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Effects of Phenobarbital on Taste Aversion Induced by X-Radiation[1,2]

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JOLICOEUR, F. B., M. J. WAYNER, D. B. RONDEAU, A. D. MERKEL AND D. A. BASSANO. *Effect of phenobarbital on taste aversion induced by X-radiation.* PHARMAC. BIOCHEM. BEHAV. 11(6) 709–712, 1979.—The effects of phenobarbital on taste aversion induced by X-radiation were examined. Rats were adapted to a 23 hr 50 min water deprivation schedule. On the Treatment Day animals were given a novel 0.125% Na saccharin solution during the 10 min drinking session and were then exposed to 100 rads of X-radiation. The saccharin solution was presented again on six subsequent Test Days. Phenobarbital in doses of 20, 40, 60 and 80 mg/kg was administered 15 min prior to drinking on the first Test Day. Results demonstrate that phenobarbital in all doses tested has a significant attenuating effect on radiation induced taste aversion.

Phenobarbital Taste aversion Drinking X-Radiation

THE results of a previously published study demonstrated that phenobarbital can significantly reduce the magnitude of LiCl induced taste aversion when administered prior to drinking on the first test day following conditioning [3]. It is necessary to determine the generality of phenobarbital's attenuation of taste aversion by determining its effect on another well known taste aversion inducing agent. In addition to LiCl, ionizing radiation, gamma or X-rays, is another widely used taste aversion inducing agent [5]. The taste aversion properties of radiation have been examined extensively in numerous studies which have demonstrated that the extent of the taste aversion effects depends on several radiation exposure parameters. Absolute radiation dose, distance from radiating source, body weight of exposed animals, and the delay between ingestion of the taste solution and radiation, are all important factors in determining the magnitude and persistence of taste aversion [2,9]. Irradiation is most effective in inducing taste aversion when animals are exposed to 100 Roentgens of radiation within 1 hr after the consumption of the taste solution [8,9]. With these exposure parameters, irradiation does not produce overt signs of toxicity and has a taste aversion effect comparable to that produced by 1.2 mEq/kg LiCl [1,4].

The purpose of this study was to examine the effects of 20, 40, 60 or 80 mg/kg phenobarbital on taste aversion induced by 100 rads of X-radiation. Results demonstrate that phenobarbital also attenuates X-radiation induced taste aversion.

METHOD

Animals

Sixty female hooded rats were selected from the Brain Research colony and placed in individual living cages in a temperature controlled room on a 12 hr light-dark cycle. At the beginning of the experiment body weights ranged from 200 to 300 g. Animals were separated into 10 groups of six 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. Within 30 min after drinking, five groups of animals were placed in individual 25×6×6 cm Plexiglas cages and exposed for 30 sec to 100 rads delivered at a rate of 200 rads per min in a field of 26×26 cm² by a Clinac 4 linear

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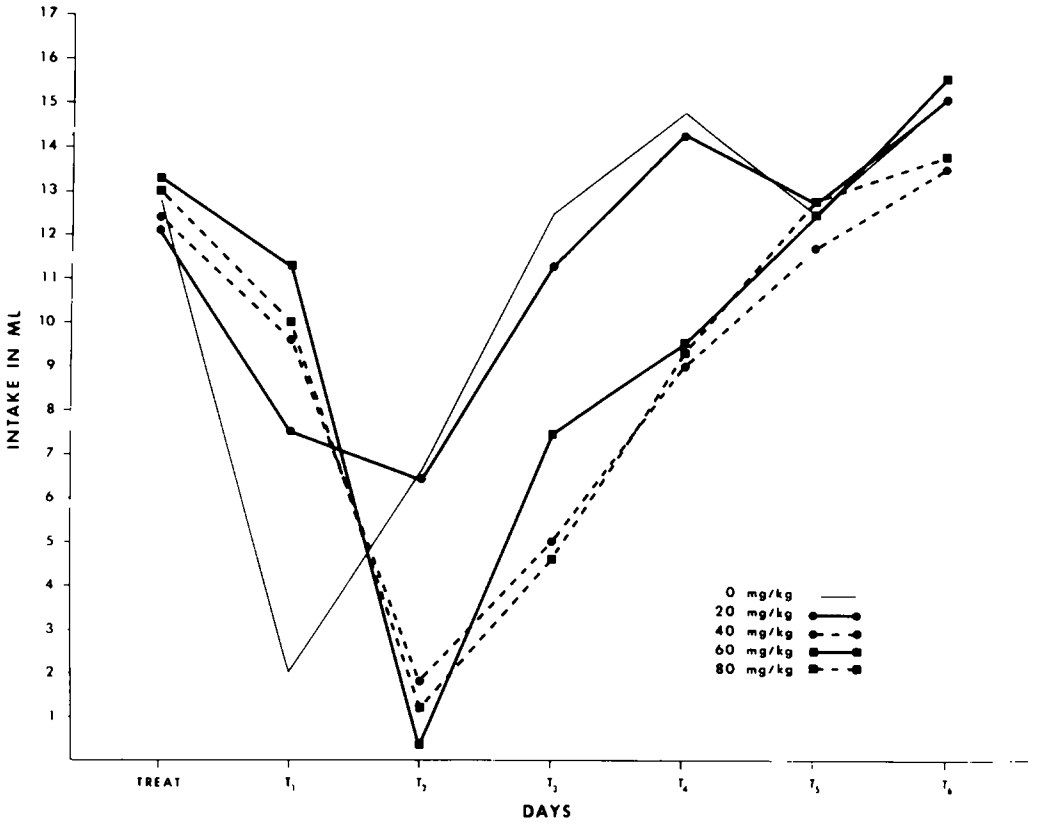

