Pharmacology Biochemistry & Behavior, Vol. 31, pp. 81–86. © Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

Antihistaminic Drugs Increase Feeding, While Histidine Suppresses Feeding in Rats

NILLA ORTHEN-GAMBILL

Tufts University, Research Building 490, Boston Ave., Medford, MA 02155

Received 1 July 1987

ORTHEN-GAMBILL, N. *Antihistaminic drugs increase feeding, while histidine suppresses feeding in rats.* PHARMACOL BIOCHEM BEHAV 31(1) 81–86, 1988.—The present studies tested the hypothesis that histamine blockade stimulates appetite, while increases in histamine levels suppress appetite. Results show that the classical antihistamines cyproheptadine and promethazine both produced significant and long-lasting increases in food intake. Pronounced appetite stimulation was also seen following the administration of doxepin, the most potent antihistamine among the antidepressants. In contrast, administration of the histamine precursor histidine produced a profound suppression in food intake. The results thus suggest that an inverse relationship may exist between histamine and food intake.

Antihistamines Histidine Histamine blockade Cyproheptadine Promethazine Doxepin
Feeding behavior Rats

THE clinical use of both antidepressant and antipsychotic drugs is frequently associated with appetite stimulation and unwanted weight gain [review (12)]. While weight gain is a common side effect of psychotherapeutic drug treatment, all antidepressants and neuroleptics are not equipotent in stimulating appetite. Among the neuroleptics, the phenothiazine derivative chlorpromazine (CPZ) possesses particularly potent weight-enhancing properties (2, 12, 15, 17, 18). Compared to other therapeutically equivalent drugs, CPZ produces 1.5–2 times greater weight gains (2), and this weight gain can be reversed by switching patients from CPZ to another neuroleptic agent.

Like the neuroleptics, all antidepressants are not equipotent in producing weight gain. Among the widely prescribed tricyclics, amitriptyline is particularly potent in stimulating appetite and weight gain (3, 5, 6, 20). Unwanted weight gain is thus seen across two different classes of psychotherapeutic drugs, but there is presently no unifying theory to account for the shared side effect.

Several lines of evidence suggest that the unwanted weight gain is not simply a function of clinical improvement. For example, significant weight gains have been noted in both drug responders and nonresponders given amitriptyline (14). Further, if drug treatment is continued after patients have recovered from depression, it can result in continued unwanted weight gain (20). It thus appears that the unwanted appetite stimulation is linked to some property of the drug itself, and is largely independent of clinical improvement.

An attempt to find a link between those antidepressants and neuroleptics which all produce weight gain reveals that they are all extremely potent antihistamines, i.e., they block histamine-1 receptors (10, 21–23). If one inspects the antihistaminic properties of a wide range of antidepressant and antipsychotic drugs, an interesting relationship emerges. Those agents which stimulate appetite also have very potent antihistaminic properties, while agents which do not stimulate appetite are very weak histamine (H) blockers. Richelson has tested the affinities of numerous psychotherapeutic agents for H-1 receptors, and based on his results, one can rank-order drugs according to their antihistaminic potency (21–23). For example, among the antidepressants, amitriptyline, which stimulates appetite, is 2000 times more potent as an H blocker than desipramine (22) which typically does not stimulate appetite. Similarly, among the neuroleptics, chlorpromazine, which increases appetite, is several hundred times more potent as an H blocker than haloperidol which is not associated with appetite stimulation and weight gain.

It thus seems possible that the antihistaminic properties of certain antidepressants and neuroleptics may mediate the weight gain seen with these drugs. The notion that H blockade may stimulate appetite is actually supported by research on regular (nonpsychiatric) antihistamines used in the treatment of allergies. For example, the commonly used antiallergy agent cyproheptadine which has potent antihistaminic (and antiserotonergic) properties, has been found to stimulate appetite both in patients with asthma, as well as in normal volunteers (16, 18, 30). Animal studies have also demonstrated the appetite-stimulating effects of cyproheptadine (4,7).

