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Differential Effects of Psychotropic Drugs on Feeding in Rats: Is Histamine Blockade Involved?

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ORTHEN-GAMBILL, N. AND M. SALOMON. *Differential effects of psychotropic drugs on feeding in rats: Is histamine blockade involved?* PHARMACOL BIOCHEM BEHAV 36(4) 837–841, 1990.—The present animal studies tested the hypothesis that drug-induced blockade of histamine-1 receptors leads to appetite stimulation. Test agents included the antipsychotic promazine which has very potent antihistaminic effects, as well as the antipsychotic haloperidol and the antidepressant desipramine which both have negligible antihistaminic effects. In support of the hypothesis, significant appetite stimulation occurred only with promazine, while the other two test agents did not increase feeding, and even produced some suppression in food intake.

Antidepressants Antihistamines Antipsychotics Appetite stimulation Feeding behavior
Histamine blockade Desipramine Haloperidol Promazine Rats

IT is well established clinically that both antidepressant and antipsychotic drug treatment can lead to unwanted appetite stimulation and weight gain [reviews: (10,20)]. However, all antidepressants and antipsychotics are not equipotent in stimulating appetite. Only certain agents within each class appear to increase feeding, while other therapeutically equivalent drugs are not linked to appetite stimulation. It thus appears that the appetite stimulation and weight gain seen with psychotherapeutic drug treatment is not a general characteristic of all psychotropic agents, but rather, is linked to some specific property of certain agents.

An attempt to find a link between those agents in both drug classes which stimulate appetite reveals that they are all extremely potent antihistamines, i.e., histamine-1 (H-1) receptor blockers (8, 15–17). In fact, only those agents which stimulate appetite are potent antihistamines, while therapeutically equivalent drugs which do not typically stimulate appetite have very weak antihistaminic effects. It thus appears that blockade of H-1 receptors may mediate the appetite stimulation seen with certain psychotherapeutic drugs.

This hypothesis was supported in a recent series of studies in this laboratory, testing the effects of several antihistaminic agents on feeding behavior in rats (12). First, the administration of two "classical" (nonpsychiatric) antihistamines produced significant and long-lasting increases in food intake. Secondly, the antidepressant doxepin, which is the most potent antihistamine among the tricyclics (15), also led to significant appetite stimulation. In contrast, when histamine (H) activity was stimulated by giving rats the H precursor histidine, a profound suppression in feeding was seen. These results thus support the hypothesis that drug-induced blockade of H-1 receptors can stimulate appetite. The results also suggest that there may be an inverse relationship between H activity and feeding.

The purpose of the present studies was to extend the above findings to antipsychotic drugs, i.e., to test whether the appetite stimulation seen with certain antipsychotic drugs may also be due to the antihistaminic properties of these drugs. More specifically, test drugs included two therapeutically equivalent antipsychotics which are at opposite extremes in terms of their antihistaminic effects. The first test agent was promazine which has extremely potent antihistaminic properties, and the second one was haloperidol which has extremely weak antihistaminic effects (16). If H receptor blockade is indeed linked to appetite stimulation, one would expect promazine, but not haloperidol, to produce increases in food intake.

The present research also tested the antidepressant desipramine which has negligible antihistaminic effects (15). As mentioned above, previous results (12) showed that appetite stimulation occurred with the antidepressant doxepin which has extremely potent antihistaminic effects. To provide a comparison to doxepin, it was thus of interest to test an antidepressant from the opposite extreme in terms of antihistaminic effects. Since desipramine has negligible antihistaminic effects, it was not expected to increase food intake.

