

HISTAMINE INHIBITS EATING WITHOUT ALTERING POSTPRANDIAL SATIETY IN RATS

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Abstract

Exogenous histamine decreases food intake and injection of H-1 antagonists increases food intake in rats. Previous work has focused on the effect of relatively large doses of histamine on eating behavior, and have not measured the effect of histamine on postprandial satiety behaviors. This work measures the effect of small and large doses of histamine and investigates the effects of an H-1 receptor antagonist on eating, drinking and postprandial satiety behavior. Twelve adult male Sprague-Dawley rats not food deprived were tested eating Nilla Wafer cookies with or without water following subcutaneous injections of .625 mg/Kg histamine, 10 mg/Kg histamine or 0.9% NaCl vehicle. The second experiment tested the effects of the H-1 antagonist dexbrompheniramine (DXB); 1 mg/Kg administered 10 minutes prior to .625 mg/Kg or 10 mg/Kg histamine on eating, drinking and satiety behavior. The 10 mg/Kg histamine inhibited eating and increase water intake, but failed to alter behavioral satiety measures. The .625 mg/Kg histamine stimulated drinking, but did not affect food intake or satiety. When DXB was given prior to histamine it reduced histamine-induced drinking, but did not affect food intake or satiety measures. These results demonstrate that exogenous histamine can inhibit eating without changing postprandial satiety, challenging the notion that endogenous histamine contributes to satiety for food in rats.

Introduction

Satiety is the feeling of satisfaction that accompanies the cessation of feeding. The physiological mechanisms for satiety have been the focus of research for several decades. Research has focused on what happens during feeding and digestion that leads to satiety. When food enters the body it follows a path from the pregastric area (mouth, pharynx and esophagus) to the gastric compartment (stomach) and finally to the intestine. Throughout each of the phases of eating and digestion, different sensory receptors detect the presence of ingested food and eventually alert the brain which organizes the cessation of eating. Research on each phase has led to many developments in our knowledge of the physiological controls of satiety.

Research using sham feeding isolates the pregastric pathway by removing food from the animal when it reaches the stomach. Simply allowing food to go through the pregastric pathway and then removing it through a gastric fistula is not sufficient in to initiate satiety following a food deprivation of 17 hours (Young et al., 1974). The gastric phase of food intake has been the focus of research involving gastric distention. When food stimulates pregastric sites, and then causes stomach distention, rats experience satiety (Kraly and Smith, 1978). Also involved in both the gastric and intestinal phases are the osmotic properties of food. Administration of osmotic loads into the gastrointestinal tract reduces food intake (Davis et al. 1975). In the intestinal phase, as well as during the gastric phase, many receptors are activated that may signal the release of neurochemicals and hormones. One of the specific hormones found to decrease food intake and increase the satiation process is cholecystokinin (CCK) (Gibbs et al., 1973). The function of other neurochemicals such as insulin, serotonin, glucagon and histamine are also being investigated.

Histamine may have a role in eating behavior in rats. It appears that there is an inverse relationship between histamine and food intake such that blockade of histaminergic function leads to increased eating, while increased histaminergic function is associated with decreased eating (Orthen-Gambill 1987). Overall, a decrease in central histamine in the hypothalamus increases food intake in rats (Mercer et al., 1994). Alternatively, peripheral administration of histidine to elevate central histamine levels inhibits food intake in rats (Schwartz, Lampart & Rose 1972). Both intraperitoneal (i.p.) (Fukagawa

et al., 1989; Orthen-Gambill & Solomon, 1992) and intracerebroventricular (i.c.v.) (Sakata et al., 1990; Sakata et al., 1991) injections of the histamine synthesis inhibitor α -fluoromethylhistidine increase eating in rats. The H-1 histamine receptor subtypes have been speculated to play an important role in appetite stimulation. For example, it has also been shown that decreases in histaminergic function, through a blockade of H-1 receptors, stimulate feeding behavior (Orthen-Gambill, 1987). Moreover, i.c.v. injections of the histamine synthesis inhibitor suggest that neuronal histamine effects feeding through H-1 receptors in the ventromedial hypothalamus and paraventricular nucleus (Sakata et al., 1990).

