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Parameters of Low-Dose Ethanol Intravenous Self-Administration in the Rat

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SINDEN, J. D. AND J. LE MAGNEN. *Parameters of low-dose ethanol intravenous self-administration in the rat.* PHARMAC. BIOCHEM. BEHAV. **16**(1) 181–183, 1982.—Male Wistar rats were able to press on an operant lever 24 hr/day for intravenous infusions of saline or ethanol at doses of 0.5, 1.0 or 5.0 mg/kg/ infusion. Only the 1.0 mg/kg/infusion group showed a significant increase in responding on the lever as a function of days, whereas the 5.0 mg/kg/infusion group showed a significant decrease in responding as a function of days. The results suggest that the reinforcing value of intravenous ethanol changes from rewarding to neutral or aversive in valence at a dose-level below that expected to produce signs of intoxication.

Ethanol self-administration Reward Rat

ETHANOL naive, heterogeneous strains of rats do not readily demonstrate intravenous self-infusion of ethanol under conditions where food and water are freely available [1]. This is in spite of the fact that the intravenous route produces the most direct temporal effect on central reinforcement mechanisms and the route circumvents the gustatory/olfactory axis which limits the spontaneous oral intake of ethanol in the rat [10].

The data that do indicate intravenous ethanol is rewarding, albeit weakly, have employed long test sessions and low doses of ethanol per infusion: within the range of 0.1 and 3.0 mg/kg/infusion [11,12]. Unlike the primate [2,14], however, the ethanol-naive rat does not appear to self-administer intravenously sufficient concentrations of ethanol to render itself tolerant to or dependent on ethanol except possibly under specialized physiological and/or environmental conditions, for example reduced body weight and fixed intervals of food delivery [8]. This suggests that, for the rat, the aversive threshold of ethanol directly administered into the blood may be below that required to produce signs of even mild physical intoxication. There is further evidence to suggest that blood-borne ethanol may be a sufficient UCS in the Conditioned Taste Aversion paradigm [3,4] although the threshold intravenous dose required to produce this effect is yet to be determined.

In the present experiment, low doses of ethanol are employed in an intravenous self-infusion paradigm and the results suggest that in the rat the reinforcing effect of self-induced ethanol changes from rewarding to either neutral or aversive in valence at dose-levels below those expected to produce physical intoxication.

METHOD

The animals were 16 naive male rats of the Wistar strain, derived from the same colony (Evic-Ceba), weighing approximately 250 g at the time of catheter implantation. All rats had ad lib access to standard laboratory chow (Pietrement) and tap water and were maintained on a 12 hr light/12hr dark cycle (0800–2000 day) and a constant room temperature (22°C±1). The rats were implanted with a chronic intrajugular catheter (Silastic) under pentobarbital anesthesia according to the techniques described previously [6]. Briefly, the catheter was designed so that when fixed in place within the right external jugular vein, the tip passed just into the auricular cavity. The catheter was then passed subcutaneously to a slit in the skin above the skull and fixed *in situ* by skull screws and dental acrylic. Following surgery, the rats were housed in cylindric Plexiglas cages where they remained for the course of the experiment. Daily following implantation, the rats were weighed and catheters were cleared with an injection of 0.2 ml saline.

Three days after catheter implantation, the rats were connected via polyethylene tubing to motor-driven syringe infusion pumps (60 ml syringe, 3 rpm motor) by means of a swivel joint and a counterbalanced system which allowed freedom of movement [6]. Following 24 hr habituation with the pumps disconnected, a lever was introduced to the right of the food cup. The rats were neither pretrained nor shaped to press the lever. Each depression of the lever delivered 0.1 ml of solution over an approximately 3 sec infusion period. If a further lever press occurred during the infusion period, it neither was counted nor lead to a further infusion. A multichannel event recorder monitored all infusions.

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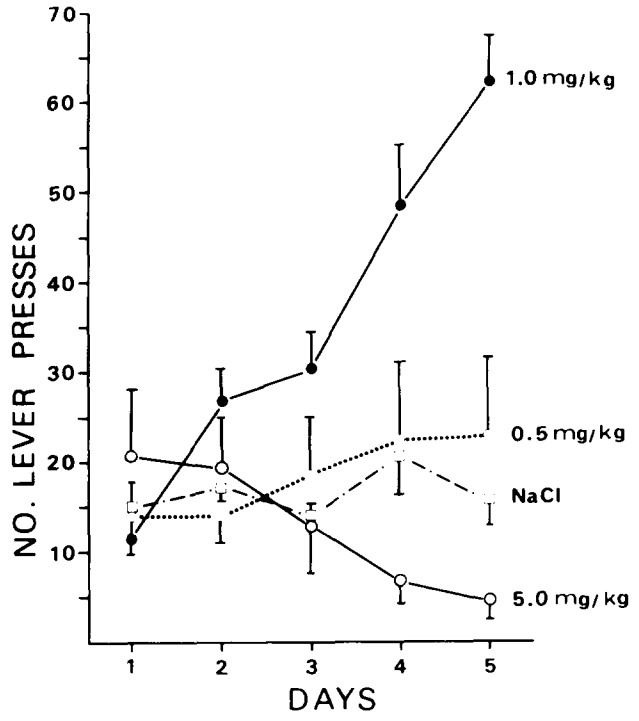

FIG. 1. Mean number of lever presses for the three ethanol groups and the saline group as a function of days of testing. The error bars indicate ±1SEM.

