Pharmacology Biochemistry & Behavior, Vol. 30, pp. 515–518. © Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

RAPID COMMUNICATION

Benzodiazepine-Induced Hyperphagia: A Test of the Hunger-Mimetic Model

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Received 18 March 1988

HUNT, T., C. X. POULOS AND H. CAPPELL. *Benzodiazepine-induced hyperphagia: A test of the hunger-mimetic model.* PHARMACOL BIOCHEM BEHAV 30(2) 515–518, 1988.—The 'hunger-mimetic' model is a prominent explanatory account of benzodiazepine-induced hyperphagia. A salient feature of food deprivation (hunger) in laboratory animals is 'finicky' eating, or an enhanced reactivity to the palatability of food. If the hunger-mimetic model is correct, a similar finicky pattern of increased eating should be observed both in hungry (food-deprived) rats and in benzodiazepine-treated, hyperphagic rats. Two groups of rats were matched on measures of ad lib baseline intake of both a highly palatable food (sweetened condensed milk) and a food low in palatability (milk adulterated with 37.5 mg% quinine). Subsequently one group was placed on a moderate food deprivation schedule while the second group was maintained on ad lib food but was injected (IP) with 5 mg/kg chlordiazepoxide (CDP) 30 min prior to food presentation tests. Single-bottle tests indicated that while the food deprived animals exhibited a greater augmentation of eating when given the high-palatability food, the animals pretreated with CDP exhibited an indiscriminate elevation of eating across both foods. Similarly, on two-bottle choice tests the food-deprived rats exhibited an enhanced preference for the high-palatability food, whereas the CDP-treated animals did not change from baseline food preference. These results fail to support the hunger-mimetic model of benzodiazepine-induced hyperphagia. Alternative models based on a perseverative, disinhibitory action of benzodiazepines are discussed.

Benzodiazepines Chlordiazepoxide Appetite Disinhibition

IT is well-established that benzodiazepines have the capacity to induce hyperphagia in laboratory animals [4, 9, 10, 12]. The 'hunger-mimetic' model is a prominent explanatory account of this phenomenon [3,12]. According to this model, benzodiazepines produce an effect comparable to the enhancement in appetite produced by food deprivation [3].

The increased eating observed in hungry (food-deprived) animals does not simply involve an indiscriminate increase in eating [7,8]. Rather, food deprivation gives rise to an enhanced reactivity to taste stimuli, resulting in what is described as 'finicky' eating [7,8]. That is when food-deprived animals exhibit a differential augmentation of consumption of highly palatable over less palatable foods.

The hunger-mimetic model of benzodiazepine-induced hyperphagia predicts that animals treated with benzodiazepine should exhibit a pattern of finicky eating similar to that of food-deprived animals. This prediction was assessed in the present study. According to the hunger-mimetic model, in single bottle tests, benzodiazepine-treated rats should behave like food-deprived rats. That is, they should exhibit a greater relative increase in consumption of high-palatability food over low-palatability food. Similarly, in a two-bottle 'choice' test, both groups would be expected to exhibit an enhanced preference for high-palatability over low-palatability food. Based on pilot data and previous research [3,5], a low dose of CDP was chosen which could be expected both to minimize the influence of other behavioral (e.g., sedative) effects and to be comparable to a moderate level of food deprivation.

METHOD

Subjects

Twenty-eight male Sprague-Dawley rats (Charles River, St. Constant, Que.), weighing 500–550 g at the start of the experiment, were individually housed in stainless steel cages and maintained on a 12:12 hr light:dark cycle. Standard laboratory food (Purina rat chow) and tap water were available ad lib throughout the experiment unless otherwise indicated.

Procedure

During an initial (21 day) habituation period, all animals were given repeated daily 30 min presentations of sweetened condensed milk (Borden's condensed milk, mixed in a 1:2 milk:tap water ratio). The milk solutions were presented in either one or two graduated Richter tubes attached to each animal's home cage. In each cage, a two-inch metal barrier served as a divider during two-bottle (Choice) presentations. Laboratory food was not available during milk presentation.

Subsequently, animals were exposed either to the regular

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'Sweet' milk, or to an isocaloric, 'Quinine' milk solution (the standard milk solution adulterated with 37.5 mg% quinine hydrochloride). A series of four single bottle 30 min milk presentations (at 48 hr intervals) were given, with each animal being exposed on alternate days either to the 'Sweet' or the 'Quinine' milk solution. Thus, on each presentation day, half of the animals received the Sweet and the remaining rats received the Quinine solution. Ad lib baseline measures of Sweet and Quinine milk intake were established for each animal over the last two days of milk presentation. Animals were then matched on these ad lib baseline intake measures, and assigned to one of two experimental groups, either 'Hunger' (n=14) or 'CDP' (chlordiazepoxide, n=14). A further ad lib baseline two-bottle Choice session was conducted on the next day. In order to assure that all animals began the 30 min choice session positioned at the Quinine milk tube, this tube was inserted into the cage just prior to insertion of the Sweet milk bottle.