Previous work with histamine and H-1 receptors has measured inhibition of food intake. There may be, however, an important difference between the inhibition of food intake and the appearance of satiety. Satiety is indicated not just by diminished eating, but also by a sequence of behaviors. Following a meal an animal typically performs a series of behaviors that begins with a brief period of grooming, which is followed by exploratory behaviors such as sniffing, rearing and locomotion and finally ending in resting (Antin et al., 1975). If the animal ceases eating without demonstrating this sequence of behaviors, one must consider whether the animal has stopped eating due to illness or malaise. For example, if a food or drug causes a rat to feel ill, it will subsequently stop eating and fail to demonstrate satiety (Smith and Gibbs, 1979). Satiety is often quantified by measures of intermeal interval (IMI), meal size (MS), latency to rest, total time spent resting and time spent grooming. Each of these measures can indicate satiety to the observer.

This study was designed to examine the role of histamine and H-1 receptors in satiety for food in rats. While it has been shown that high, pharmacological levels of histamine will inhibit food intake, it remains unclear whether physiological levels of histamine can suppress eating and induce satiety. This experiment will test both a relatively large dose of histamine (10 mg/Kg) and a small dose near the threshold for affecting behavior in rats (.625 mg/Kg). Satiety behavior, as well as food intake, will be measured. The rats will not be food deprived and will eat a palatable meal (a cookie). Tests will be run both with and without water to assess whether histamine's effect upon drinking indirectly affects eating or satiety.

A second study will examine the role of H-1 receptors in satiety. The smaller dose of histamine will be administered following an injection of dexbrompheniramine (DXB), a well-known H-1 receptor antagonist. DXB has been shown to inhibit drinking initiated by histamine injection (Kraly et al., 1996). If the H-1 receptor is necessary for satiety elicited by histamine, then the H-1 antagonist should block satiety behavior, and food intake should be similar to controls. By dissociating between receptor subtypes one can further identify the role of H-1 receptors in satiety behavior. This second experiment will also measure food intake and satiety behavior. The rats will not be food deprived and will eat a palatable meal.

Methods

Animals

Twelve adult Sprague-Dawley male rats (250-350 g) were housed individually in conventional wire-mesh cages on a 12:12-h light/dark cycle. Rats had continuous access to pellet chow (Purina) and tap water (unless deprived during a test). The tap water was available through stainless steel spouts attached to two graduated glass cylinders mounted on the wall of the cage. All experimental protocols were reviewed and approved by the institutional animal care and use committee.

Experiment 1

Prior to testing each rat was weighed and the water bottles were removed from each cage. Subcutaneous injections of 0.9% NaCl, .625 mg/Kg histamine or 10 mg/Kg histamine were given. Histamine dosage was calculated based on concentrations necessary to elicit drinking behavior in rats. Threshold for affecting drinking behavior by shortening latency to drink is .625 mg/Kg histamine (Kraly and June, 1982). A large dose of 10mg/Kg is four times greater than the ED50 of histamine, yet is smaller than the debilitating dose of 20 mg/Kg (Kraly and June, 1982). A simple counterbalancing was used for drug dosage and for drug

versus vehicle. Half of the rats first received NaCl followed by one of the two doses of histamine. This was followed by another injection of NaCl and then a final injection of the other histamine dose. The other half of the rats received one of the two histamine doses, followed by NaCl, then the remaining histamine dose and finally another NaCl. Immediately following each injection a measured amount of 3 cookies (Nabisco Nilla Wafers) were placed in each cage. Rats were free to eat for 1 h. Behavior for each rat was observed and recorded every minute by an observer using pencil and paper. Behavioral measures included eating, exploring/rearing, grooming the face, grooming the body and resting. Satiety was measured by the latency to rest and the number of minutes spent grooming. After 1h. cookies were removed and total food intake was determined by measuring the remaining amount. Water was returned to the cage at the conclusion of each test, and tests were separated by at least 2 days.

