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Barbiturate Dependence and Drug Preference[1]

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TANG, M., K. AHRENDSEN AND J. L. FALK. *Barbiturate dependence and drug preference*. PHARMAC. BIOCHEM. BEHAV. **14**(3) 405–408, 1981.—Rats exposed to a daily 3-hr session of intermittent food delivery ingested physical-dependent levels of a 1 mg/ml sodium phenobarbital solution. This chronic, voluntary, high level of session phenobarbital intake had no effect on 21-hr home cage barbiturate preference. Substitution of water for phenobarbital during the session after 7.5 weeks precipitated various spontaneous withdrawal signs in some of the animals by the 24th hr of drug withdrawal but no change was found in home-cage barbiturate preference at any time. Physical dependence alone does not seem to play a crucial role in the maintenance of drug intake behavior.

Barbiturate Phenobarbital Physical dependence Withdrawal Drug abuse
Schedule-induced behavior Adjunctive behavior Drug preference

A NUMBER of intermittent food-pellet delivery schedules have been shown to induce a water polydipsia extending over the length of the daily experimental session [4,5]. When ethanol was substituted for water as the drinking fluid, the resulting chronic ethanol polydipsia was sufficient to produce severe physical dependence in rats [6, 7, 8]. Such a schedule-induction technique is extended now to produce physical-dependent levels of phenobarbital oral self-administration in rats. Any change in phenobarbital preference resulting from exposure to the schedule-induction situation is also evaluated.

Physical dependence has traditionally been attributed a major role in excessive drug-taking behavior. Evidence favoring such a concept, however, is not strong. Positive results come mainly from work done with the opiates (e.g. [15]); but evidence from research involving these and other drugs is either nonsupportive or inconclusive [1, 3, 16]. The concept that physical dependence is the major determinant of chronic, excessive drug-taking is studied here in barbiturate-dependent rats by assessing the effect of drug withdrawal on barbiturate preference.

METHOD

Animals

A total of eight male, albino rats of the Holtzman strain were used in the present study (mean body weight = 340 g, range: 319–365 g). All animals were housed individually in Acme stainless-steel cages in a temperature-controlled room with a 12-hr light-dark cycle.

Procedure

Animals were reduced gradually to 80% of their free-feeding body weights by limiting food rations (Purina Lab Chow, pelleted) over a period of 2 weeks. Water was freely available. After the animals were reduced to 80% body weight, they were divided into 2 equal groups (N=4). At 7:00 a.m. each day animals in the schedule-induced group were weighed and placed into Plexiglas experimental chambers (30×26×23 cm) each equipped with a stainless-steel food pellet receptacle. A 45-mg Noyes food pellet was automatically delivered into the food receptacle every 60 sec for the next 3 hr, thus giving a total of 180 pellets. Animals in the control group received identical treatment with the exception that the 180 pellets were given as a single ration at the beginning of the 3-hr feeding session. At the end of the session all animals were returned to their home cages. During the first 18 days of the experiment any food rations necessary to maintain them at 80% body weight were given immediately after the end of the feeding session. The food rationing time was delayed 3 hr starting on Day 29 in order to increase home-cage fluid consumption. Fluids were always available from stainless-steel, ball-bearing spouts attached to Nalgene graduated tubes. Each experimental chamber was equipped with a single drinking tube while 2 tubes were available in the home cage. The left-right position of the 2 tubes was reversed daily. From days 1 (first exposure to 3-hr feeding session) to 32, distilled water was available in the experimental chamber. Both drinking tubes in the home cage also contained distilled water. A 1 mg/ml sodium phenobarbital solution was substituted for water in one of the home

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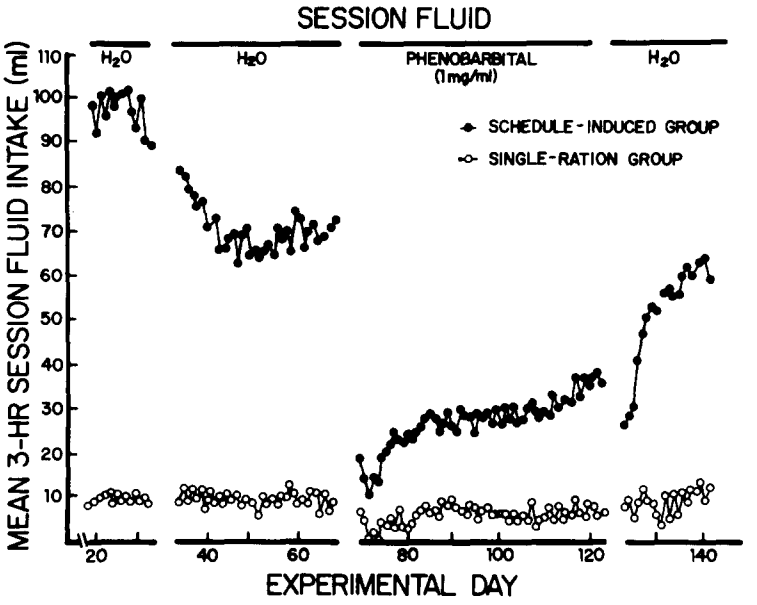