Based on the above information, the present studies were aimed at testing the hypothesis that drugs which have potent antihistaminic properties will all produce increases in food intake in rats. Specific test drugs included the two "classical" antihistamines cyproheptadine and promethazine, as

well as the antidepressant doxepin which is the most potent antihistamine among the tricyclics. The expectation was that all these agents would produce increases in food intake. A second hypothesis to be tested concerned the effects of increasing central H levels. If H blockade can stimulate appetite, it was thought that the opposite condition, i.e., an increase in H levels, could perhaps inhibit food intake. The test agent in this case was histidine which is the precursor of histamine. Previous research has shown that peripheral administration of histidine can significantly increase central H levels (28). The expectation was that histidine administration would lead to decreases in food intake.

GENERAL METHOD

Animals and Diets

The subjects in all experiments were male Sprague-Dawley rats (CD-outbred, Charles River Laboratories, Wilmington, MA), weighing 300–325 g at the beginning of the experiment. All animals were housed individually in standard laboratory cages, in a temperature-controlled room (21°C), with a 12-12 hr reversed light-dark cycle (lights off: 1000–2200 hr).

All animals were maintained on ad lib feeding schedules, and given either ground Purina Chow No. 5001 (Experiments 1 and 5), or a palatable liquid diet (Experiments 2, 3, and 4) 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). In all experiments, animals also had ad lib access to water.

Procedure

All studies involved a within-subject design, and each study contained 7–10 subjects. On the day before each drug injection, each rat received an intraperitoneal (IP) injection of distilled water (control), and cumulative food intake (FI) was then measured at fixed intervals postinjection. On drug days, each rat received an IP injection of active agent, and cumulative FI was 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 different drug doses were tested in decreasing order of magnitude. Specific details for each experiment were as follows:

Experiment 1 (n=8) investigated the effects of the antiallergy agent cyproheptadine hydrochloride monohydrate (CYP) on Purina Chow intakes. The drug was generously donated by Merck Sharp & Dohme Research Laboratories. CYP was dissolved in distilled water and tested at 3 dose levels: 1.25, 2.5, and 5.0 mg/kg. Food and water intakes were measured at 2, 4, and 24 hr postinjection.

Experiment 2 (n=10) tested the effects of 0.625 and 1.25 mg/kg CYP on liquid diet intakes. As antihistaminic drugs are known to produce dry mouth, the switch from a dry to a liquid diet was designed to counteract possible confounding effects of decreased salivation. Food and water intakes were measured at 1, 2, 4, 6, and 24 hr postinjection.

Experiment 3 (n=10) investigated the effects of the antiallergy agent promethazine hydrochloride (PRO) (Wyeth Laboratories) on liquid diet intakes. The drug was dissolved in distilled water, and test doses included 0.5 and 1.0 mg/kg. Food and water intakes were measured at 1, 2, 4, 6, and 24 hr postinjection.

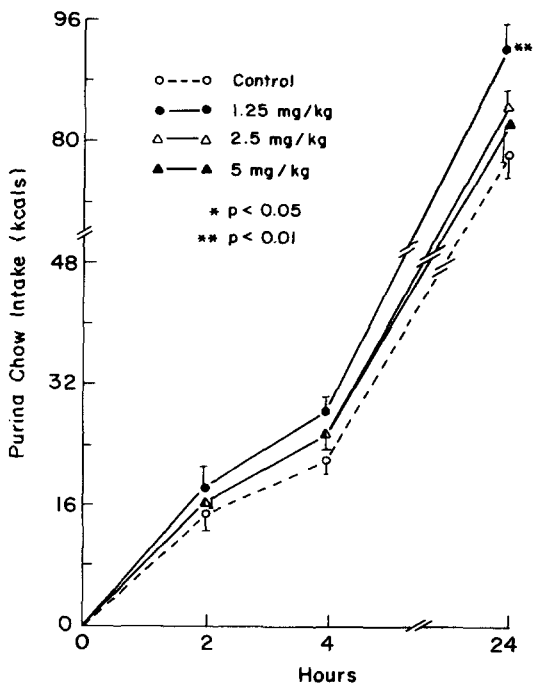

FIG. 1. Cumulative Purina Chow intakes (kcal) at 2, 4, and 24 hr following the administration of 0, 1.25, 2.5, and 5.0 mg/kg of cyproheptadine. *Significantly different from control values, based on the Newman-Keuls test.