A second set of tests was performed using the same experimental paradigm only with water availability during each test. The amount of water in the remaining water bottle was measured and drinking was used as a behavioral measure. Following the conclusion of testing, the total water intake was determined and the second water bottle was returned.

Experiment 2

Rats from experiment 1 were used in this test to further clarify the role of histamine in eating. Rats were housed as described in experiment 1. These rats were tested to examine the effects of the H-1 antagonist Dexbrompheniramine (DXB) on eating. DXB was chosen as the H-1 antagonist because of evidence citing its ability to inhibit drinking elicited by histamine (Kraly 1982). The 1 mg/Kg DXB dosage was chosen because it is the threshold dose to abolish histamine related drinking when combined with the H2 antagonist cimetidine (Kraly 1982).

Prior to testing rats were weighed. The amount of water in each bottle was measured. I.P. injections of 0.9% NaCl or DXB were given. These injections were followed 10 minutes later with subcutaneous injections of 0.9% NaCl or .625 mg/Kg histamine. The sequence of the testing was counterbalanced. In test 1, all rats received 0.9% NaCl. In test 2, half the rats received .625 mg/Kg histamine. They then received 1 mg/Kg DXB followed by .625 mg/Kg histamine in test 3. The other half of the rats received the reverse order of tests 2 and 3. In test 4, all rats received 0.9% NaCl. Immediately following the injection 3 cookies were weighed and placed in each cage. Rats fed freely for 1 h. Behavior was measured as described for experiment 1 every minute. After 1 h. cookies were removed and weighed; and total water intake was determined. Tests were separated by at least 2 days.

A second variation of this experiment was performed. The only difference was a change in the histamine dosage to 10 mg/Kg.

Data Analysis

Planned, within-group comparisons were made with a matched-pairs, two tailed t -test. α level was chosen as 0.05.

Results

Experiment 1

.625 mg/Kg histamine

Non food deprived rats without access to water ate a mean of 5.96 grams of cookie. Histamine failed to inhibit food intake; mean food intake was 5.98 g cookie following a .625 mg/Kg dose of histamine, $t(11)=0.04$, $p>.05$ (Figure 1). The .625 mg/Kg histamine dose also failed to shorten latency to rest and failed to increase the number of rests as an index of satiety (Table 1).

When water was available, non food deprived rats ate a mean of 5.67 g of cookies. Similar to the no water condition, histamine failed to significantly inhibit food intake; mean food intake was 4.96 g cookie following a .625 dose of histamine, $t(11)=-1.66$, $p>.05$ (Figure 1). The .625 mg/Kg histamine also failed to change latency to rest or number of rests (Table 1). The .625 mg/Kg histamine dose significantly increased water intake to 5.75 ml, which was almost double baseline (2.29 ml) for drinking, $t(11) = 4.47$, $p<.001$ (Figure 1).