METHOD

Animals and Diets

The subjects in all experiments were male Sprague-Dawley rats

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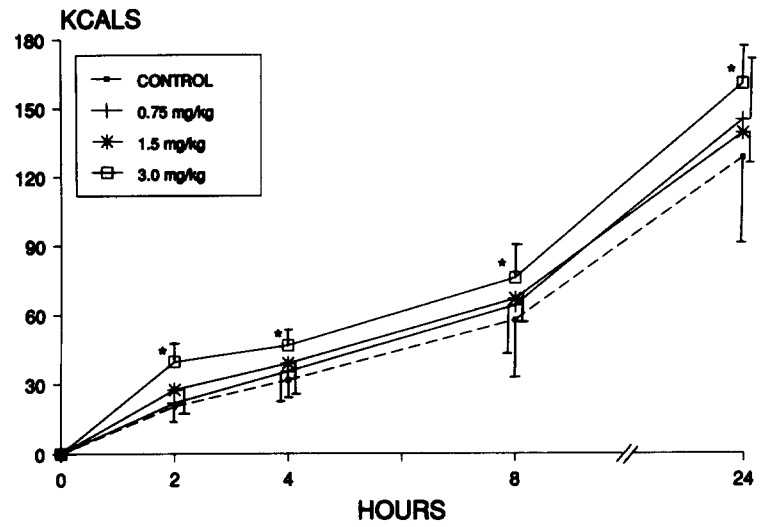

FIG. 1. Cumulative caloric intakes at 2, 4, 8, and 24 hr following IP administration of saline and 0.75, 1.5, and 3.0 mg/kg of promazine. *Significantly different from control.

(CD-outbred, Charles River Laboratories, Wilmington, MA), weighing 250–300 g at the beginning of the experiment. All animals were housed individually in standard stainless steel cages, in a temperature-controlled room (21°C), with a reversed light-dark cycle (lights off: 1000–2200 hr).

All animals were maintained on ad lib feeding schedules, and given a palatable liquid diet which consisted of vanilla-flavored Carnation Instant Breakfast (generously donated by Carnation Company). The Instant Breakfast was dissolved in whole milk (15 g powder/100 ml milk). Fresh diet was provided twice per day, since the liquid diet can turn sour after extended exposure to room temperature. In addition to the liquid diet, all animals also had ad lib access to water throughout the experiments. The main reason for using a liquid diet was to avoid the possibly confounding influence of dry mouth, a side effect of antihistaminic drugs. Further, it was desirable to continue with the same diet that was used in earlier studies, to allow the present results to be compared to earlier findings.

Procedure

All experiments included a 10-day baseline period to allow animals to become used to the diet as well as daily handling. Each study involved a within-subject design with 11 rats per study. Before the start of drug injections, all rats received an intraperitoneal (IP) injection of distilled water to familiarize subjects with the injection procedure. No measurements were taken at this time. Two days later, all rats received a second injection of distilled water (control injection), and this time cumulative food and water intakes were measured at 2, 4, 8, and 24 hr postinjection. On drug days, each rat received an IP injection of active agent, and cumulative food and water intakes were again measured at the same fixed intervals postinjection. All injections were given at 1000 hr, the beginning of the dark portion of the daily light-dark cycle. The medium dose of active agent was tested first, followed by the high and then the low doses. Drug injections were separated by at least 5 days.

Experiment 1 investigated the effect of the antipsychotic drug promazine, generously donated by Wyeth Laboratories (Philadelphia, PA). The test drug was dissolved in distilled water and tested at 3 dose levels: 0.75, 1.5, and 3.0 mg/kg.

Experiment 2 tested the effects of the antipsychotic drug haloperidol (McNeil Pharmaceutical, Spring House, PA), dissolved in distilled water, and tested at the following 3 dose levels: 0.25, 0.5, and 1.0 mg/kg.

Experiment 3 tested the effects of the antidepressant desipramine (Merrell Dow Pharmaceuticals, Cincinnati, OH), dissolved in distilled water, and tested at the following 3 dose levels: 2.5, 5.0, and 10.0 mg/kg.

Data Analysis

In all studies, food and water intake data represent cumulative intakes, measured at 2, 4, 8, and 24 hr postinjection. All food intake data are expressed in kilocalories (Instant Breakfast contains 1.23 kcal/g). At each time point, cumulative intakes for control and drug injections were compared using one-way analyses of variance (ANOVA) for repeated measures. In appropriate instances, the ANOVAs were followed by multiple comparison tests (paired t-tests with Bonferroni correction factor). An asterisk in the figure denotes that food intake was significantly different from control values, with a p-value of at least 0.05.