FIG. 1. Mean session fluid intakes for schedule-induced (N=4) and single-ration (N=4) groups.

cage drinking tubes from days 33–68, giving the animals a choice of either water or phenobarbital. On day 69, the drinking fluid in the experimental chamber also was changed to 1 mg/ml sodium phenobarbital. Thus, for the next 52 days all animals were drinking sodium phenobarbital solution during the 3-hr feeding session and given a choice between phenobarbital solution and water for the remaining 21 hr spent in their home cages. On day 122, water was substituted for phenobarbital solution during the feeding session. These fluid conditions were maintained for the remainder of the experiment. Fresh sodium phenobarbital solution was made every 48 hr.

Serum phenobarbital levels were determined for all animals on a selected day toward the end of the chronic session phenobarbital intake phase. Serum was sampled at 3 times relative to session drinking: immediately before the session, immediately after the session, and 1 hr post-session. A 10 μl blood sample was drawn from the tail tip and analyzed by gas chromatography according to a method detailed previously [11].

RESULTS

Mean fluid intakes for both schedule-induced and control groups during the 3-hr feeding sessions are presented in Fig. 1. When water was the sole drinking fluid for both session and home-cage situations, a typical polydipsic level of water intake (mean for last 10 days=96 ml) occurred in the schedule-induced group but not in the single-ration group. After introduction of 1 mg/ml sodium phenobarbital solution as one of the two fluids available in the home cage (water being the other), there was a gradual reduction in session water intake which stabilized at about 70 ml. Substitution of 1 mg/ml sodium phenobarbital for water as the session fluid resulted in a sharp decrease in session intake which partially recovered after 2 weeks. The mean daily intake for the last 10 days under this condition was 35 ml thus effecting an oral dose of 126 mg/kg over 3 hr. Reinstatement of water as the session drinking fluid produced an immediate drop in intake which, over a 2-week period, returned to approximately the level before phenobarbital was first introduced into the session. The 3-hr session fluid intake for the control group remained low but relatively stable throughout the duration of the experiment. Substituting 1 mg/ml sodium phenobarbital solution for water during the 3-hr session produced persistently lower intakes amounting to a mean difference of 2 ml. When session phenobarbital was withdrawn (days 122–142) the amount of distilled water ingested in the 3 hr gradually returned in 2 weeks in the level of that prior to session phenobarbital exposure. Table 1 shows the serum phenobarbital levels at 3 time periods in relation to the feeding session when most of the phenobarbital was being ingested. These serum level determinations were done for both groups on day 105 when phenobarbital solution was the fluid choice offered at the home cage. Note that although both groups entered the 3-hr feeding session with essentially the same serum phenobarbital levels (immediately pre-session), the immediately- and 1-hr post-session serum values were significantly higher for the schedule-induced group, $F(1,7)=15.00$, $p<0.01$ and $F(1,7)=8.31$, $p<0.05$, thus reflecting the schedule-induced animals' elevated session intake.

TABLE 1

MEAN SERUM PHENOBARBITAL CONCENTRATIONS FOR BOTH INTERMITTENT-FEEDING AND SINGLE-RATION GROUPS BEFORE AND AFTER THE 3-HR FEEDING SESSION

	Serum Phenobarbital Concentrations (μg/ml)	
Time Sampled	Schedule-Induced	Control
Immediately pre-session	11.50	7.64
Immediately post-session	101.11	32.42
1-hr post-session	69.10	29.68

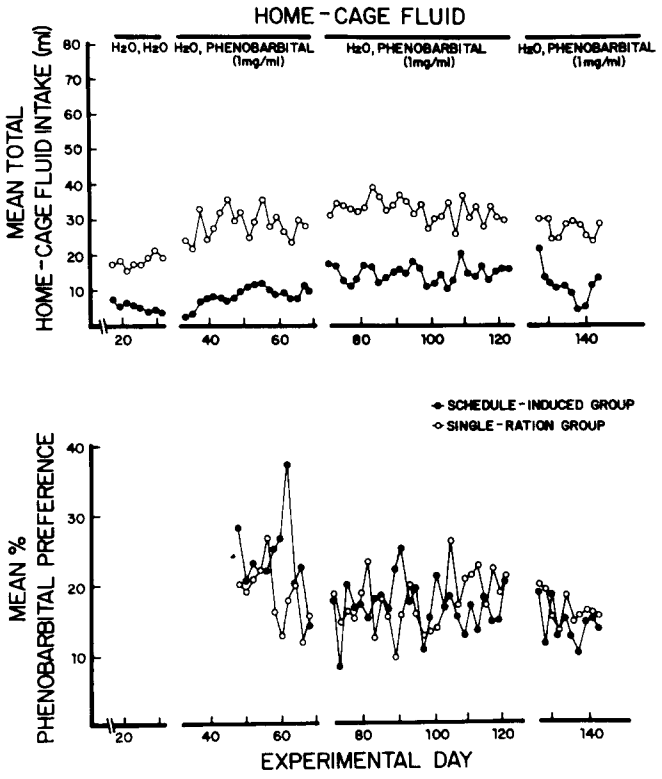

FIG. 2. Mean total home-cage fluid intakes (upper panel) and percent phenobarbital preference (lower panel) for schedule-induced (N=4) and single-ration (N=4) groups. Two fluid bottles continuously available for 21 hr daily.