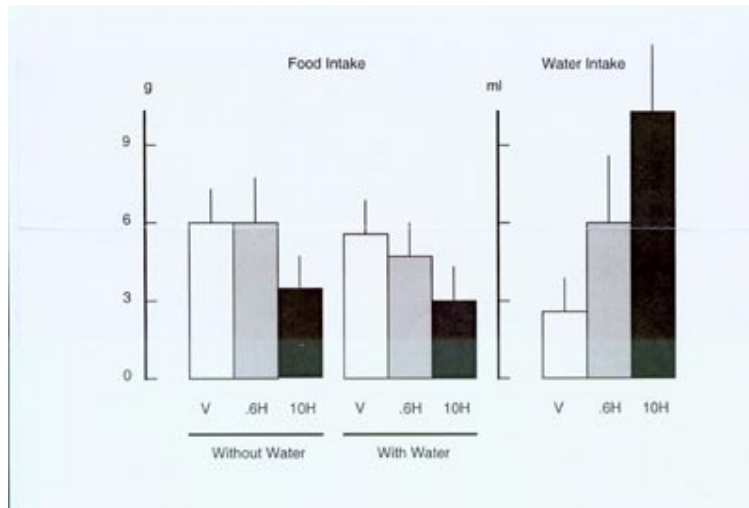


Figure 1. Mean 60-min food intake (g) in non-food deprived rats without water (left 3 bars), with water (middle 3 bars), and mean 60-min water intake (ml) after injections of SC 0.9% NaCl (vehicle, v), .625 mg/Kg histamine (.6H) or 10 mg/Kg histamine (10H). Vertical lines represent standard deviation.

10 mg/Kg histamine

In contrast, non food deprived rats without access to water administered 10 mg/Kg histamine showed inhibition of food intake; mean food intake was 3.35 g cookie following histamine, $t(11)=-5.53$, $p<.001$ (Figure 1). Despite the significant inhibition of food intake, the 10 mg/Kg histamine dose (as did the .625 mg/Kg histamine) failed to shorten latency to rest and failed to increase the number of rests used here as indexes of satiety (Table 1).

Similar to the non water condition, the 10 mg/Kg histamine dose inhibited food intake; mean food intake was 3.07 g cookie following histamine, $t(11)=7.16$, $p<.001$ (Figure 1). The 10 mg/Kg histamine also failed to change latency to rest or number of rests (Table 1). The 10 mg/Kg histamine dose significantly increased water intake to 10.67 ml, which was more than triple baseline (2.17 ml) for drinking, $t(11) = 8.57$, $p<.001$ (Figure 1).

| | NaCl | .625 mg/Kg histamine | 10 mg/Kg histamine |
|--|-------|----------------------|--------------------|
| Mean latency to rest without water (min) | 32.25 | 33.75 | 23.25 |
| Mean number of rests without water (min) | 23.36 | 23.92 | 27.17 |
| Mean latency to rest | 38.67 | 40.50 | 32.67 |

| | | | |
|---------------------------------------|-------|-------|-------|
| with water (min) | | | |
| Mean number of rests with water (min) | 16.33 | 16.42 | 17.92 |

Table 1. Effects of histamine on mean latency to rest and number of rests both with and without water.

Experiment 2

.625 mg/Kg histamine

Eating and Resting

Non food deprived rats with access to water ate a mean of 6.02 g cookie. The .625 mg/Kg histamine dose failed to inhibit food intake (as was seen in experiment one). Mean food intake was 6.40 g cookie following a .625 mg/Kg dose of histamine, $t(11)=0.04$, $p>.05$ (Figure 2). There was also no effect of an H-1 antagonist on eating behavior; mean food intake was 6.40 grams when a 1 mg/Kg DXB injection preceded a .625 mg/Kg histamine injection.

Despite histamine's failure to produce an effect on latency to rest, DXB given prior to histamine significantly shortened the latency to rest. The H-1 antagonist affected behavior caused by .625 mg/Kg histamine; shortening mean latency to rest from 50.25 minutes to 38.58 minutes, $t(11) = 3.00$, $p<.01$. There was no significant difference in latency to rest between baseline and the DXB prior to histamine condition (Table 2). There was no effect of histamine or DXB plus histamine on number of rests ($p>.05$).