Experiment 4 (n=8) tested the effects of the antidepressant doxepin hydrochloride (DOX) (generously donated by Pfizer Pharmaceuticals) on liquid diet intakes. DOX is the most potent histamine blocker among the antidepressants (26). The drug was dissolved in distilled water, and test doses included 3 and 15 mg/kg. Food intakes were measured at 1, 2, 4, 8, and 24 hr postinjection.

Experiment 5 (n=7) investigated the effects of L-histidine (Sigma Chemical), the amino acid precursor of histamine, on Purina Chow intakes. A dose of 500 mg/kg of histidine was used, as previous research (28) has demonstrated that this dose is most effective in elevating central histamine levels. Histidine was dissolved in distilled water, and food intakes were measured at 1, 3, and 6 hr postinjection.

Data Analysis

In each experiment the control data represent a mean of several control injections which were not significantly different from each other. In all studies, food intake data represent cumulative intakes measured at fixed intervals postinjection. At each time point, cumulative food intakes for drug and control injections were compared using one-way analyses of variance for repeated measures. In appropriate instances, the ANOVAs were followed by Newman-Keuls multiple comparison tests. An asterisk in the figures denotes that food intake was significantly different from control values.

RESULTS

Experiment 1—Acute Effects of Cyproheptadine on Purina Chow Intakes

As can be seen from Fig. 1, a reversed dose-response

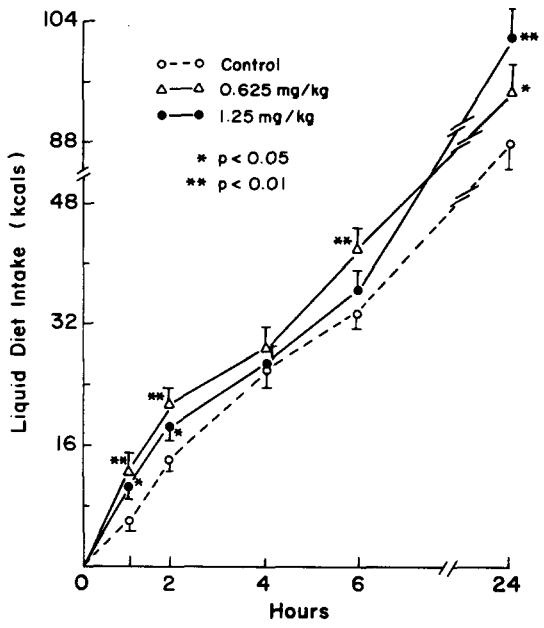

FIG. 2. Cumulative intakes of liquid diet (kcal) at 1, 2, 4, 6, and 24 hr following the administration of 0, 0.625, and 1.25 mg/kg of cyproheptadine. *Significantly different from control values, based on the Newman-Keuls test.

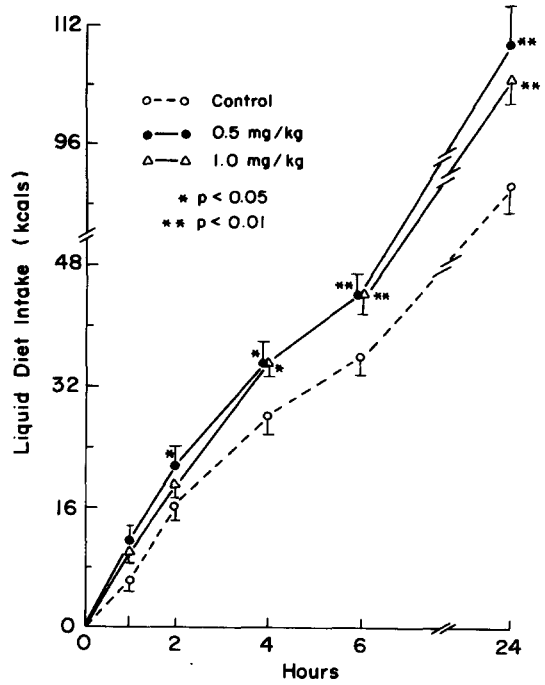

FIG. 3. Cumulative intakes of liquid diet (kcal) at 1, 2, 4, 6, and 24 hr following the administration of 0, 0.5, and 1.0 mg/kg of promethazine. *Significantly different from control values, based on the Newman-Keuls test.

