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The Blockade of H_1 Receptors Attenuates the Suppression of Feeding and Diuresis Induced by Inhibition of Histamine Catabolism

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LECKLIN, L. AND L. TUOMISTO. *The blockade of H_1 receptors attenuates the suppression of feeding and diuresis induced by inhibition of histamine catabolism*. PHARMACOL BIOCHEM BEHAV **59**(3) 753–758, 1998.—Metoprine elevates brain histamine content by blocking the conversion of histamine to methylhistamine. It suppresses food intake, increases water intake, and induces diuresis in rats. In the present experiment, to study which receptors were involved in these metoprine-induced changes, H_1, H_2, and H_3 receptor blockers were administered to metoprine (10 mg/kg IP)-treated rats. The food and water consumption and urine excretion were measured at 10 and 24 h after the drug administration. It was found that systemic administration of the H_3 receptor antagonist, thioperamide (5 mg/kg IP), supplemented the feeding suppressive effect of metoprine. In addition to this, the H_1 receptor antagonist mepyramine (20 mg/kg IP) antagonized the suppression of feeding in metoprine-treated rats, whereas the H_2 receptor antagonist, ranitidine (100 mg/kg IP), had no effect. Mepyramine also decreased the diuretic response to metoprine, whereas ranitidine or thioperamide were virtually without effect. The present results show that elevation of brain histamine content by inhibiting the catabolism of histamine suppresses food intake, and this effect of metoprine can be abolished by pretreatment with antihistamines. Although the blockade of H_1 receptors also attenuates the diuretic response to metoprine, further studies are needed to understand the mechanisms that mediate the effects of metoprine on water balance. © 1998 Elsevier Science Inc.

Antihistamines Feeding behavior Histamine H_1 receptors Metoprine Rats Thioperamide

IN 1973, Clineschmidt and Lotti (3) first reported that histamine plays a suppressive role in feeding behavior in cats, and since then the role of neuronal histamine in the regulation of appetite control has been a matter of major research interest. Histamine, when infused into the third cerebroventricle (ICV), has been found to suppress feeding not only in cats but also in rats (17) and goats (30). Histidine, a brain-penetrating precursor of histamine, has a similar feeding suppressive effect after systemic administration (19,26). On the other hand, H_1 receptor blockers have been reported to elicit feeding when they are infused into the third cerebroventricle (4,6,22,23) or into the hypothalamic areas involved in the integration of satiety signals, i.e., ventromedial hypothalamus (VMH) or paraventricular nucleus (PVN) (18,23). H_1 receptor blockers do not, however, stimulate feeding when administered into lateral hypothalamus or other hypothalamic nuclei (18,23). Based on these findings it has been suggested that endogenous histamine acts as a satiety modulating agent in the VMH, and it controls feeding behavior through H_1 receptors (18).

Elevation of endogenous histamine levels by inhibiting the catabolism of histamine by metoprine has been shown to suppress food intake (14,15) in a way similar to exogenously applied histamine (3,17). Metoprine is a histamine-*N*-methyltransferase inhibitor, which blocks the conversion of histamine to methylhistamine (8). Due to the high liposolubility of the compound and its good penetration into the brain, metoprine after its systemic administration causes a long-lasting increase in the brain histamine content (5,31). In addition to its effects on feeding, metoprine increases water intake and induces diuresis (13). In an attempt to characterize the pharmacology of these phenomena, the present study examined whether systemically administered H_1 or H_2 receptor blockers antagonize the metoprine-induced changes in food intake and water balance. Because metoprine may also cause changes that are not related to elevated brain histamine levels (29),

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the effect of the H_3 receptor antagonist, which increases the release and synthesis of endogenous histamine, on metoprine-induced changes was also studied.