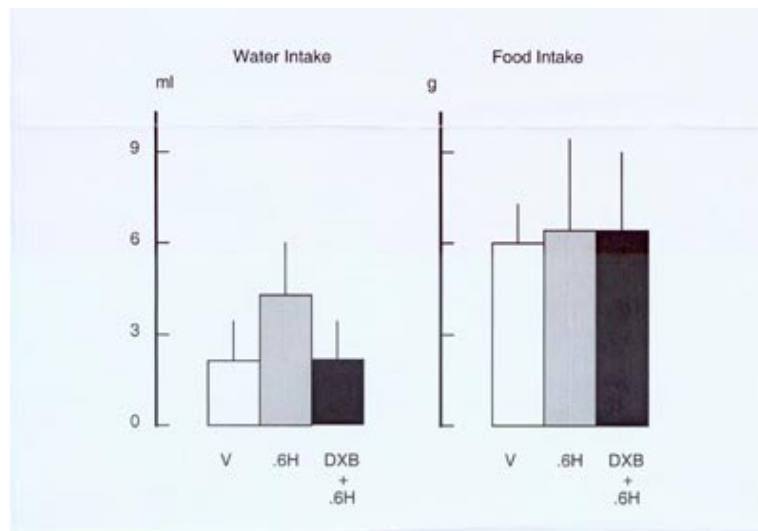


Figure 2. Mean 60-min water intake (ml) (left 3 bars) and mean 60-min food intake (g) (right 3 bars) after injections of 0.9% NaCl (vehicle, v), .625 mg/Kg histamine (.6H) or 1 mg/Kg DXB prior to .625 mg/Kg histamine (DXB + .6H). Vertical lines represent standard deviation.

| | NaCl | .625 mg/Kg histamine | DXB plus .625 mg/Kg histamine |
|----------------------------|-------|----------------------|-------------------------------|
| Mean latency to rest (min) | 44.21 | 50.25 | 38.58* |
| Mean number of | 12.75 | 5.75 | 8.67 |

| | | | |
|-------------|--|--|--|
| rests (min) | | | |
|-------------|--|--|--|

Table 2. Effects of .625 mg/Kg histamine and DXB prior to .625 mg/Kg histamine on mean latency to rest and number of rests.

Water Intake

As seen in experiment one, rats injected with .625 mg/Kg histamine showed increased water intake. Mean water intake was almost double baseline, increasing to 4.42 ml following histamine, $t(11)=5.20$, $p<.01$ (Figure 2). Injections of DXB before histamine inhibited histamine induced drinking, significantly reducing water intake to 2.25 ml water, $t(11) = 3.95$, $p<.01$.

10 mg/Kg histamine Eating and Resting

The 10 mg/Kg histamine dose inhibited food intake (as was seen in experiment one). Mean food intake decreased to 3.50g cookie following a 10 mg/Kg dose of histamine, $t(11)=5.47$, $p<.01$ (Figure 3). DXB had no effect on histamine's ability to alter eating. DXB plus 10 mg/Kg inhibited eating behavior from baseline, $t(11) = 2.77$, $p<.05$, which was similar to the effects on food intake when histamine was given alone.

Despite the inhibition of food intake, both the 10 mg/Kg histamine and the DXB plus histamine failed to shorten latency to rest and number of rests as an index of satiety, $p>.05$, (Table 3).

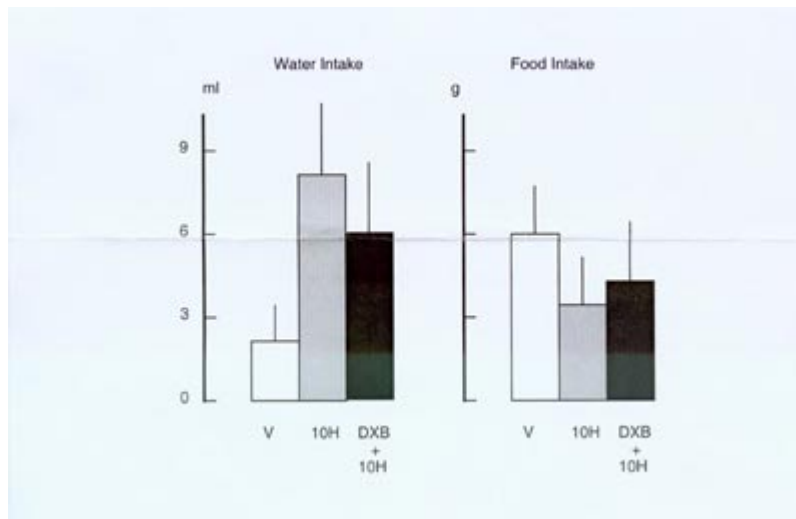


Figure 3. Mean 60-min water intake (ml) (left 3 bars) and mean 60-min food intake (g) (right 3 bars) after injections of 0.9% NaCl (vehicle, v), 10mg/Kg histamine (10 H) or 1mg/Kg DXB prior to 10 mg/Kg histamine (DXB + 10H). Vertical lines represent standard deviation.

