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The Effects of Phenobarbital on Lithium Chloride Induced Taste Aversion[1,2]

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JOLICOEUR, F. B., M. J. WAYNER, D. B. RONDEAU AND A. D. MERKEL. *The effects of phenobarbital on lithium chloride induced taste aversion.* PHARMAC. BIOCHEM. BEHAV. 9(6) 845–847, 1978.—The dose related effects of phenobarbital on LiCl induced taste aversion were examined. Rats were adapted to a 23 hr 50 min water deprivation schedule. On the Treatment Day animals were offered a novel 0.125% saccharin solution during the 10 min drinking session and were then administered 3.0 mEq/kg LiCl. The saccharin solution was presented again on six subsequent Test Days. Sodium phenobarbital 20, 40, 60 and 80 mg/kg was administered 15 min prior to drinking on the first Test Day. Results indicated that all doses significantly attenuated taste aversion with the maximal effect occurring with the 60 mg/kg dose.

Phenobarbital Taste aversion Drinking Lithium chloride

THE RESULTS of a study on the effects of sodium phenobarbital on forced ethanol consumption indicated that the combination of phenobarbital administration and ethanol ingestion on drug days produced an aversion for the ethanol solutions as indicated by decreased ethanol intakes on post drug days [4]. Of special interest was the finding that following the decreases in postdrug ingestion increased ethanol intakes occurred again upon subsequent administration of phenobarbital. If the postdrug reductions in ethanol consumption were due to a taste aversion effect of phenobarbital, it seemed appropriate to determine if phenobarbital could counteract the effect of a well known taste aversion inducing agent.

The purpose of the present study was to examine the effects of 20, 40, 60 and 80 mg/kg phenobarbital on LiCl induced taste aversion. Taste aversion to a saccharin solution was produced by the administration of 3 mEq/kg LiCl, a dose previously found to be most effective in producing taste aversion [3].

METHOD

Animals

Sixty female hooded rats were selected from our colony and placed in individual living cages in a temperature controlled room having a 12 hr light-dark cycle. At the beginning of the experiment, body weights ranged from 200–300 g. Animals were separated into 10 groups of 6 animals each.

Procedure

After four days of adaptation, animals were water deprived for 23 hr and 50 min and placed on a daily 10 min drinking schedule. On Day 10, the Treatment Day, animals were given a 0.125% Na saccharin solution during the 10 min drinking session. Immediately following drinking, five groups of animals were injected subcutaneously with 3.0 mEq/kg of LiCl in a volume of 4.61 ml/kg. These groups will be referred to as the LiCl treated groups. The five other groups received an equal volume of 0.9% NaCl. These groups will be designated nontreated control groups. On Days 11 and 12, water was presented during the drinking session. Then every third day from Day 13–28, animals were offered 0.125% Na saccharin during the drinking sessions. These days constituted the six post treatment test days. Two days of water presentation were interspersed between each test day. On the first test day, Day 13, each of the five LiCl treated groups received either 0, 20, 40, 60 or 80 mg/kg of sodium phenobarbital. These same doses of phenobarbital were distributed among the five nontreated control groups. All injections were given subcutaneously, 15 min before drinking. Sodium phenobarbital was dissolved in 0.9% NaCl and concentrations were adjusted so that none of the injection volumes exceeded 0.5 ml. On the remaining test days animals were allowed to drink the saccharin solution without any other pharmacological or experimental manipulation.

All drinking fluids were presented in 100 ml graduated plastic cylinders equipped with stainless steel ball point drinking spouts. Food, standard Purina Rat Chow, was available throughout the experiment except for two hours following drinking on the Treatment Day in order to eliminate any possible food associated aversion.

RESULTS

The results obtained with the LiCl treated and the non-

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treated control groups are presented in Figs. 1 and 2, respectively, where mean saccharin intakes in ml are presented as a function of the critical days. Data were analyzed by means of two 5×7 ANOVA's with repeated measures on the last factor [10]. Individual analyses were carried out for the LiCl treated groups and for the nontreated control groups. The two factors included in each analysis were Groups and Days. Each of the five groups, receiving one dose of phenobarbital on Test Day 1, contributed to one level of the Group factor. The Treatment Day and each of the six Test Days constituted the levels of the Day factor.

