Pharmacology Biochemistry & Behavior, Vol. 12, pp. 803–806. Printed in the U.S.A.

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

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Received 3 September 1979

WAYNER, E. A., G. SINGER, M. J. WAYNER AND F. C. BARONE. *The effects of several barbiturates on lithium chloride induced taste aversion.* PHARMAC. BIOCHEM. BEHAV. 12(5) 803–806, 1980.—The effects of single doses of five barbiturates on LiCl induced saccharin aversion were examined. Twenty three hour fluid deprived rats were offered a novel 0.125% saccharin solution and then were injected with either 3.0 mEq/kg LiCl or 0.9% saline. On the first test day after conditioning the animals were injected with either 60 mg/kg sodium phenobarbital, 80 mg/kg sodium barbital, 30 mg/kg sodium amobarbital, 20 mg/kg sodium secobarbital, 9 mg/kg sodium pentobarbital or 0.9% saline, 15 min prior to the drinking session. Results indicate that only 9 mg/kg pentobarbital, 60 mg/kg phenobarbital, and 80 mg/kg barbital were effective in attenuating the LiCl induced saccharin aversion on the day of administration. In addition, dipsogenic effects for only 60 mg/kg phenobarbital and 30 mg/kg amobarbital were observed in the saline treated control groups. A synergistic interaction between the effects of LiCl and sodium phenobarbital, barbital, and secobarbital was also observed. Lithium chloride plus these barbiturates resulted in a longer term aversion to saccharin than LiCl alone and no barbiturate produced saccharin aversion when administered without LiCl.

LiCl induced saccharin aversion Taste aversion Barbiturates Sodium amobarbital Sodium barbital Sodium pentobarbital Sodium phenobarbital Sodium secobarbital

ANIMALS administered a toxic agent, such as LiCl, following a novel taste experience will subsequently avoid that stimulus. This phenomenon is well established and has been referred to as bait shyness or learned taste aversion [3]. In general, a wide variety of agents have been used to induce aversions to many different flavored substances [10].

Hypnotic drugs, in particular the barbiturates, are among some of the substances that have been used to induce conditioned taste aversions [13]. In addition to being effective in inducing taste aversion, the barbiturates are also well known dipsogenic agents and induce copious consumption of water [8,11]. Some barbiturates, such as phenobarbital, have also been shown to increase the consumption of aversive or non-preferred solutions such as saline [2], ethanol [4], and citric acid [14] as well as a preferred saccharin solution [14]. Secobarbital and pentobarbital have also been reported to be strong dipsogens [11,12] while the dipsogenic effect of amobarbital is questionable [8,11].

It has recently been reported that the administration of some barbiturates 15 min prior to testing can significantly attenuate LiCl induced saccharin aversion [5,6]. In these experiments 60 mg/kg sodium phenobarbital, 30 mg/kg sodium amobarbital, and 15 mg/kg sodium pentobarbital significantly reduced the magnitude of a LiCl induced saccharin aversion when administered on the first day after conditioning. The effect was not associated with a general increase in fluid intake induced by the barbiturates. Other barbiturates such as barbital and hexobarbital did not attenuate the saccharin aversion. In addition, phenobarbital and amobarbital administration resulted in a decrease in saccharin consumption which was greater than that observed for LiCl administration on subsequent test days. The effect was attributed to either a barbiturate induced saccharin aversion or a synergistic interaction of the barbiturates with the effects of 3.0 mEq/kg LiCl pretreatment. However, the fact that post-barbiturate saccharin consumption in saline pretreated

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control groups was not decreased when compared to a saline injected control group indicated that a synergistic interaction of LiCl and barbiturate administration on saccharin aversion occurred.

The present experiment was designed to examine barbiturate effects on LiCl induced taste aversion and to replicate and extend the findings reported in previous studies [5,6] in a different strain of rats. The effects of five barbiturates: 60 mg/kg phenobarbital, 80 mg/kg barbital, 30 mg/kg amobarbital, 20 mg/kg secobarbital and 9 mg/kg pentobarbital, on saccharin aversion were determined. These drugs and dosages were employed as previous findings indicated that they produced a maximum dipsogenic effect when administered to fluid deprived rats [7, 8, 11, 12].

METHOD

Animals

Seventy-two Wistar derived male rats 90–120 days old and 325–375 g were individually housed in wire mesh cages (33×20×23 cm). They were maintained on ad lib food on a 12 hr light/dark cycle at constant temperature (21°C) for the duration of the experiment. The animals were randomly assigned to 12 groups of 6 animals per group and were weighed and handled daily throught the experiment.