curve was obtained for the 3 tested doses of CYP, i.e., the lowest dose of the drug produced the greatest stimulation of food intake. The drug-induced increase in Purina Chow intakes was significant at 24 hr postinjection, $F(3,21)=6.02$, $p<0.004$. Multiple comparison tests revealed that food intakes following the lowest dose of CYP (1.25 mg/kg) were significantly higher than control values at 24 hr postinjection. While the other tested doses of CYP also produced slight elevations in food intake, these differences did not reach statistical significance. Water intakes were not affected by drug administration.

Experiment 2—Acute Effects of Cyproheptadine on Liquid Diet Intakes

As can be seen from Fig. 2, both doses of CYP produced significant increases in liquid diet intakes, both at the beginning and end of the test period. ANOVAs for each time point revealed significant differences at 1 hr, $F(2,18)=5.8$, $p<0.011$, 2 hr $F(2,18)=6.93$, $p<0.006$, 6 hr, $F(2,18)=9.33$, $p<0.002$, and 24 hr postinjection, $F(2,18)=9.55$, $p<0.001$. Multiple comparison tests revealed that the 0.625 mg/kg dose of CYP produced significant appetite stimulation at 1, 2, 6, and 24 hr postinjection, while the 1.25 mg/kg dose of CYP led to significant increases in food intake at 1, 2, and 24 hr postinjection. Water intake was not affected by drug administration.

Experiment 3—Acute Effects of Promethazine on Liquid Diet Intakes

As can be seen from Fig. 3, both doses of PRO produced long-lasting increases in liquid diet intakes. ANOVAs for each time point showed significant drug effects at 2 hr, $F(2,18)=3.88$, $p<0.04$, 4 hr, $F(2,18)=7.71$, $p<0.004$, 6 hr, $F(2,18)=8.08$, $p<0.003$, and 24 hr postinjection, $F(2,18)=18.25$; $p<0.0001$. Multiple comparison tests revealed that the lower dose of PRO (0.5 mg/kg) produced significant elevations in food intake at 2, 4, 6, and 24 hr postinjection, while the higher dose (1.0 mg/kg) significantly elevated food intake at 4, 6, and 24 hr postinjection. Water intake was not affected by drug administration.

Experiment 4—Acute Effects of Doxepin on Liquid Diet Intakes

As can be seen from Fig. 4, both doses of doxepin produced appetite stimulation, particularly towards the end of the test period. ANOVAs for each time point showed that drug effects were significant at 8 hr, $F(2,14)=4.31$, $p<0.035$, and 24 hr postinjection, $F(2,14)=26.42$, $p<0.0001$. Multiple comparison tests revealed that both doses of DOX produced significant increases in liquid diet intakes at 8 and 24 hr postinjection. The increase in food intake following the lower dose of DOX (3 mg/kg) was particularly striking at 24 hr, as animals consumed nearly twice as many calories as they did following control injections.

Experiment 5—Acute Effects of Histidine on Purina Chow Intakes

As can be seen from Fig. 5, histidine administration produced a pronounced suppression in food intake throughout the test period. More specifically, Purina Chow intakes were significantly suppressed at 1 hr, $F(1,6)=11.39$, $p<0.015$, 3 hr, $F(1,6)=13.76$, $p<0.01$, and 6 hr postinjection, $F(1,6)=21.8$, $p<0.003$.