For the LiCl treated groups, the two factors were significant: Group, $F(4,25)=7.54$, $p<0.01$; Days, $F(6,150)=104.02$, $p<0.01$. The critical Group by Days interaction was also significant, $F(24,150)=7.29$, $p<0.01$. In order to analyze the significant interaction, simple main effect analyses were carried out at each level of the Day factor. Except for Treatment Day, all main effects were significant; Test Day 1, $F(4,100)=5.45$, $p<0.01$; Test Day 2, $F(4,100)=6.89$, $p<0.01$; Test Day 3, $F(4,100)=16.59$, $p<0.01$; Test Day 4, $F(4,100)=16.46$, $p<0.01$; Test Day 5, $F(4,100)=2.91$, $p<0.05$; and Test Day 6, $F(4,100)=3.04$, $p<0.05$. Post hoc Dunnett or Tukey A tests were then performed in order to compare individual groups at each test day. These tests revealed the following significant differences. On Test Day 1 each dose of phenobarbital significantly increased saccharin consumption when compared to the 0 mg/kg saline group ($p<0.01$). On Test Day 2, the saccharin intakes of the 40, 60 and 80 mg/kg groups were significantly decreased in comparison with the 20 mg/kg group ($p<0.05$) but not with the 0 mg/kg group. On both Test Days 3 and 4, saccharin intakes of the 40, 60 and 80 mg/kg groups were significantly depressed in comparison with the 0 mg/kg saline and the 20 mg/kg groups ($p<0.01$). Finally, the 80 mg/kg group drank significantly less when compared to the 0 mg/kg and 20 mg/kg groups on Test Day 5 ($p<0.01$) and when compared to the 20 mg/kg group on Test Day 6 ($p<0.01$).

The ANOVA performed on the data of the nontreated control groups revealed a significant Day effect; $F(6,24)=71.34$, $p<0.01$. The Group factor was not significant. The interaction Group by Days was significant; $F(24,150)=9.56$, $p<0.01$. As described previously, the significant interaction was analyzed by means of simple main effect analyses at each level of the Day factor. Significant main effects were found on Test Day 1, $F(4,115)=28.06$, $p<0.01$ and on Test Day 2, $F(4,115)=4.39$, $p<0.01$. Post hoc Dunnett and Tukey A tests were then performed so that comparisons between individual groups could be made at each significant test day. These tests revealed the following significant differences: on Test Day 1, all doses of phenobarbital significantly increased saccharin consumption in comparison with the 0 mg/kg saline injection ($p<0.01$). On Test Day 2, saccharin intakes for the 40, 60 and 80 mg/kg groups were significantly decreased when compared with the 0 mg/kg saline groups.

In summary, the preceding statistical analyses indicate that the administration of 20, 40, 60 and 80 mg/kg of phenobarbital prior to drinking on Test Day 1 significantly enhanced saccharin consumption of both LiCl treated and nontreated control animals. It was also found that the administration of the three highest doses of phenobarbital on Test Day 1 resulted in significantly reduced saccharin intakes of Test Days 2, 3 and 4 in the LiCl treated animals and on Test Day 2 in the nontreated control animals.

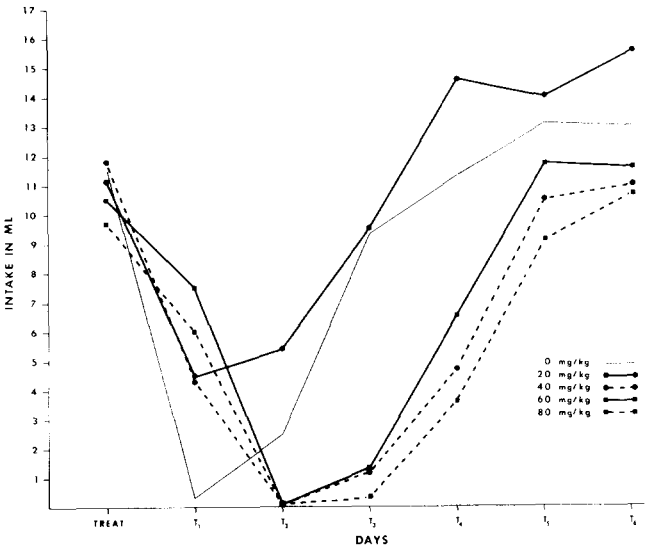

FIG. 1. Mean saccharin intakes for each group of LiCl treated animals presented as a function of the Treatment Day (TREAT) and each of the six Test Days (T1–T6). LiCl was administered immediately following the drinking on the Treatment Day. The various doses of Phenobarbital were injected 15 min prior to drinking on Test Day 1.

