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Production of Physical Dependence on Ethanol by a Short Drinking Episode Each Day[1]

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TANG M. AND J. L. FALK. *Production of physical dependence on ethanol by a short drinking episode each day.* PHARMACOL BIOCHEM BEHAV **19**(1) 53–55, 1983.—A 3-hr schedule-induced ethanol polydipsia regimen was used in rats to elevate blood alcohol concentration to a single intoxicating peak each day. After 3 weeks, and again after 3.5 months, animals were tested for the presence of physical dependence by exposure to a brief auditory stimulus (key shaking) at 7 and 11 hr after ethanol polydipsia. Withdrawal signs were observed only at 11 hr when blood ethanol levels had returned to zero. No such signs were observed when animals were made water polydipsic. While sufficient, continuous elevation of blood ethanol concentration is not necessary for the development of a demonstrable physical dependence. A limited daily ethanol binge was sufficient.

Schedule-induced polydipsia Ethanol overdrinking Ethanol dependence Blood ethanol concentrations Ethanol withdrawal seizures

IT IS generally accepted that the maintenance of a state of continuous blood ethanol elevation is necessary for physical dependence to develop (e.g., [12, 20, 22]). On the other hand, there are various studies suggesting that even a single dose of ethanol results in mild withdrawal signs that are detectable 7–11 hr after the dose (e.g., [10, 16, 19, 21]). If the physiological consequences of relatively brief, daily exposures to ethanol do not readily dissipate, but accumulate over time, physical dependence might result, even though blood ethanol concentration is not elevated for the major portion of each day. A test of this possibility would involve the imposition of a condition allowing blood ethanol concentration to rise to a single intoxication peak once each day and dissipate. Further, it would be of interest to demonstrate that this single peak can result from a short, daily, voluntary binge.

METHOD

Animals

Fourteen male, albino, Holtzman rats with an initial mean body weight of 361 g (range: 331–381 g) were housed individually in standard, stainless-steel cages in a temperature-controlled room with a 12 hr light-dark cycle (lights on: 0700–1900 hr).

Procedure

All animals were gradually reduced to 80% of their free-feeding weights by limiting food rations (Purina Lab Chow, pelleted) over a 2-week period. After the animals had stabilized at 80% body weight, they were moved into a room with continuous lighting. Each animal was housed in a Plexiglas chamber (30×26×23 cm) equipped with a stainless-steel food pellet receptacle and a fluid source on one wall of the chamber. The fluid source consisted of a stainless-steel, ball-bearing spout (Ancare TD-300) attached to a Nalgene graduated cylinder. Animals were given daily 3-hour schedule-induction (binge) sessions during which a 45-mg Noyes food pellet was automatically delivered into the food receptacle once every 60 seconds (180 pellets/3-hr session).

The 14 animals were divided into two equal groups (N=7 each) differing only in the type of fluid available during the binge sessions: 5% (v/v) ethanol (Group I) and distilled water (Group II). Water was the sole available fluid during the remaining 21 hours of each day. All animals were tested for susceptibility to audiogenic seizures at 7 hr post-session after 3 weeks and again after 3.5 months of exposure to the daily binging sessions. A third test was given after another 2 weeks (4 months) at 11 hr post-session. This test consisted of a 30-second exposure to a high frequency sound (key shaking). In order to determine blood alcohol levels, a tail blood sample was obtained from each animal immediately following the 3.5 and 4 month tests. Other tail blood samples also were obtained from the animals at 0, 1, 2, 4 and 9 hr post-session during the period between 3.5 and 4.5 months. At the end of that period, the session fluid conditions were reversed for the two groups: Group I now had water available during the session while Group II was given the 5% ethanol solution. Distilled water remained as the sole fluid available during

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the non-session period. All animals were tested for withdrawal signs at 7 and 11 hr post-session after 3 weeks and again at 11 hr post-session after 3.5 months of exposure to this new session-fluid condition. Tail blood samples were obtained from all ethanol-drinking animals immediately following each test. Blood samples were again sampled at 0 and 1 hr post-session 4 days after the last dependence test was administered. Each sample (50 μl) was analyzed for ethanol concentration by the gas chromatographic method of Le Blanc [14].

RESULTS

Table 1 shows the ethanol intakes for both groups of animals during their respective ethanol-session phases. Each value is composed of data obtained from the ten days that immediately preceded each exposure to the key-shaking test. Analysis of variance revealed that the alcohol intakes were not significantly different either between groups or between the 3rd and 14th week. Blood ethanol levels at various intervals after an ethanol-binging session are presented in Fig. 1. Panel A shows the mean (+S.E.) ethanol elimination rate of animals in Group I after being exposed to daily ethanol binging sessions for 3.5 months. A similar elimination rate for Group II animals is presented in Panel B. In all cases except one, blood ethanol levels for individual rats remained elevated for over 7 hr after the drinking session.

When tested for susceptibility to audio-induced seizures 7 hr after an ethanol binge session, none of the Group I animals showed any signs of physical dependence following either 3 weeks or 3.5 months of daily ethanol exposure. Retesting these animals 2 weeks later (4 months) at 11 hr post-session when their blood ethanol levels were practically zero (see Fig. 1, Panel A) produced a very different picture. Four out of 7 of these ethanol-binging animals reacted to key shake: one had a tonic-clonic seizure, one showed a running fit that lasted for a few seconds and the remaining two showed milder signs of hyperreactivity and Straub tail. None of the Group II animals (binging water up to this point) showed any reaction to the key shaking during the three physical dependence tests. However, when these Group II animals were tested at 11 hr post-session after ethanol replaced water as the binging fluid for 3 weeks, one animal (No. 14) showed a 5-sec convulsion episode while two others exhibited milder signs (hyppereactivity and Straub tail). Furthermore, these same 3 animals all reacted to the 11-hr post-session key shaking during the 3.5 month test as well. Animal No. 14 convulsed again for almost 20 sec this time; the other two rats' reactions were similar in both nature and intensity to those observed during the 3-week test. As in the case of the Group I animals, the 7-hr post-session testing failed to induce any reaction in these rats. No reaction was observed in any of the now water-binging Group I rats during these last 3 tests.