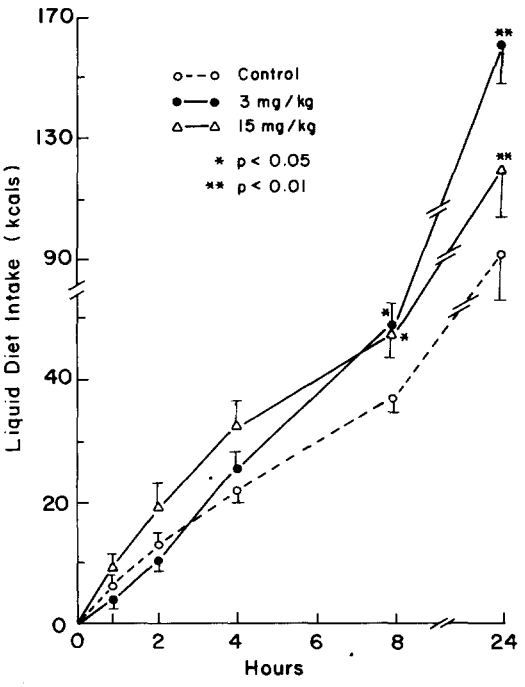

FIG. 4. Cumulative intakes of liquid diet (kcal) at 1, 2, 4, 8, and 24 hr following the administration of 0, 3, and 15 mg/kg of doxepin. *Significantly different from control values, based on the Newman-Keuls test.

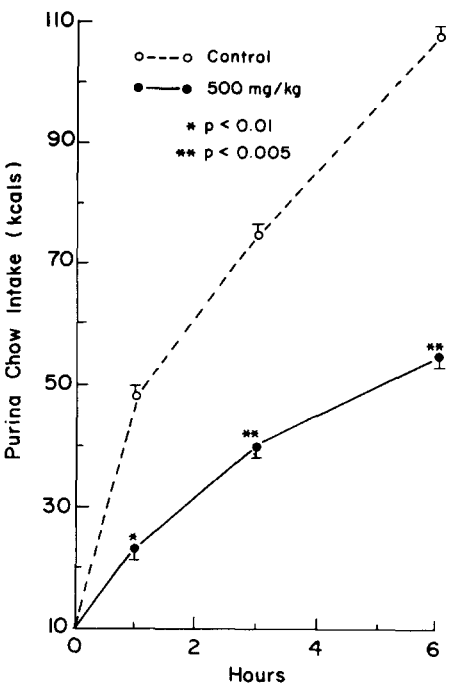

FIG. 5. Cumulative Purina Chow intakes (kcal) at 1, 3, and 6 hr following the administration of 0 and 500 mg/kg of histidine. *Significantly different from control values.

DISCUSSION

To summarize the main research findings, all 3 test drugs with potent antihistaminic properties (i.e., cyproheptadine, promethazine, and doxepin) produced significant increases in food intake, while a pronounced decrease in food intake was observed following histidine administration. The results thus support the hypothesis that histamine (H) blockade is associated with appetite stimulation, while increased H levels are associated with appetite suppression.

The basis for the above hypothesis came from clinical reports showing unwanted weight gain with the use of certain antidepressants and neuroleptics. As mentioned before, all these appetite-stimulating drugs are also very potent H blockers. On the other hand, therapeutically similar drugs which do not stimulate appetite are very weak H blockers. It thus seemed possible that the antihistaminic properties of certain psychotherapeutic drugs may mediate the unwanted weight gain seen with these drugs. Since the appetite-stimulating antidepressants and neuroleptics have other major neurochemical effects in addition to H blockade, initial experiments were done using "classical" antihistamines.

The first two experiments showed that the "classical" (nonpsychiatric) antihistamine cyproheptadine produced significant and long-lasting increases in food intake. While some appetite stimulation was observed with Purina Chow, the effect was much more pronounced with the liquid diet. Since antihistaminic drugs are known to cause dry mouth (22), this side effect might have affected the animals' willingness to eat dry, powdered chow, which could have created a misleading experimental artifact. The use of a liquid diet circumvented possible problems linked to decreased salivation, and thus appeared to be a better choice in studies testing antihistaminic drugs. The liquid diet is also more palatable than chow, which may provide a better parallel to clinical studies where patients are typically found to overindulge on highly palatable (and often sweet) foods. In the present studies, animals always had simultaneous access to water, as well as the liquid diet, so they did not have to consume the liquid diet as a source of fluid. The results suggest that antihistaminic drugs do not directly affect fluid intake, as water intakes were not altered by drug administration in either diet condition.

While cyproheptadine is the most potent H blocker among the classical antihistamines, it also has potent antiserotonergic properties which may have contributed to the observed effects. It was thus important to test a regular antihistamine without the antiserotonergic properties of cyproheptadine. Promethazine was chosen for this purpose, and the results show that food intakes were significantly increased throughout the 24-hour test period. It thus appears that serotonin blockade is not a crucial factor in the appetite stimulation seen with regular antihistamines.