The rats were randomly assigned to four infusion conditions (four rats per group): either sterile 0.9% NaCl or ethanol mixed with saline at one of the following doses: 0.5, 1.0 or 5.0 mg/kg/infusion. The alcohol solutions were individually prepared each day. Twenty four hr per day for five consecutive days, the rats had free access to food, water and the operant lever in their home cages.

RESULTS AND DISCUSSION

The mean number of lever presses and hence infusions for each level of ethanol dose or saline control during the five days of testing is presented in Fig. 1. It can be seen that ethanol produces a dose-related change in responding as a function of days. A two-way ANOVA with one repeated measure yielded a significant ethanol dose main effect, $F(3,12)=7.36$; $p<0.01$, days main effect, $F(4,48)=5.60$; $p<0.01$ and also as indicated by the different slopes of each of the curves in Fig. 1, a significant interaction between Dose and Days, $F(12,48)=8.83$; $p<0.01$. All four animals in the 1.0 mg/kg/infusion group showed reliable ethanol self-administration by day 5, infusing a mean of 62.5 mg/kg/day (range 50–74). As demonstrated in Fig. 1, these rats displayed a substantial and significant day-to-day increase in activity on the operant lever which clearly suggests a rewarding effect. Only one rat in the 0.5 mg/kg/infusion group manifested ethanol self-administration and the group data in Fig. 1 indicate no difference from the saline group. By day 5 these rats were infusing a mean of only 11.5 mg/kg/day (range 4.5–20) and overall the data suggest this dose is below reward threshold. On the other hand, no rats in the 5.0 mg/kg/infusion condition developed self-administration and Fig. 1 indicates a day-to-day reduction in lever pressing to the level of an almost complete inhibition of responding. The ethanol intake of this group by day 5, a mean of 24 mg/kg/day (range 10–45), was below the level reached by the 1.0 mg/kg/infusion group.

TABLE 1

THE TEMPORAL PATTERN OF LEVERPRESSING ON DAY 5 OF TESTING (% FREQUENCY)

	Number of responses within 5 min period					
Infusion Condition	1	2	3	4	5	6
Saline	64	29	7	—	—	—
0.5 mg/kg	51	21	14	5	7	2
1.0 mg/kg	39	27	20	9	2	3
5.0 mg/kg	87	13	—	—	—	—

An analysis of response patterns on day 5 presented in Table 1 revealed that at the 5.0 mg/kg/infusion dose, rats seldom took more than one injection at a time, while at the 1.0 mg/kg/infusion dose, 61% of infusions occurred in series of responses, largely composed of 2–3 responses in a 5 min interval followed by a pause of variable duration. A somewhat similar temporal response pattern has been observed in rats for intravenous morphine [13]. Interestingly, at 1.0 mg/kg/ethanol infusion, the response series observed here were never greater than 6 and were generally 3 or less per 5 min interval which suggests that at this dose, ethanol self-administration is quite rapidly self-limiting or satiating.

Overall, the data largely confirm and extend other reports demonstrating reinforcement with low doses of intravenous ethanol in naive rats [11,12] but indicate that such reward is quantitatively low and appears to occur within a very narrow range of unit dose levels, in that ethanol ceases to be rewarding at 5 mg/kg/infusion. In order to produce ethanol self-administration of higher unit doses than approximately 1 mg/kg/infusion it appears necessary to preimpose periods of intoxication [7] or to establish a schedule of food delivery [8].

It is unlikely that the reduction in lever-pressing observed at 5.0 mg/kg/infusion represents a local irritant effect on the peripheral vascular system as the concentration of ethanol at this dose level was approximately 1.5% w/v in saline, well below the concentration expected to produce such irritant effects [5]. Further, the hourly or daily quantities of ethanol infused by any of the groups would be unlikely to produce signs of physical intoxication, although it is possible that other non-specific depressant effects of 5 mg/kg ethanol could have reduced the response rate [9]. In this respect it should be noted that 74% of lever-pressing for ethanol occurred within the activity phase (night) of the day/night cycle, in line with primate self-administration data [2]. Another possible explanation is that the infusions of ethanol are activating central rewarding and aversive neural systems depending on dose. In either case, the threshold dose at which naive rats learn to limit their self-infusions of ethanol is low, and presumably explains to a large degree why ethanol-naive rats fail to intravenously self-administer intoxicating quantities of ethanol.

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