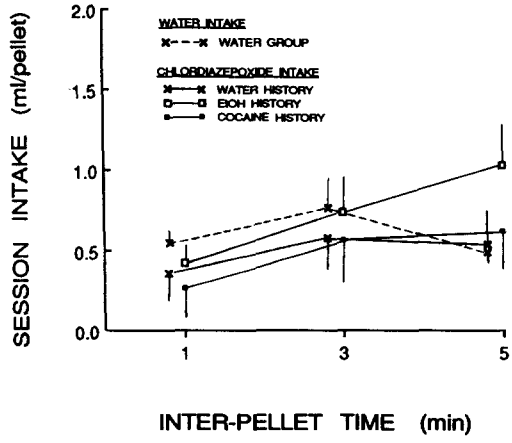

FIG. 2. Mean (SE) intakes (ml/pellet) of chlordiazepoxide solution (0.25 mg/ml) for 3 groups of rats, which had polydipsia histories for different fluids, in 3-hr sessions under a FT 1-min schedule-induction baseline condition and under FT 3- and 5-min probe conditions. FT 1-min baseline drinking and probe drinking is also shown for the Water History Group during the initial-history phase when distilled water was its session fluid.

this intake change for each animal in the Water-History and Ethanol-History Groups, the Mann-Whitney U-test yields a group-difference significance level of 0.057. Considering the small number in each group (N = 4) this significance level indicates a difference of probable reliability.

DISCUSSION

Investigations on the reinforcing efficacy of chlordiazepoxide have yielded mixed outcomes. Positive results were reported for chlordiazepoxide in monkey intravenous self-injection experiments (25,30), as well as negative results (2). For the intragastric route of self-administration, positive results in rats (7) and monkeys (30), as well as negative results for the monkey (1), have been reported. It is of interest that some of the experiments that have reported positive results for self-administration of the benzodiazepines used a drug-substitution paradigm in which pentobarbital was the baseline drug being self-administered (25,29), while those yielding negative or quite modest levels of self-administration used cocaine as the baseline drug (2,21). This picture is borne out by recent research. Limited success was obtained with diazepam self-injection in rhesus monkeys when the baseline drug was cocaine, but with a pentobarbital baseline all animals self-injected at least one dose level, including three that failed to self-inject diazepam under the cocaine baseline (5). Further investigations employing a pentobarbital baseline found that all monkeys self-injected flurazepam and most self-injected lorazepam and estazolam (23). Humans with histories of sedative abuse self-administered diazepam (18–20, 22), whereas those lacking such a history failed to self-administer diazepam (10,24), lorazepam (9), or flurazepam (11). Research on both nonhuman primates and humans, then, indicates that a history of sedative self-administration can transform benzodiazepines with weak or uncertain reinforcing efficacy into agents with increased potential for abuse. The present experiment confirmed a previous study that found no abuse potential for chlordiazepoxide solution, as measured by the schedule-induced drinking response to FT 3- and 5-min probes, in rats having only a history of water overindulgence prior to the institution of chlordiazepoxide solution overdrinking (16). Further, the Cocaine-History Group results indicated that merely a history of schedule-induced overindulgence of an agent with high abuse potential was not sufficient to markedly elevate the abuse potential of chlordiazepoxide. A history with respect to the sedative agent ethanol, however, was effective.

It should be noted that there were no appreciable differences in the FT 1-min polydipsic intake levels for the three fluids (water, cocaine and ethanol solutions) used for the three groups in the initial-history phase (Fig. 1), nor did their FT 1-min induced intakes for chlordiazepoxide solution differ appreciably in the second phase (Fig. 2). Therefore, the probe differences found for the groups cannot be attributed to any history of different degrees of polydipsic response to the fluids employed in the differential-history phase, nor can they be attributed to any differentially biased FT 1-min polydipsic baseline for chlordiazepoxide solution. The latent effects on chlordiazepoxide abuse potential produced by the different drug overindulgence histories were revealed only by the probes. This is reminiscent of the findings by Barrett and his associates that there is a latent, altered response to drugs produced by different shock-contingency histories that is revealed by later drug probes of comparable, current shock-schedule baseline behavior (3,4). Likewise, differential histories of ethanol versus glucose solution preferences can affect later ethanol versus glucose solution preference intakes in spite of an intervening baseline of comparable, current preference behavior (28).

The precise characteristics of drug histories sufficient to transform marginally reinforcing benzodiazepines into agents with augmented abuse potentials remain to be determined. Bergman and Johanson (5) suggest that overlapping stimulus properties may be crucial. Certainly, pentobarbital, ethanol and many of the benzodiazepines have degrees of stimulus properties and other pharmacological actions in common. Further, human drug abuse patterns indicate considerable commonality between alcohol abuse and the abuse of other sedative agents, which includes several of the benzodiazepines. Surveys of alcoholic patients indicate that a prevalent problem is the coabuse of other sedative agents (8, 17, 27). For example, 33% of patients being treated for chronic alcoholism had urines positive for benzodiazepines, and 54% of these individuals were considered abusers (6). The weight of the evidence, then, indicates that both animals and humans with a history of alcohol or sedative abuse are more likely to use and abuse benzodiazepines.

Schedule-induced overindulgence of a drug solution provides both a method for evoking the phenomenon of drug abuse and indicates the set of determinants that might be important in its genesis and maintenance. Inasmuch as the variables giving rise to schedule-induced polydipsia can also induce other behavioral excesses, such as attack and hyperactivity [see (14) for a review], they allow the evaluation of abuse potential under conditions that favor the generation of a variety of exaggerated behaviors. This places drug abuse within a context of environmental determinants of a host of exaggerated behaviors of which drug abuse is but one example. Factors encompassing both current environmental circumstances (maintaining schedule, probe conditions) and remote drug history interact with the intrinsic pharmacological properties of the drug currently available to determine abuse potential.

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