Due to the development of strong side-preferences in 2 of the animals (1 in each group) the data presented in Fig. 2 are 2-day mean values. As shown in the upper panel, total home-cage mean fluid intake for the control animals was substantially higher than that for the schedule-induced group. This was the case throughout all phases of the experiment. Note that when food rationing was delayed 3 hr after the feeding session (starting on day 39) the total home-cage intakes were successfully elevated for both groups. The persistent difference in total home-cage fluid consumption between the 2 groups was not accompanied by any systematic differences in phenobarbital preference when the fluid choice consisted of 1 mg/ml sodium phenobarbital and distilled water (lower panel). Withdrawal of phenobarbital from the session on day 122 resulted in a 1-day increase (6 ml) in total fluid intake for the schedule-induced animals. There was, however, no change in phenobarbital preference for either group. The resulting increase in 1 mg/ml phenobarbital solution intake during the first 21 hr after session phenobarbital withdrawal was less than 2 ml for the schedule-induced group.

Withdrawal signs of varying severity were observed in the 2 schedule-induced animals with the highest phenobarbital intake. During the 3-hr feeding session on the second session-phenobarbital withdrawal day, the animal with greatest daily phenobarbital intake (164 mg/kg/3-hr period) showed muscle tremors while being transported from the home cage to the session cage. In addition, 81 of the 180 session food pellets were left in the food tray at the end of the 3-hr feeding period and 2 g of the food supplement given 3-hr post-session was also not consumed. The second animal (143 mg/kg/3-hr period) also exhibited muscle tremors and hyperactivity during the second withdrawal day. No disruption in feeding and drinking, however, was observed in this animal. All symptoms disappeared in both animals by the third withdrawal day.

DISCUSSION

When rats were exposed to a daily 3-hour intermittent-feeding regimen they orally self-administered a substantial volume (35 ml) of 1 mg/ml sodium phenobarbital solution during the session. This voluntary, daily, high level of session barbiturate intake persisted throughout the 7.5-week drug-availability period and was reflected in peak serum concentrations that approximated those produced by a 60 mg/kg subcutaneously administered dose of phenobarbital [14]. However, in spite of the excessive barbiturate intake during the intermittent feeding session, there was never any carry-over of high drug intake into the home-cage consumption period. Thus, this excessive drug intake seems specific to the environmental conditions generated by the intermittent schedule. Control animals given a single ration of food at the beginning of the 3-hour session ingested less than 10 ml of the barbiturate solution. This difference in session phenobarbital intake, however, was not accompanied by any difference in home-cage phenobarbital preference between the two groups. Examination of Fig. 1 reveals a slow but sustained rise in the schedule-induced group's daily session phenobarbital intake. This increase cannot be attributed to an adaptation to the aversive taste of the phenobarbital solution since similar increases were not observed in the control group. Furthermore, for both groups, neither barbiturate preference nor absolute drug intake in the home-cage showed any increasing trend over the same period of time. It is possible that the schedule-induced animals were already ingesting a maximal amount of phenobarbital for a 3-hour period, in which case the increase observed could reflect the development of tolerance. Thus, as the animals became more tolerant to the barbiturate they would be able to consume a greater amount of the drug.

Development of physical dependence to phenobarbital using the present oral self-administration technique is demonstrated in those animals that exhibited withdrawal signs when water was substituted for phenobarbital during the 3-hour session. The time-course associated with the development of and the recovery from withdrawal signs closely approximates that observed by using various other induction methods in rats [2, 12, 13], mice [9,10] and monkeys [17]. The advantage of the schedule-induced oral self-administration method over other techniques lies in its voluntary ingestion aspect. Not only is the oral route the preferred route of administration in human barbiturate abuse, but the variables exacerbating and attenuating drug-taking can be studied.

Exposure to an intermittent feeding schedule for 3 hours each day can induce sufficient phenobarbital solution intake during that period to produce physical dependence in rats. Withdrawal of the barbiturate during this 3-hour period, however, did not result in any increase in phenobarbital preference during the remaining 21-hour period. A lack of compensatory increase in phenobarbital preference persisted in spite of the various withdrawal signs exhibited. This result argues against the notion that physical dependence on the barbiturates might have a major role in the maintenance of excessive drug-taking behavior.

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