Immediately after the ad lib baseline data were collected, the animals in the Hunger group were placed on a food deprivation schedule. Access to food was restricted to four lab chow pellets (16–20 g) each day (given at least 30 min after any milk presentation). This may be compared to a daily average intake of approximately seven lab show pellets (28–35 g) under ad lib conditions. The animals in the CDP group continued to have free food access as before. On the next day, all animals were weighed and given IP injections of physiological saline.

Over the following two days, single-bottle test presentations of milk were conducted for each experimental group, using a counterbalanced order of Sweet and Quinine milk presentation as described previously. On each test day, animals in the Hunger group received IP injections of physiological saline 30 min prior to the milk presentation. Animals in the CDP group received IP injections of 5 mg/kg CDP (chlordiazepoxide HCl, Hoffman-La Roche Limited). On the following day a two-bottle Choice session was conducted, with subjects being presented with both 'Sweet' and 'Quinine' milk 30 min after being given IP injections of either physiological saline (Hunger group) or 5 mg/kg CDP (CDP group).

RESULTS

Ad Lib Baseline Data

Using the matching procedure described earlier, the baseline intake data (±SEM) for single-bottle presentation of Sweet and Quinine milk solutions were 17.9 ml (±1.3) and 5.8 ml (±1.3) respectively for the Hunger group, and 19.3 ml (±1.2) and 5.6 ml (±0.98) respectively for the CDP group. Thus, the Quinine milk solution was clearly less preferred. This observation is confirmed by the ad lib baseline two-bottle choice data. The Sweet and Quinine milk intake levels were: 14.0 ml (±1.4) and 5.21 ml (±1.6) respectively for the Hunger group, and 14.1 ml (±1.3) and 4.6 ml (±1.2) respectively for the CDP group.

Single-Bottle Test Presentations

For each subject, the Sweet and Quinine milk intake over the two single-bottle test presentations were compared to that subject's ad lib baseline intake levels, and the average difference from baseline (ml) calculated for both groups. Statistical comparisons were conducted using *t*-tests (two-tailed, $p<0.05$). Consumption of Sweet milk was significantly increased both for Hunger, $t(13)=5.68$, and CDP, $t(13)=4.73$, groups. Quinine milk intake was also significantly increased for both groups, $t(13)=2.27$, and $t(13)=5.17$ respectively (see Fig. 1). Virtually identical mean increases in consumption (ml) of the Sweet milk were observed for both the Hunger (8.86±1.56) and CDP (9.36±1.98) animals, $t(26)=0.20$. However, a marginally significant between-group difference occurred in the corresponding Quinine milk data (ml). Comparison of Quinine milk intake of the Hunger group (3.50±1.54) versus the CDP group (7.71±1.49) yielded a difference which approached statistical significance using a two-tailed *t*-test criterion ($p<0.07$) and which was within the range for statistical significance when a one-tailed *t*-test, $t(26)=1.97$, $p<0.05$, was applied. Furthermore, whereas a differential augmentation of consumption of Sweet over Quinine milk was observed in the Hunger group, $t(13)=2.35$, the CDP-treated rats exhibited a similar magnitude of increased consumption across both the Sweet and Quinine milk presentations, $t(13)=0.67$ (see Fig. 1).

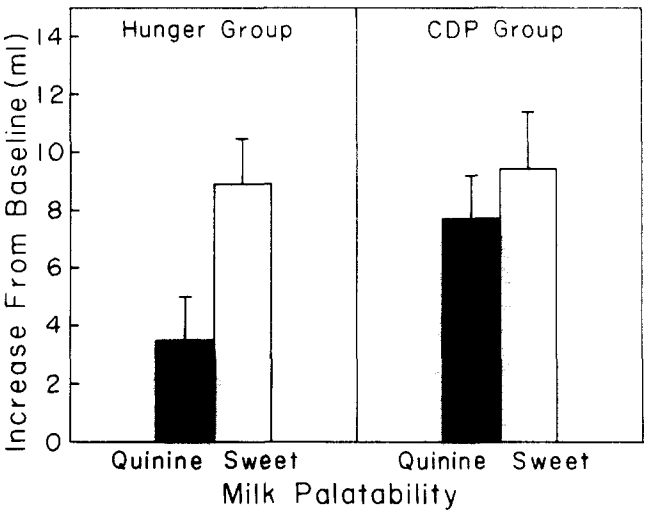

FIG. 1. Mean (±SEM) increase from baseline intake scores (ml) recorded over two consecutive Single-Bottle Test Days for animals in Hunger or CDP treatment groups presented with either Sweet milk (empty bar) or quinine-adulterated milk (solid bar).

Two-Bottle (Choice) Test Presentations

The average levels of intake (±SEM) of Sweet and of Quinine milk were 18.0 ml (±1.9) and 2.1 ml (±0.8) for the Hunger group and 22.7 ml (±3.1) and 7.9 ml (±2.0) for the CDP group. Overall, the CDP animals consumed more than did the food-deprived animals, $t(26)=3.62$. The test data were transformed into preference scores with the Quinine milk intake of each animal being expressed as a percentage of the total (Sweet and Quinine) milk intake. Ad lib baseline choice data were similarly transformed. As can be seen from Fig. 2, the animals in the Hunger group exhibited a significantly reduced preference ratio for the Quinine milk on the Test day relative to their ad lib baseline, $t(13)=2.17$. In contrast, the animals in the CDP group exhibited no significant change in their preference ratio for the Quinine milk, $t(13)=0.34$. If anything, these animals exhibited a slight (non-significant) increase in preference ratio for the Quinine milk.