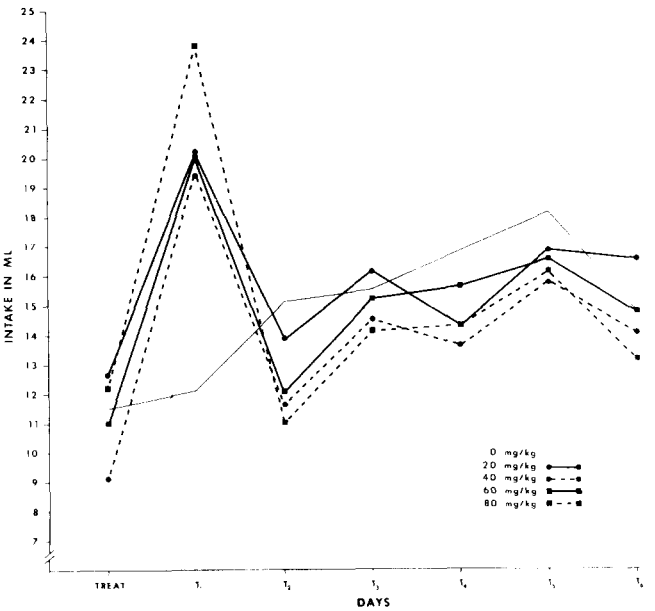

FIG. 2. Mean saccharin intakes for each group of animals presented as a function of the Treatment Day (TREAT) and each of the six Test Days (T1–T6). Physiological saline was administered immediately following drinking on the Treatment Day. The various doses of Phenobarbital were injected 15 min prior to drinking on Test Day 1.

DISCUSSION

The results of this study demonstrate that phenobarbital can attenuate LiCl induced taste aversion, when it is administered prior to drinking on the first test day following conditioning. As can be seen in Fig. 1, the four doses of

phenobarbital increased saccharin acceptance on the first Test Day in LiCl treated animals, with the greatest effect occuring with the 60 mg/kg dose. Although phenobarbital does not completely inhibit the occurrence of taste aversion, it considerably diminishes its magnitude. It should be noted that this attenuating effect of phenobarbital occurred with a conditioning dose of LiCl that has been shown previously to be most effective in inducing taste aversion [3].

One of the phenobarbital's well known pharmacological effects is to enhance drinking in ad lib and water deprived animals [2, 5, 8]. Increased saccharin consumption following phenobarbital was found in the nontreated control animals of this study (Fig. 2). The observed attenuation in taste aversion might then be attributed to phenobarbital's general enhancing effect on drinking. However, a close examination of the results reveals that the dose related effects of phenobarbital on drinking in control animals do not follow closely those observed in LiCl treated animals. As can be seen in Fig. 2, saccharin consumption in control animals was increased to a similar degree of 20, 40 and 60 mg/kg of phenobarbital and was maximally enhanced by the 80 mg/kg dose. On the other hand, in the LiCl treated animals, the attenuation in taste aversion was most prominent with the 60 mg/kg dose and was noticeably weaker with the 20 and 40 mg/kg doses of phenobarbital. It does not appear that the attenuating effect of phenobarbital on taste aversion can be related solely to a dipsogenic effect; even though the attenuation of taste aversion by phenobarbital is correlated with the enhancing effect of the drug on the consumption of mildly aversive solutions in rats [1, 4, 6].

Another interesting result is the significant reduction in saccharin consumption on Test Days 2, 3 and 4 displayed by the LiCl treated groups that were administered the three highest doses of phenobarbital on Test Day 1 (Fig. 1). The reduction did not occur with the 20 mg/kg group. These animals displayed a recovery curve in their saccharin intake similar to the one observed with the 0 mg/kg saline group. It appears that the pairing of saccharin with the three highest doses of phenobarbital on Test Day 1, compounded with the original association with LiCl on the Treatment Day, resulted in a prolonged diminution in saccharin consumption on the subsequent Test Days. The data obtained with the nontreated control groups illustrate the taste aversion properties of 40, 60 and 80 mg/kg phenobarbital. As shown in Fig. 2, the groups injected with these doses on Test Day 1 displayed lower saccharin intakes on Test Day 2 when compared to the 0 mg/kg and 20 mg/kg groups. This particular effect of phenobarbital is not surprising since previous studies have shown the drug to be an effective taste aversion agent [7,9].

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