Drugs

All barbiturates, sodium salts, were generously supplied by Eli Lilly and Co. On the day of injection, the drugs were dissolved in physiological saline and injected SC in a volume of 1 mg/kg. The barbiturate dosages were, 60 mg/kg phenobarbital, 9 mg/kg pentobarbital, 30 mg/kg amobarbital, 80 mg/kg barbital and 20 mg/kg secobarbital. Lithium chloride (0.65 M) was dissolved in distilled water and was injected SC in a volume of 4.61 ml/kg (3.0 mEq/kg). This dose of LiCl has been reported to induce maximum saccharin aversion [9]. All drugs were administered at room temperature.

Procedure

The animals were adapted to a 23 hr fluid deprivation schedule for 7 days. On the day of conditioning (ID) animals were offered only 0.125% saccharin solution for the 1 hr drinking session in 100 ml plastic graduated drinking tubes clipped to the home cages. Thirty minutes after drinking, thirty-six rats were injected with LiCl. The other thirty-six animals were designated as saline controls and were injected with 0.9% saline. For the next two days the animals were offered water for the 1 hr drinking session. On Day 4, test day 1 (TD 1), 15 min before drinking groups of 6 animals each previously administered LiCl were injected SC with either 0.9% saline, 60 mg/kg phenobarbital, 80 mg/kg barbital, 9 mg/kg pentobarbital, 30 mg/kg amobarbital or 20 mg/kg secobarbital. Groups of 6 animals each from the saline pretreated control group received the same injections. Again only 0.125% saccharin solution was available during the drinking session.

Saccharin solution was presented on four subsequent days, 7, 10, 13 and 16 (test days: TD 2–TD 5). No other pharmacological manipulations occurred for the rest of the experiment. All drinking fluids were presented at room temperature in 100 ml plastic graduated cylinders fitted with rubber stoppers and stainless steel drinking spouts. Food was available ad lib during the experiment except on ID and TD 1 to avoid possible compounding of food aversion effects. In addition, saccharin solution was stored in a room adjacent to where the animals were housed to ensure exposure to the test solution only on test days and to avoid the interference of olfactory cues in taste aversion acquisition and extinction [1].

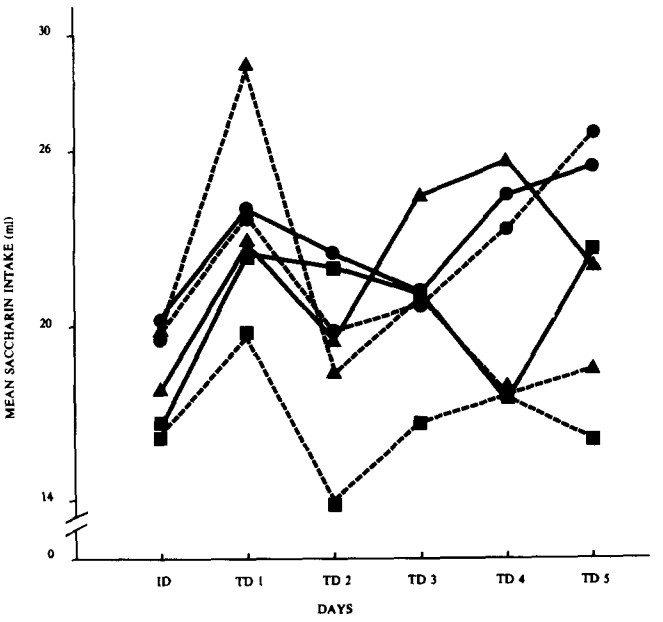

FIG. 1. Mean saccharin intakes for all groups injected with 0.9% saline on ID as a function of test day (TD 1–TD 5): phenobarbital (▲----▲), barbital (■----■), amobarbital (■———■), secobarbital (●----●) or pentobarbital (▲———▲) or 0.9% saline (●———●) were administered on TD 1.

The data were analyzed by two two-factor ANOVA's (TD 1 treatment×Days). Separate analyses were performed on each pretreatment group (LiCl or saline on ID). Further tests were made using simple main effects analysis and post hoc Dunnett's (ID=baseline or control condition) or Tukey A comparison where appropriate [15].