The experiments with cyproheptadine and promethazine also demonstrate that very small drug doses are needed to produce appetite stimulation. In fact, the results indicate a reversed dose-response curve, i.e., the smaller the dose, the greater the stimulation of food intake. Previous (unpublished) studies in this laboratory had shown that no appetite stimulation was produced by high doses of cyproheptadine, and significant increases in food intake only occurred when the drug dose was systematically lowered. As antihistaminic drugs are known to cause sedation (22), this side effect might mask any possible appetite-stimulating effects of higher drug doses. The very low doses used in the present studies cause

minimal sedation, which may have allowed the appetite-stimulating effects of the drug to be revealed.

Once appetite-stimulation had been demonstrated with classical antihistamines, the next experimental step was to test an antidepressant which is also a potent histamine blocker. Doxepin is the most potent antihistamine among the tricyclics, and according to the hypothesis, it was expected to produce appetite stimulation. As the results of Experiment 4 indicate, doxepin produced significant and long-lasting increases in food intake, which mirrors clinical findings concerning antihistaminic antidepressants. Of course antidepressants like doxepin also have other major neurochemical effects in addition to their antihistaminic properties, and these other effects could also contribute to the observed appetite stimulation. More specifically, acute neurotransmitter changes produced by tricyclic antidepressants include reuptake blockade of norepinephrine and/or serotonin [e.g., (29)]. It is unlikely, however, that reuptake blockade is responsible for the appetite stimulation seen with certain antidepressants. Several antidepressants share very similar effects on reuptake blockade, and yet only some of them produce appetite stimulation. For example, the commonly used tricyclics amitriptyline and desipramine both block norepinephrine reuptake. In fact, desipramine is more potent than amitriptyline at blocking norepinephrine reuptake (24), and yet only amitriptyline is clinically associated with weight gain. With regard to the present studies, doxepin is also less potent than desipramine at blocking norepinephrine reuptake (24), but doxepin still produced significant appetite stimulation. With regard to desipramine, other animal studies (19) have shown that this antidepressant does not stimulate appetite. In the present context it is also of interest to note that desipramine is one of the weakest histamine blockers among the antidepressants [e.g., (24)]. Although clinical improvement with antidepressants may well be linked to norepinephrine reuptake blockade, it appears that drug-induced weight gain is not directly related to this neurochemical change. As mentioned above, the most striking common feature between the appetite-stimulating antidepressant agents is their potent antihistaminic effect. As this antihistaminic feature is also shared by appetite-stimulating neuroleptics, it will be of interest to test the appetite-stimulating effects of such agents in rats. If neuroleptics with potent antihistaminic properties also produce increases in food intake in rats, such results would greatly strengthen the present theory.

While the antidepressant amitriptyline (AMI) was not tested in the present studies, it should be noted that a certain paradox exists with regard to the effects of AMI on food intake. As mentioned earlier, AMI is frequently associated with appetite stimulation and weight gain in humans. As AMI is also a very potent antihistamine, the clinical findings support the present theory of a possible link between histamine blockade and appetite stimulation. However, animal studies with AMI typically fail to show increases in food intake following AMI administration [e.g., (19)]. Such negative findings are of course problematic for the present theory, but certain methodological considerations may be important. We have just completed two studies with AMI (manuscript in preparation) and our results do in fact show that AMI can produce appetite stimulation in rats. The crucial factor appears to be dose, i.e., appetite stimulation only occurs at extremely low doses. Like others [e.g., (19)], we failed to see increases in food intake with typically used doses of AMI, but when the dose was systematically reduced to very low levels, significant appetite stimulation did indeed occur. Under certain conditions, AMI can thus produce increases in food intake, which of course supports the hypothesis presented in this paper.