RESULTS

Experiment 1—Promazine (PRO)

As can be seen from Fig. 1, PRO produced elevations in food intake. ANOVAs at each time point revealed that food intake was significantly increased at every measurement point in the test period, i.e., at 2 hr, $F(3,30)=6.35$, $p<0.002$; at 4 hr, $F(3,30)=3.08$, $p<0.042$; at 8 hr, $F(3,30)=4.68$, $p<0.008$; and at 24 hr postinjection, $F(3,30)=15.55$, $p<0.0001$. Multiple comparison tests revealed that the high dose of PRO significantly increased food intake at every measurement point, while the effect of the two lower doses did not reach significance.

With regard to water intakes, PRO had a suppressive effect at 4 hr, $F(3,30)=4.35$, $p<0.12$; at 8 hr, $F(3,30)=4.75$, $p<0.008$;

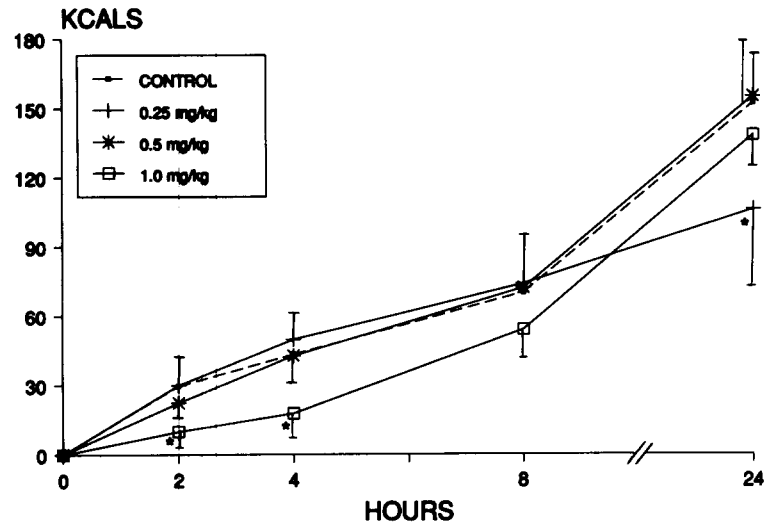

FIG. 2. Cumulative caloric intakes at 2, 4, 8, and 24 hr following IP administration of saline and 0.25, 0.5, and 1.0 mg/kg of haloperidol. *Significantly different from control.

and at 24 hr postinjection, $F(3,30)=3.59$, $p<0.025$. Multiple comparison tests showed that the lowest dose of PRO accounted for the suppression in all cases, whereas the two higher doses of PRO did not affect water intake.

As can be seen from Fig. 2, HAL did not stimulate feeding. In fact, food intake was significantly suppressed at 2 hr, $F(3,30)=12.92$, $p<0.0001$; at 4 hr, $F(3,30)=18.63$, $p<0.0001$; and at 24 hr postinjection, $F(3,30)=9.05$, $p<0.0001$. Multiple comparison tests revealed that the highest dose (1.0 mg/kg) of HAL produced significant suppression in food intake at 2 and 4 hr, while the lowest dose produced significant suppression at 24 hr.

Water intakes following HAL administration were not significantly different from controls, except at 2 hr, $F(3,30)=8.18$, $p<0.0001$. Multiple comparison tests revealed that the medium dose (0.5 mg/kg) of HAL significantly suppressed water intake at the first measurement point.

Experiment 3—Desipramine (DES)

As can be seen from Fig. 3, DES suppressed feeding throughout the test period. In fact, ANOVAs showed that food intake was significantly suppressed at each time point, i.e., at 2 hr, $F(3,30)=13.47$, $p<0.0001$; at 4 hr, $F(3,30)=24.43$, $p<0.0001$; at 8 hr, $F(3,30)=33.55$, $p<0.0001$; and at 24 hr, $F(3,30)=7.52$, $p<0.001$. Multiple comparison tests revealed that all 3 doses of DES produced significant suppression in food intake at 2, 4, and 8 hr, and the highest dose also significantly suppressed appetite at 24 hr postinjection.