RESULTS

Mean saccharin intakes in ml for the saline-barbiturate groups are shown in Fig. 1. The analysis revealed overall significant main effects for TD 1 treatment, $F(5,30)=3.24$, $p<0.05$, and days $F(5,150)=13.91$, $p<0.01$. The interaction term was also significant, $F(25,150)=3.849$, $p<0.01$. Analysis of simple main effects across days within each barbiturate group revealed significant differences for all groups (phenobarbital $F(5,150)=11.34$, amobarbital $F(5,150)=5.00$, pentobarbital $F(5,150)=6.21$, saline $F(5,150)=2.86$, $p\leq 0.01$; secobarbital $F(5,150)=5.09$, barbital $F(5,150)=2.67$, $p\leq 0.05$). The between groups comparisons were not significant ($p>0.05$). Post hoc Dunnett comparisons across days utilizing the intake on ID as baseline revealed that the saline, pentobarbital, amobarbital, and secobarbital groups increased saccharin intakes as a function of test days ($p<0.001$). No significant differences were observed over days in the barbital and phenobarbital groups. However, saccharin intake on TD 1 in the amobarbital and phenobarbital groups was significantly elevated over baseline ($p<0.001$). This effect might be attributed to a dipsogenic action of both drugs.

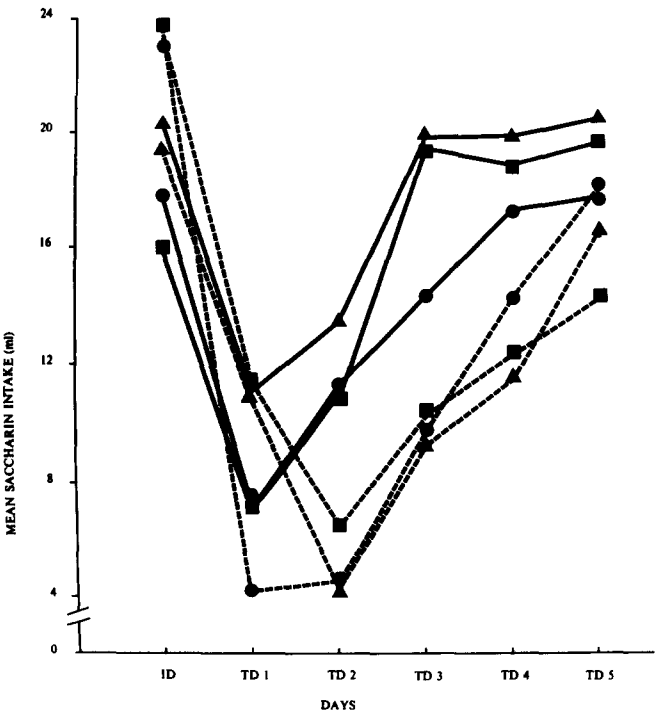

FIG. 2. Mean saccharin intakes for all groups injected with LiCl on ID as a function of test day (TD 1–TD 5): phenobarbital (▲----▲), barbital (■----■), amobarbital (■———■), secobarbital (●----●) or pentobarbital (▲———▲) or 0.9% saline (●———●), were administered on TD 1.

Mean saccharin intakes in ml for the LiCl-barbiturate groups are illustrated in Fig. 2. The analysis revealed overall significant main effects for TD 1 treatment, $F(5,30)=2.85$, $p\leq0.05$, and days $F(5,150)=73.00$, $p\leq0.01$. The interaction term was also significant, $F(25,150)=5.15$, $p\leq0.01$. Analysis of simple main effects across days within each barbiturate group revealed significant changes in saccharin intakes for all groups: saline $F(5,150)=9.75$, pentobarbital $F(5,150)=9.59$, phenobarbital $F(5,150)=14.92$, barbital $F(5,150)=17.99$, amobarbital $F(5,150)=14.11$, and secobarbital $F(5,150)=32.50$, $p<0.01$. Post hoc Dunnetts' comparisons with ID as baseline revealed that saccharin intake by the amobarbital, pentobarbital, and saline groups was depressed only on TD 1 and TD 2 ($p<0.001$). However, saccharin intake by animals receiving LiCl in conjunction with secobarbital, phenobarbital and barbital were significantly lower than baseline on all test days ($p<0.001$) except phenobarbital on TD 5. These findings indicate that phenobarbital, barbital, and secobarbital when given in conjunction with LiCl produce a long term and large magnitude saccharin avoidance.