FIG. 1. Mean saccharin intakes for each group of radiated animals presented as a function of the Treatment Day (Treat) and each of the six Test Days (T1-T6). Animals were exposed to 100 rads of X-radiation following drinking on the Treatment Day. The various doses of Phenobarbital were administered 15 min prior to drinking on Test Day 1.

accelerator (Varian Associates). The five other groups were also placed in individual Plexiglas cages and were given sham radiation under the X-ray equipment for a period of 30 sec. Following the treatment session, all animals were returned to their individual living cages. On Days 11 and 12, water was presented during the drinking session. Then every third day from Days 13 to 28, animals were offered 0.125% Na saccharin during the drinking sessions. These days constituted the six posttreatment days. Two days of water presentation were interspersed between each test day. On the first test day, Day 13, each of the five radiated groups received either 0, 20, 40, 60 or 80 mg/kg of sodium phenobarbital. These same doses of the drug were distributed among the five non-radiated 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 manipulations.

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

RESULTS

The results obtained with the radiated groups and non-radiated control groups are illustrated 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 second factor [12]. Individual analyses were carried out for the radiated groups and for the non-radiated 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 radiated groups in Fig. 1, the Day factor was significant, $F(6,150)=95.16$, $p<0.01$. The Group factor was not significant. The Group by Days interaction was significant, $F(24,150)=7.63$, $p<0.01$. This interaction was analyzed by means of simple main effect analyses at each level of the Day factor. The following significant main effects were found: Test Day 1, $F(4,90)=11.26$, $p<0.01$, Test Day 2, $F(4,90)=6.9$, $p<0.01$, Test Day 3, $F(4,90)=9.06$, $p<0.01$ and Test Day 4, $F(4,90)=8.31$, $p<0.01$. Post hoc Dunnett and Tukey 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 signifi-

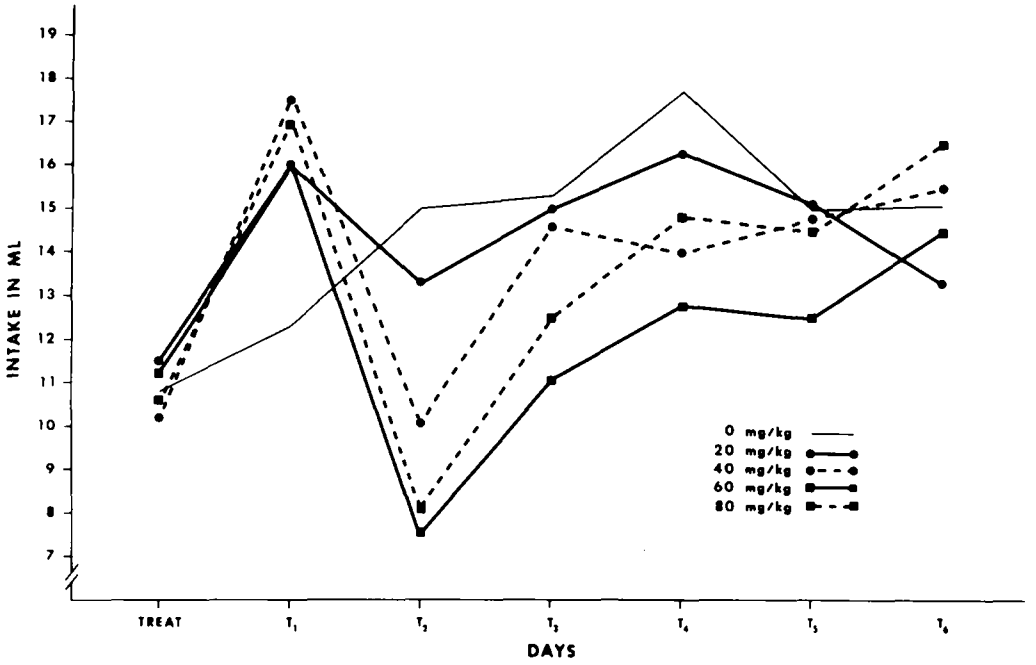

FIG. 2. Mean saccharin intakes for each group of non-radiated animals as a function of the Treatment Day (TREAT) and each of the six Test Days (T1-T6). A sham radiation session was performed immediately following drinking on the Treatment Day. The various doses of Phenobarbital were injected 15 min prior to drinking on Test Day 1.

cantly enhanced saccharin intakes in comparison with 0 mg/kg saline groups ($p<0.01$). On Test Days 2, 3 and 4, the saccharin consumption of the 40, 60 and 80 mg/kg groups were significantly reduced in comparison to the 0 mg/kg and 20 mg/kg groups ($p<0.01$).