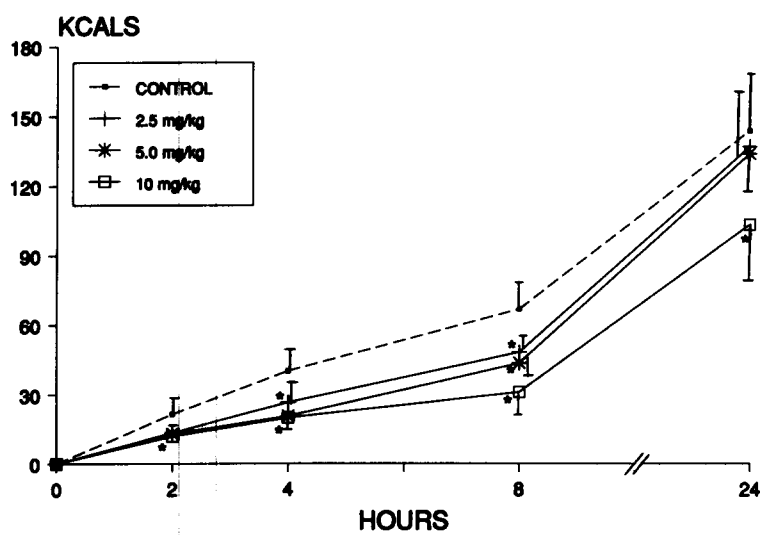

FIG. 3. Cumulative caloric intakes at 2, 4, 8, and 24 hr following IP administration of saline and 2.5, 5.0, and 10 mg/kg desipramine. *Significantly different from control.

Water intake was not affected by DES at the first two measurement points, but was suppressed by drug administration at 8 hr, $F(3,30)=3.32$, $p<0.033$ and at 24 hr, $F(3,30)=5.42$, $p<0.004$. Multiple comparison tests showed that the suppression was produced by the high dose of DES at both time points.

DISCUSSION

To summarize the main findings, the antipsychotic drug promazine produced significant and long-lasting increases in food intake. In contrast, the second antipsychotic test drug haloperidol did not stimulate feeding, and in fact suppressed food intake at the highest dose level. The antidepressant desipramine also failed to increase feeding, and actually suppressed food intake at all tested dose levels. The results support the general hypothesis that antihistaminic drug effects (i.e., histamine-1 receptor blockade) can stimulate feeding. Appetite stimulation only occurred with the antipsychotic promazine which has extremely potent antihistaminic properties (16), while feeding was not increased by the antipsychotic haloperidol or the antidepressant desipramine which both have negligible antihistaminic effects (15,16).

The present studies are part of a larger project testing the hypothesis that the antihistaminic properties of certain psychotropic drugs may mediate the unwanted appetite stimulation seen with the clinical use of these agents. More specifically, recent studies in this laboratory (12) tested the appetite-stimulating effects of two classical antihistamines, as well as the antidepressant doxepin which is the most potent antihistamine among the antidepressants (15). All three test agents produced significant and long-lasting increases in feeding, thus supporting the hypothesis that appetite stimulation and histamine-1 receptor blockade may be linked.

The purpose of the present studies was two-fold. First, it was important to test an antidepressant with negligible antihistaminic effects, to provide a comparison to the previously tested antidepressant doxepin. The antidepressant desipramine was chosen for this purpose. As mentioned above, doxepin has extremely potent antihistaminic effects, and it produced significant appetite stimulation (12). In contrast to doxepin, desipramine has extremely weak histamine-blocking properties (26), and it was not therefore expected to increase feeding in the present studies. The results (Fig. 3) show that desipramine indeed did not increase feeding, and actually produced a suppression in food intake, which is in agreement with other animal research on desipramine (7,11). Taken together, our earlier findings with doxepin and the present results with desipramine suggest that histamine antagonism may in fact mediate the appetite stimulation seen with doxepin, since antihistaminic potency is a major difference between the two tested antidepressants. Of course one should recognize that the test agents also affect other neurotransmitter systems besides histamine. More specifically, acute changes produced by prototypical antidepressants include reuptake blockade of norepinephrine (NE) and/or serotonin (5-HT) (23). These changes may be crucial for the therapeutic actions of antidepressants, but it is unlikely that they contribute to appetite stimulation. While the present test agents both block the reuptake of NE, desipramine is much more potent than doxepin in this regard (17), and yet appetite stimulation was only seen with doxepin. Perhaps NE uptake blockade and the resulting potentiation of noradrenergic transmission might actually help explain the suppression in feeding seen with desipramine in the present studies. Other agents which produce noradrenergic stimulation, such as cocaine (6), are of course known to be potent appetite suppressants.