DISCUSSION

These results tend to substantiate and extend previous findings [5,6]. However, in these previous studies the effects of various doses of each barbiturate were examined while only a single dose of each drug was employed here and some of the discrepancies might reflect dosage, sex, and strain differences. In addition, the previous studies utilized a 10 min drinking period while a 1 hr test session was used in the present study. A longer test session might reveal a longer duration effect of the barbiturates on saccharin consumption. Since food was removed from the cages on ID and TD 1 but was present on Days TD 2–TD 5, post prandial drinking might account for an increase in fluid consumption on these days and the decrease in phenobarbital, barbital, and secobarbital groups might be attributed to a decrease in food intake because these animals also decreased in body weight. However, food intake was not measured during the test session.

Although Jolicoeur *et al.* [6] reported taste aversion attenuation on the day of administration with 30 mg/kg amobarbital and a post drug decrease in saccharin intake, these effects were not observed under the present conditions with the same dose. It should be noted however that the saccharin intake in the saline-amobarbital group increased even though a dipsogenic effect was not observed in the previous studies. Although contradictory, the results of both studies indicate that the attenuation by the barbiturates cannot be attributed to their dipsogenic action. The small but insignificant effect of phenobarbital and pentobarbital on saccharin aversion on test day TD 1 are also in agreement with the previously published results [5,6].

Unlike the results of the previous study [6], 80 mg/kg of barbital does attenuate taste aversion under these conditions (unpublished data) and confirms the slight but insignificant effect reported here. Dose effect relations with phenobarbital and barbital and with repeated administrations will be published in the future.

REFERENCES

1. Ader, R. A note on the role of olfaction in taste aversion learning. *Bull. Psychon. Soc.* **10**: 402–404, 1977.
2. Falk, J. L. and G. C. Burnidge. Fluid intake and punishment attenuating drugs. *Physiol. Behav.* **6**: 199–202, 1970.
3. Garcia, J., W. G. Hankins and K. W. Rusiniak. Behavioral regulation of the milieu interne in man and rat. *Science* **185**: 824–831, 1974.
4. Jolicoeur, F. B., D. B. Rondeau, M. J. Wayner, R. B. Mintz and A. D. Merkel. Barbiturates and alcohol consumption. *Biobehav. Rev.* **1**: 177–196, 1977.
5. Jolicoeur, F. B., M. J. Wayner, D. B. Rondeau and A. D. Merkel. The effects of phenobarbital on LiCl induced taste aversion. *Pharmac. Biochem. Behav.* **9**: 845–847, 1978.
6. Jolicoeur, F. B., M. J. Wayner, A. D. Merkel, D. B. Rondeau and R. B. Mintz. The effects of various barbiturates on LiCl induced taste aversion. *Pharmac. Biochem. Behav.* **12**: 613–617, 1980.
7. Maickel, R. P. and G. J. Maloney. Effects of barbital on deprivation-induced water consumption in rats. *Physiol. Behav.* **8**: 1175–1178, 1972.

8. Maickel, R. P. and G. J. Maloney. Effects of various drugs on deprivation induced water consumption. *Neuropharmacology* **12:** 777–782, 1973.
9. Nachman, M. and J. H. Ashe. Learned taste aversion in rats as a function of dosage, concentration and route of administration of LiCl. *Physiol. Behav.* **10:** 73–78, 1973.
10. Riley, A. L. and L. L. Baril. Conditioned taste aversions: A bibliography. *Anim. Learn. Behav.* **4:** 1S–13S, 1976.
11. Schmidt, H., Jr. and L. Dry. Dose and time as variables in barbiturate action upon water ingestion. *Am. J. Physiol.* **204:** 817–820, 1963.
12. Schmidt, H., Jr. and S. J. Moak. Some drug effects influencing barbiturate facilitation of water ingestion. *Am. J. Physiol.* **196:** 397–410, 1959.
13. Vogel, J. R. and B. A. Nathan. Learned taste aversion induced by hypnotic drugs. *Pharmac. Biochem. Behav.* **3:** 189–194, 1975.
14. Wayner, M. J., D. B. Rondeau, F. B. Jolicoeur and E. A. Wayner. Effects of phenobarbital on saccharin and citric acid intake in fluid deprived rats. *Pharmac. Biochem. Behav.* **4:** 335–337, 1976.
15. Winer, B. J. *Statistical Principles in Experimental Design.* New York: McGraw-Hill, 1962.