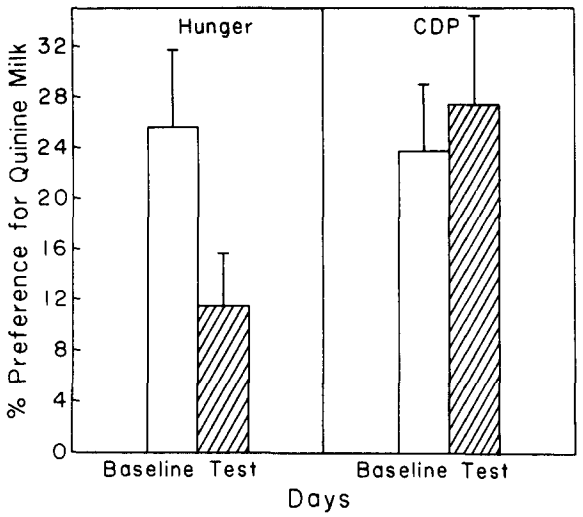

FIG. 2. Mean (±SEM) percent preference for Quinine-adulterated milk observed in Hunger and CDP treatment on Two-Bottle Choice Baseline (empty bars) or Test (striped bars) Days.

DISCUSSION

The present results fail to support the hunger-mimetic model of benzodiazepine-induced hyperphagia. In the single-bottle test, animals in the food-deprived, Hunger group exhibited significantly less of an increase in eating of a low-palatability, quinine-adulterated food as compared to that seen with a high-palatability, sweet food. The CDP-treated rats showed an equivalent increase in eating regardless of whether the food was of high or low palatability. In the two-bottle Choice test, the Hunger group exhibited a reduced preference for the Quinine food, whereas the CDP group showed no such change in preference. While attention may be drawn to the fact that the CDP animals consumed more overall in this Choice test than did the Hunger animals, this would not appear to alter the interpretation of the preference data. If anything, according to a hunger-mimetic model of CDP action, a greater hyperphagic drug effect should act like increased hunger and therefore increase the degree of finicky eating. Thus, the greater total volume of food intake seen in the CDP-treated animals makes this group's apparent failure to exhibit any shift in food preference all the more significant. In short, the results indicate that whereas animals in the Hunger group exhibited a finicky pattern of increased eating [7], the CDP-treated animals showed an indiscriminate elevation in eating of both high-palatability and low-palatability foods.

There have been other studies which have directly compared the effects of food deprivation to those of benzodiazepine administration. In 1967, Margules and Stein compared the effects of food deprivation and of oxazepam treatment on the behavior of rats in a Geller-Seifter 'conflict' paradigm [9]. The rate of suppressed operant responding (maintained by food presentation and punished by electric shock) was increased by pretreatment with oxazepam but was not altered by food deprivation. Wise and Dawson [12] reported that diazepam treatment was not as effective as was food deprivation in motivating acquisition of operant responding maintained by food presented over six 90 min daily sessions. This difference was attributed to the failure of the benzodiazepine treatment to induce the increased general activity (and exploratory behavior) commonly associated with food deprivation. The findings cited above then, would appear to provide additional evidence of important differences in the behavioral profiles of the increased eating associated with hunger and with benzodiazepine administration.

The findings of the present paper extend the understanding of benzodiazepine-induced hyperphagia. First, it would appear that a simple 'hunger-mimetic' explanatory model [3] is not sufficient to account for the discrepancy in pattern of eating response observed between the food-deprived, hungry animals and the CDP-treated animals. Second, the present evidence suggests that the stimulatory effect of benzodiazepines on food consumption does not interact with appetitive, motivational factors associated with food palatability. That is, there is an increase in eating (hyperphagia) without a change in relative preference for the high- (versus low-) palatability foods. This finding is consistent with a previous report indicating no interaction between a manipulation of food texture (lab chow pellets or powder) and CDP-induced hyperphagia in rats [5]. It would appear that the present data are most consistent with an interpretation of the disinhibitory action of benzodiazepines as reflecting a 'perseverative' or 'impulsive' quality as has been suggested by some recent research in this regard [6,11]. In contrast to an idea of a simple drug-induced diminution of inhibitory signals [9], such a notion carries with it the implication of a more pervasive disruption of inhibitory mechanisms. This view is in keeping with recent reports, both in the animal and human research literatures, of benzodiazepine-induced interference with the adaptive capacity to switch response sets (e.g., [1,2]).

ACKNOWLEDGEMENTS

Funds for this research were provided by Grant A2612 from the Natural Sciences and Engineering Research Council of Canada. We thank Hoffman-La Roche Limited for the gift of chlordiazepoxide hydrochloride.

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