The ANOVA performed on the data of the nonradiated control groups in Fig. 2 revealed a significant Group effect, $F(4,25)=3.44$, $p<0.05$, and a significant Day effect, $F(6,150)=27.35$, $p<0.01$. The Group by Day interaction was also significant, $F(24,150)=4.46$, $p<0.01$. Simple main effect analyses revealed significant main effects for Test Day 1, $F(1,130)=4.87$, $p<0.01$; Test Day 2, $F(4,130)=12.15$, $p<0.01$; Test Day 3, $F(1,130)=4.31$, $p<0.01$. Post hoc Dunnett's tests indicated 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 in comparison with the 0 mg/kg group. On Test Days 3 and 4, saccharin consumption of the 60 and 80 mg/kg groups was significantly reduced compared to the 0 mg/kg group ($p<0.01$).

In summary, saccharin consumption of both the radiated and the non-radiated control animals was significantly enhanced on Test Day 1 following the administration of 20, 40, 60 and 80 mg/kg phenobarbital. Following the administration of the three highest doses of phenobarbital on Test Day 1, saccharin intakes were significantly decreased on Test Days 2, 3 and 4 in the radiated animals and on Test Day 2 in the non-radiated control animals. Saccharin consumption of the 60 and 80 mg/kg non-radiated control groups were also depressed on Test Days 3 and 4.

DISCUSSION

The effects of phenobarbital on radiation induced taste aversion closely parallel the previously reported effects of the drug on taste aversion produced by LiCl [3]. The administration of the four doses of phenobarbital on the first Test Day following conditioning significantly reduced the magnitude of taste aversion in radiated animals (Fig. 1). As was the case with LiCl, the dose of 60 mg/kg of phenobarbital was most effective in attenuating taste aversion induced by radiation. The radiated group injected with this dose of the barbiturate drank 92% of the amount of saccharin consumed by the non-radiated control animals receiving 0.9% NaCl, indicating a nearly complete reversal of the taste aversion effect. Taken together, these results demonstrate that phenobarbital has a strong taste aversion attenuating effect, which is independent of the treatment utilized to induce the aversion.

Phenobarbital is a well known dipsogenic substance [7,11]. This characteristic of the drug was observed in the non-radiated control groups of this study. As shown in Fig. 2, administration of all doses of phenobarbital significantly increased saccharin consumption on Test Day 1. Another documented pharmacological action of the barbiturate is its ability to induce taste aversion when paired with the consumption of a relatively novel sapid solution [6,10]. The taste aversion inducing property of the drug was confirmed again in the present study. In both radiated and non-radiated groups, the injection of the three highest doses of phenobarbital on Test Day 1 resulted in significantly depressed saccharin intakes on subsequent Test Days.

REFERENCES

1. Barker, L. M. and J. C. Smith. A comparison of taste aversion induced by radiation and lithium chloride in CS-US and US-CS paradigms. *J. comp. physiol. Psychol.* **87**: 644–654, 1974.
2. Garcia, J., W. G. Hankins and K. W. Rusiniak. Behavioral regulation of the milieu interne in man and rat. *Science* **185**: 823–831, 1975.
3. 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**: 845–847, 1978.
4. Nachman, M., and J. H. Ashe. Learned taste aversions in rats as a function of dosage, concentration, and route of administration of LiCl. *Physiol. Behav.* **10**: 73–78, 1976.
5. Riley, A. L. and L. L. Baril. Conditioned taste aversions: A bibliography. *Anim. Learn. Behav.* **4**: 1S–13S, 1976.
6. Rondeau, D. B., F. B. Jolicoeur, R. Kachanoff, P. Scherzer and M. J. Wayner. Effects of phenobarbital on ethanol intakes in fluid deprived rats. *Pharmac. Biochem. Behav.* **3**: 493–497, 1975.
7. Schmidt, H., Jr. Water intake as an index of drug action. In: *Thirst in the Regulation of Body Water*, edited by M. J. Wayner. Oxford: Pergamon Press, 1964, pp. 185–209.
8. Smith, J. C., D. D. Morris and J. Hendricks. Conditioned aversion to saccharin solution with high dose of X-rays as the unconditioned stimulus. *Radiat. Res.* **22**: 507–510, 1964.
9. Smith, J. C. Radiation: Its detection and its effects on taste preference. *Prog. physiol. Psychol.* **4**: 53–118, 1971.
10. Vogel, J. R. and B. A. Nathan. Learned taste aversions induced by hypnotic drugs. *Pharmac. Biochem. Behav.* **3**: 189–194, 1975.
11. Watson, P. J. and V. C. Cox. An analysis of barbiturate-induced eating and drinking in the rat. *Physiol. Psychol.* **4**: 325–332, 1976.
12. Winer, B. J. *Statistical Principles in Experimental Design*. New York: McGraw-Hill, 1962.