While the main hypothesis concerned the possible link between histamine (H) blockade and appetite stimulation, it was also of interest to explore the opposite condition, i.e., a possible link between increased H levels and appetite suppression. As H does not cross the blood-brain barrier, peripheral administration of H itself is not effective in elevating central H levels. However, other research (28) has shown that central H levels can be increased through peripheral administration of the H precursor histidine. Experiment 5 thus tested the effects of histidine administration on food intake. A dose of 500 mg/kg of histidine was chosen as the test dose, since other research (28) has shown that this particular dose is most effective in elevating central H levels. The results clearly indicate that food intake was significantly suppressed throughout the entire test period, which supports the hypothesis of a possible link between H stimulation and appetite suppression. This finding is in agreement with the results of other researchers (25) who also found that peripheral administration of histidine, at the same dose level as used in the present studies, produced a decrease in food intake. Further, these investigators (25) also showed that the observed suppression in food intake was associated with significant increases in central H levels. Since the present study did not include direct measures of central H levels, one should of course be careful about concluding that the histidine-induced appetite suppression was a result of increased central H levels. Histidine may also suppress feeding through peripheral effects, and studies are now in progress to address this point.

Although very little is presently known about the role of H in neural functioning and behavior, the amine is considered a putative neurotransmitter which has been clearly localized in the brain (26, 27, 30). With regard to possible effects on feeding behavior, it is of interest to note that the highest concentrations of H are found in the hypothalamus (1,25) which has traditionally been thought to play a crucial role in the central regulation of feeding behavior [e.g., reviews (9,11)].

The role of H in food intake has been directly tested by injecting the amine into the lateral ventricle of cats (8). The intraventricular injections of H produced a profound and long-lasting suppression in feeding behavior, without causing any other notable deficits in behavior. Further, the suppressive action of H on food intake could be blocked by pretreatment with antihistamines. These data on central H administration fit nicely with the present findings on peripheral histidine administration, as the two procedures stimulate H activity in different ways, with both leading to pronounced appetite suppression. Based on these data, one could speculate that H may normally play an inhibitory role in appetite regulation. In support of this idea, it can be noted that the highest concentration of H is found in the ventromedial nucleus of the hypothalamus (VMH) (1,25), an area traditionally thought to play an inhibitory role in feeding behavior (9,11). Further, central administration of H has an excitatory effect on VMH neurons (27). If one accepts the possibility that H may normally inhibit food intake, then it would not be surprising to observe that blockade of H, as produced by antihistaminic drugs, can lead to increases in food intake, presumably because of drug-induced disinhibition of feeding. In other words, the appetite stimulation observed in the

present studies with the classical antihistamines as well as the antihistaminic tricyclic may occur because these agents can block the inhibitory effect H may normally play in feeding behavior.

In summary, the present results suggest that there may be an inverse relationship between H and food intake, such that H blockade is associated with appetite stimulation, while increased H levels are associated with appetite suppression.

ACKNOWLEDGEMENTS

The author would like to thank Holly Dushkin and Melinda Salomon for their expert help in conducting the experiments and analyzing the results. This research was supported in part by National Institute of Neurological and Communicative Disorders and Stroke, grant number NS 22591-01 BPO.