| | NaCl | 10 mg/Kg histamine | DXB plus 10 mg/Kg histamine |
|----------------------------|-------|--------------------|-----------------------------|
| Mean latency to rest (min) | 41.50 | 32.42 | 34.08 |
| Mean number of rests (min) | 13.00 | 12.75 | 17.92 |

Table 3. Effects of 10 mg/Kg histamine and DXB prior to 10 mg/Kg histamine on mean latency to rest and number of rests.

Water Intake

As seen in experiment one, rats injected with 10 mg/Kg histamine showed increased water intake. Mean water intake increased from 2.17 ml to 8.25 ml following the 10 mg/Kg dose of histamine, $t(11)=10.93$, $p<.01$ (Figure 3). Injection of DXB prior to histamine failed to abolish histamine-induced drinking, but did significantly reduce it; mean water intake was 6.17 ml water, $t(11) = 2.93$, $p<.05$ (Figure 3).

Discussion

Relatively small doses (.625 mg/Kg) of histamine failed to affect food intake or postprandial satiety behavior, but did affect drinking behavior. Relatively large, pharmacological doses (10 mg/Kg) of histamine decreased food intake and increased water intake, but failed to alter several behavioral measures of satiety. The H-1 receptor antagonist DXB inhibited the histamine induced drinking, but had no effect on food intake or behavior.

In addition to measuring food intake in these experiments, behavior was observed for one hour following the feeding of cookies. One can examine behavior following a meal to determine if the rat is satiated. For example, the distinction between the inhibition of food intake and the appearance of satiety can be made by the appearance of a sequence of behaviors including grooming, exploring and culminating in resting (Antin et al., 1975). If the animal ceases eating without demonstrating the satiety sequence of behaviors, one must consider whether the animal has stopped eating due to illness or malaise, or due to the activation of endogenous satiety signals (Smith and Gibbs, 1979). Previous research studying the effects of histamine on eating has focused on the decrease of food intake without measuring indexes of postprandial satiety. This study examined both food intake and satiety after histamine injections to determine if the two were correlated. Satiety was quantified by measures of meal size, latency to rest and total time spent resting. When injected with histamine, regardless of dose, rats failed to demonstrate a change in the latency to rest measure or the total time spent resting. However, rats demonstrated a histamine-induced inhibition of eating after relatively large doses of 10 mg/Kg. Even though food intake was reduced, the failure of histamine to demonstrate a shorter latency to rest or an increased number of rests indicates satiety was unaffected by injection of histamine.

The 10 mg/Kg histamine dose had the effect of decreasing food intake, which is consistent with reports of exogenous histamine's ability to decrease eating (Orthen-Gambill 1987). Even though food intake decreased, rats failed to demonstrate a change in behavioral measures for satiety in the work reported here. The 10 mg/Kg dose increased water intake to almost four times greater than baseline (Figure 3), which was also consistent with previous reports (Kraly and June, 1982). Changes in food and water intake indicated that the histamine dose was large enough to be physiologically meaningful. Since histamine affected eating and drinking behaviors, but failed to alter satiety measures it may be concluded that there is a disassociation between histamine's ability to decrease food intake and its ability to initiate postprandial satiety. One explanation for this disassociation may be that the affect of pharmacological doses (10 mg/Kg) of histamine on food intake may be related to nonspecific deleterious side effects associated with such large dose.