TABLE 1

MEAN (±S.E.) DAILY SESSION INTAKE OF ETHANOL (g/kg) OF RATS DRINKING 5% ETHANOL DURING 3-HR SCHEDULE-INDUCTION SESSIONS

	3 weeks	3.5 months
Group I	5.62 ± 0.35	5.87 ± 0.17
Group II	5.54 ± 0.40	5.87 ± 0.51

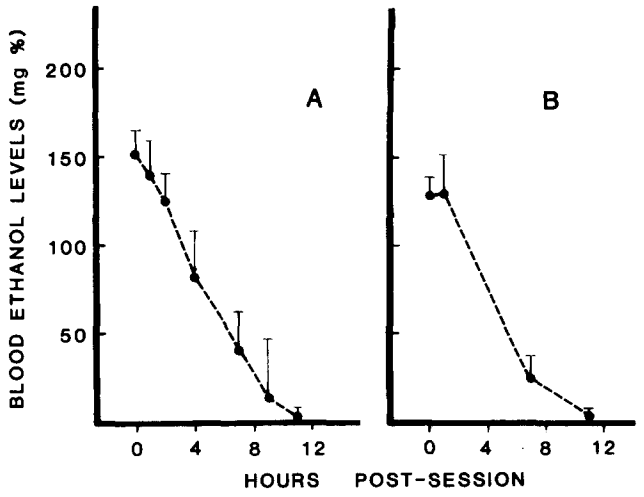

FIG. 1. Blood ethanol concentrations (mg/%) for Group I (Panel A) and Group II (panel B) rats (N=7 each group) determined 0–11 hr after a 3-hr schedule-induced ethanol (5%) polydipsia session.

DISCUSSION

It is generally recognized, on the basis of numerous studies on alcohol and other drugs, that chronic, continuous elevation of blood drug level is a sufficient and quite efficacicious way of producing physical dependence [1, 3, 4, 5, 6, 7, 9, 13, 17, 18]. Several methods resulting in chronic blood ethanol concentration (BEC) elevation demonstrate the power of this maneuver to induce severe physical dependence. Frequent ethanol imposition during each 24-hour cycle chronically by gavage [3, 4, 5], liquid diet [7], or inhalation [11] can result in physical dependence. Likewise, methods allowing almost continuous ethanol consumption opportunities can yield severe abstinence signs upon the removal of access to ethanol: intravenous self-administration [2,23], schedule-induced polydipsia [6], and programmed voluntary consumption in humans [13,18]. Even chronic elevation to fairly high BEC levels for a few days by intubation [15] or inhalation [10] resulted in withdrawal seizures.

Relatively few studies have attempted to produce physical dependence by more limited ethanol treatments, perhaps because there is a strong assumption that continuous elevation is not only a sufficient condition but also a necessary one for the induction of physical dependence on drugs. In the present experiment, a daily 3 hour ethanol binge was sufficient to induce a physical dependence which, while not evident in all animals or florid in the manifest cases, clearly indicated a physiologically dependent status. An experiment from this laboratory [20] containing a group (Group II) similar in certain respects to the present one reported no evidence of physical dependence. However, both the ethanol-exposure regimen and the abstinence testing time differed from the present procedure. Rats given chronic, single, daily ethanol doses for 30 days and then withdrawn exhibited decreased startle thresholds [8]. In the same vein, nonalcoholic humans drinking for only a few hours each day exhibited morning abstinence effects in their auditory evoked responses [24].

In the light of studies reporting withdrawal-like effects from even a single dose of ethanol, it is perhaps not surprising that limited daily ethanol exposure episodes can result in physical dependence. Mild but unmistakable withdrawal signs occurred after a single, large, intraperitoneal dose of ethanol in mice [10]. Similarly, both drug-induced [16,21] and brain-stimulation-induced [19] seizures were potentiated by a single dose of ethanol at a time when the ethanol had been eliminated.

There is little doubt that chronic, continuous elevation of BEC produces a more severe final dependence state than discontinuous exposure. The schedule-induction procedure designed to maintain an elevated BEC for most of each 24-hour cycle [6] produced a greater incidence and severity of abstinence signs than observed in the present experiment. Goldstein's [11] work confirms that timed interruptions in exposure to an ethanol inhalation environment result in a less severe final level of dependence. Mice given four cycles of 3 days of ethanol inhalation and 1 day without do not progressively increase in physical dependence as do those exposed continuously to ethanol for the 12 days.

The mild to moderate dependence produced in rats induced to engage in a daily 3-hour binge may mimic the drinking and eventual physiologic status of humans who drink habitually but only for a limited segment of the day. Consider the individual who imbibes one or two drinks at lunchtime, has one or two before dinner, consumes a portion of a bottle of wine with dinner and finishes the day with a nightcap or two. The daily, episodic BEC elevation may be approaching a dependence risk not unlike the one demonstrated to accrue in the present study.

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