The second purpose of the present studies was to test our hypothesis with antipsychotic drugs. The results on classical antihistamines, as well as antidepressant drugs, had supported the idea that there is a link between antihistaminic drug effects and appetite stimulation. If the same relationship could be demonstrated for antipsychotic drugs, the general theory would be greatly strengthened. The antipsychotic test agents promazine and haloperidol represent opposite extremes in terms of antihistaminic properties, i.e., promazine has extremely potent antihistaminic effects, while haloperidol has negligible antihistaminic effects (16). As reported above, only promazine produced a significant and long-lasting stimulation of feeding, while haloperidol did not increase feeding, and actually produced some suppression in food intake. These findings thus provide further support for the hypothesis that drug-induced histamine-1 receptor blockade is linked to appetite stimulation. It should be recognized that nonhistaminergic neurochemical changes may also contribute to the observed drug effects on feeding. Prototypical antipsychotic drugs are potent dopamine (DA) receptor blockers (23), and these effects should be considered. While DA blockade may be crucial for the therapeutic effects of antipsychotic drugs, it is unlikely that these neurochemical changes contribute to appetite stimulation. Both antipsychotic test agents block DA receptors, but haloperidol is much more potent than promazine in this regard (16), and yet only promazine produced increased feeding. In general, the present findings with antipsychotic drugs are in agreement with other animal studies. For example, other research with promazine also shows appetite stimulation (4). Further, the antipsychotic agents chlorpromazine (14,18) and clozapine (2) have also been found to stimulate feeding in animals. As these agents also have potent antihistaminic effects (16), the positive feeding data lend further support to our hypothesis. With regard to haloperidol, our present findings are in agreement with other studies showing no increase, or even a suppression in feeding with haloperidol (3, 19, 25).

The present hypothesis that antihistaminic drug effects may be linked to appetite stimulation is not so surprising if one considers the possibility that histamine (H) may normally play an inhibitory role in feeding. H is a putative neurotransmitter which has been clearly localized in the brain [reviews: (9, 13, 22)], and the highest concentration is found in the hypothalamus (1, 9, 24), which of course is thought to play a major role in the central regulation of feeding. Animal studies using central administration of H (5), or peripheral administration of the H precursor histidine (12,21), have all shown significant appetite suppression. If the inhibitory role of H on feeding is blocked with antihistaminic drugs, feeding may increase through drug-induced disinhibition. In other words, appetite stimulation may occur with antihistaminic drugs because these agents block the suppressive effect H may normally have on feeding.

In general, the present studies, as well as earlier findings from this laboratory (12), indicate that one should not make generalizations about antidepressant or antipsychotic drugs and feeding. The results show that significant increases in feeding only occurred with those test agents which have potent antihistaminic effects. Therapeutically equivalent test agents which lack antihistaminic effects did not increase feeding, and even produced a suppression in food intake. The present focus on histamine-1 receptor blockade may help explain some of the seemingly contradictory findings in the literature, i.e., why some studies on psychotropic agents and feeding report appetite stimulation, while others may observe the opposite. If psychotropic drugs are rank-ordered according to antihistaminic potency, one could perhaps demonstrate a continuum of drug effects on feeding, ranging from significant stimulation all the way to significant suppression. Psychotropic agents may thus form a broad spectrum with regard to feeding, and appetite stimulation may only occur with agents which have unique neurochemical features, such as potent antihistaminic effects.

In summary, the present findings with antipsychotic drugs, combined with our earlier findings with antidepressant drugs (12),

support the hypothesis that the antihistaminic properties of certain psychotropic drugs may mediate the stimulatory effects of these agents on feeding. To provide a closer parallel to clinical studies, future animal experiments should include chronic drug administration, as clinical weight gain with psychotropics typically occurs with long-term drug exposure.

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