The .625mg/Kg histamine dose increased drinking, but had no effect on food intake or satiety behavior (Figure 2). The dose was chosen because it is reported to be near the threshold for shortening the latency to drink (Kraly and June, 1982), and may therefore mimic a physiological level of histamine that follows eating. In this study, the .625 mg/Kg histamine dose increased drinking behavior showing that it was behaviorally effective. Since it failed to change food intake or satiety behavior, the results challenge the notion that endogenous histamine is involved in eating behavior. On the other hand, if endogenous histamine is involved with satiety, it may be that doses sufficient for activating drinking mechanisms are lower than the threshold for activating satiety mechanisms. However, even the 10 mg/Kg histamine dose,

which is four times greater than the ED50 for histamine induced drinking, failed to affect postprandial satiety. An alternative interpretation is that injection of exogenous histamine is an inadequate method for activating an endogenous histamine mechanism for postprandial satiety.

To further examine the role of endogenous histamine in satiety, experiment two examined the role of the H-1 receptor in eating behavior and satiety. The H-1 receptor has been implicated in playing a role in eating and drinking behavior. Administration of H-1 receptor antagonists decreases water intake in response to injections of exogenous histamine (Kraly, 1982; Gerald and Maickal, 1972). When the H-1 antagonist DXB was given prior to histamine injections results were consistent with previous research: DXB administered prior to histamine reduced histamine-induced water intake. This study showed that the DXB completely eliminated histamine induced drinking in the .625 mg/Kg histamine condition, and significantly reduced water intake in the 10 mg/Kg histamine condition (Figures 2 and 3).

In contrast to its effect of reducing histamine induced drinking, DXB prior to histamine failed to effect food intake. This appears inconsistent with the reports that i.c.v. administration of H-1 receptor antagonists increases food intake (Sakata et al., 1990). However, the experimental conditions differ between those experiments and this study. The earlier report used food-deprived rats eating chow, while this experiment used non-food deprived rats eating cookies. Experiment two demonstrated that food intake decreased as a result of a 10 mg/Kg histamine injection, but DXB was unable to reverse that effect. If blocking H-1 receptors fails to reverse the effects of histamine-induced reduction of food intake, then it further challenges the role of endogenous histamine's involvement in food intake and satiety. It may be that the large, pharmacological dose of histamine made the animal feel ill and therefore it ate less. The deleterious side effects are not necessarily related to the function of H-1 receptors.

Results from experiments 1 and 2 challenge the notion that endogenous histamine has a role in postprandial satiety. The .625 mg/Kg histamine dose may mimic an endogenous histamine level that is near the threshold for eliciting drinking. As would be predicted, the .625 mg/Kg dose was effective in altering drinking behavior, yet demonstrated no affect on eating or satiety behavior. This confirmed that the dosage was physiologically and behaviorally meaningful. It appears that increased levels of histamine that might mimic endogenous levels are not sufficient to affect eating behavior. The 10 mg/Kg histamine, a dose that is most certainly pharmacological (Kraly and Jones, 1998), decreased eating behavior, but still failed to alter satiety measures. This indicates that large exogenous levels of histamine are also insufficient to affect satiety, and that the decrease in food intake may simply have been related to nonspecific anorexic effects from such a large dose.

This work challenges the role of endogenous histamine in satiety for food. Previous research has looked mainly at pharmacological doses of histamine and has shown the effect of decreased food intake (Orthen-Gambill, 1987; Sakata et al., 1990). The work reported here confirms the reduced food intake resulting from large doses of histamine, but it is inconsistent with the notion that endogenous histamine contributes to satiety. Experiments one and two differed from previous reports in that they used non-food deprived animals eating cookies and employed a limited dose range for histamine and the H-1 antagonist. To further examine the role of endogenous histamine in satiety, future experiments should be performed in different conditions (e.g. different types of food; food deprivation) using a wide range of doses. Moreover, the roles of the H-2 and H-3 receptors need to be examined for their contribution to satiety. It may be that histamine can contribute to satiety behavior in different conditions through the use of different receptors.

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