REFERENCES

1. Adam, H. M.; Hye, H. K. A. Concentrations of histamine in different parts of brain and hypophysis of cat, and its modification by drugs. Br. J. Pharmacol. Chemother. 28:137–152; 1966.
2. Amdisen, A. Drug-produced obesity: experiences with chlorpromazine, perphenazine, and clopenthixol. Dan. Med. Bull. 11(6):182–189; 1964.
3. Arenillas, L. Amitriptyline and body weight. Lancet February 22:432–433; 1964.
4. Baxter, M. G.; Miller, A. A.; Soroko, F. E. The effect of cyproheptadine on food consumption in the fasted rat. Br. J. Pharmacol. 39:229p; 1970.
5. Blackwell, B. Adverse effects of antidepressant drugs: Part 1: Monoamine oxidase inhibitors and tricyclics. Drugs 21:201–219; 1981.
6. Brown, J. H. Amitriptyline and excessive appetite. Can. Med. Assoc. J. 97:1361; 1967.
7. Chakrabarty, A. S.; Pillai, R. V.; Anand, B. K.; Singh, B. Effect of cyproheptadine on the electrical activity on the hypothalamic feeding centres. Brain Res. 6:561–569; 1967.
8. Clineschmidt, B. V.; Lotti, V. J. Histamine: Intraventricular injection suppresses ingestive behavior of the cat. Arch. Int. Pharmacodyn. 206:288–298; 1973.
9. Grossman, S. The neuroanatomy of eating and drinking behavior. In: Krieger, D. T.; Hughes, J. C., eds. Neuroendocrinology. Sunderland, MA: Sinauer Associates; 1980:131–140.
10. Hall, H.; Ogren, S-E. Effects of antidepressant drugs on histamine-h1 receptors in the brain. Life Sci. 34:597–605; 1984.
11. Hernandes, L.; Hoebel, B. G. Basic mechanisms of feeding and weight regulation. In: Stunkard, A. J., ed. Obesity. Philadelphia: W. B. Saunders Company; 1980:25–47.
12. Kalucy, R. S. Drug-induced weight gain. Drugs 19:268–278; 1980.
13. Klett, C. J.; Caffey, E. M. Weight changes during treatment with phenothiazine derivatives. J. Neuropsychiatry 2(2):102–108; 1960.
14. Kupfer, D. J.; Coble, P. A.; Rubinstein, D. Changes in weight during treatment for depression. Psychosom. Med. 41(7):535–544; 1979.
15. Lassenius, B.; Osterman, E. Complications following prolonged treatment with chlorpromazine. Nord. Med. 55(23):798–801; 1956.
16. Lavenstein, A. F.; Dacaney, E. P.; Lasagna, L.; Van Metre, T. E. Effect of cyproheptadine on asthmatic children. JAMA 180(11):912–916; 1962.
17. Mefferd, R. B.; Labrosse, E. H.; Gawienowski, A. M.; Williams, R. J. Influence of chlorpromazine on certain biochemical variables of chronic male schizophrenics. J. Nerv. Ment. Dis. 127:167–179; 1958.
18. Noble, R. E. Effect of cyproheptadine on appetite and weight gain in adults. JAMA 209(13):2054–2055; 1969.
19. Nobrega, J. N.; Coscina, D. V. Effects of chronic antidepressant treatment on feeding behavior in rats. In: Hoebel, B. G.; Novin, D., eds. The neural basis of feeding and reward. Brunswick, ME: Haer Institute for Electrophysiological Research; 1982: 525–534.
20. Paykel, E. S.; Mueller, P. S.; De La Vergne, P. M. Amitriptyline, weight gain, and carbohydrate craving: a side effect. Br. J. Psychiatry 123:501–507; 1973.
21. Richelson, E. Tricyclic antidepressants and neurotransmitter receptors. Psychiatr. Ann. 9:186–194; 1979.
22. Richelson, E. Tricyclic antidepressants: interactions with histamine and muscarinic acetylcholine receptors. In: Enna, S., ed. Antidepressants: Neurochemical, behavioral, and clinical perspectives. New York: Raven Press; 1981:53–73.
23. Richelson, E. Pharmacology of antidepressants in use in the United States. J. Clin. Psychiatry 43(11):4–11; 1982.
24. Richelson, E.; Pfenning, M. Blockade by antidepressants and related compounds of biogenic amine uptake into rat brain synaptosomes: most antidepressants selectively block norepinephrine uptake. Eur. J. Pharmacol. 104:277–286; 1984.
25. Scheiner, J. B.; Morris, P.; Anderson, H. Food intake suppression by histidine. Pharmacol. Biochem. Behav. 23:721–726; 1985.
26. Schwartz, J-C. Minireview: histamine as a transmitter in the brain. Life Sci. 17:503–518; 1975.
27. Schwartz, J-C. Histaminergic mechanisms in the brain. Annu. Rev. Pharmacol. Toxicol. 17:325–339; 1977.
28. Schwartz, J-C.; Lampart, C.; Rose, C. Histamine formation in rat brain in vivo: effects of histidine loads. J. Neurochem. 19:801–810; 1972.
29. Silverstone, T.; Schuyler, D. The effects of cyproheptadine on hunger, calorie intake, and body weight in man. Psychopharmacologia 40:335–340; 1975.
30. Taylor, K. M.; Feller, E. G.; Snyder, S. H. Regional localization of histamine and histidine in the brain of the rhesus monkey. Brain Res. 41:171–179; 1972.