METHOD

Animals

Male Wistar rats weighing 298 ± 24 g were used. The rats were kept in plastic metabolic cages (Tecniplast® 1700), where they had free access to tap water and powdered R36 chow (Finnewos Aqua Oy, Turku, Finland). The animal room was artificially illuminated with a 14 L:10 D cycle (lights on from 0700–2100 h). The ambient temperature was 20 ± 1°C and relative air humidity 50 ± 10%. The experimental protocol was approved by the local committee for animal experimentation.

Experimental Design

The rats received an IP injection of metoprine at a dose of 10 mg/kg or vehicle just before the start of the dark phase. The other drugs administered (all IP) were mepyramine 5, 10, or 20 mg/kg, ranitidine 100 mg/kg, or thioperamide 5 mg/kg with saline as control. Because mepyramine has a relatively short duration of action compared to the other drugs used, the dose 20 mg/kg of mepyramine was given in two parts: half the dose being administered at the same time with metoprine, and the rest of the dose 6 h later to ensure a blockade of the H_1 receptors, especially during the dark phase of the diurnal cycle when the rats ingest the majority of their daily food and water intake and are generally more active. All injections were given in a volume of 1 ml/kg body weight. Food and water intake and urine flow were measured 10 h and 24 h after metoprine administration.

Drugs

The H_1 receptor blocker, mepyramine maleate, was purchased from Sigma Chemical Co. (St. Louis, MO) and the H_3 blocker, thioperamide maleate, from Research Biochemicals International (USA). The H_2 blocker, ranitidine hydrochloride, was a gift from Orion Corporation (Helsinki, Finland) and metoprine from Dr J. Duch from the Wellcome Research Laboratories. Metoprine was dissolved in a minimal quantity of 10% lactic acid and diluted with 0.9% saline to a final concentration of 10 mg/ml. All the other drugs were dissolved in saline. The doses are expressed as the free base.

Calculations and Statistical Analyses

Food and water intake and urine volume were calculated per rat body weight per hour and then the group means ± SEM were calculated. The statistical differences between groups were analyzed using one-way analysis of variance followed by the post hoc comparisons with the test of Duncan. When the presumptions of the one-way analysis of variance were not fulfilled, the nonparametric Mann–Whitney *U*-test was used.

RESULTS

Metoprine treatment suppressed feeding throughout the 24-h observation period. Food intake in metoprine-treated rats was approximately 50% that of controls during 10-h dark, $F(12, 87) = 15.4$, $p < 0.01$, and 14-h light phases, $F(12, 87) = 15.7$; $p < 0.01$, of the experiment, and therefore a significant decrease in 24-h food consumption was also detected in metoprine-treated rats, $F(12, 87) = 36.0$, $p < 0.01$ (Figs. 1 and 2). The H_1 receptor blocker mepyramine at the dose of 5 mg/kg had no effect on metoprine-induced decrease in food consumption (data not shown here), but the higher doses tended to attenuate the suppression of feeding. The dose 20 mg/kg of mepyramine significantly increased 24-h food intake in metoprine-treated rats, $F(12, 87) = 36.0$, $p < 0.01$ (Fig. 1). The blockade of H_1 receptors itself after injection of 10 mg/kg mepyramine caused no changes in feeding behavior. The higher mepyramine dose markedly decreased food intake during the dark period, $F(12, 87) = 15.4$, $p < 0.05$, and increased it during the light hours, $F(12, 87) = 15.7$, $p < 0.05$, but total 24-h food intake remained unchanged. The H_2 receptor blocker, ranitidine, also decreased food consumption during the dark hours of the experiment, $F(12, 87) = 15.4$, $p < 0.05$. Total 24-h food intake in ranitidine-treated rats did not differ from that of the controls (Fig. 1). The H_3 receptor blocker, thioperamide, supplemented the feeding suppressive effect of metoprine. After combined treatment with metoprine and thioperamide, statistically significant decreases in the food consumption during the light hours, $F(12, 87) = 15.7$, $p < 0.05$, as well as in the total 24-h food consumption, $F(12, 86) = 36.0$, $p < 0.01$, compared to metoprine-treated rats were observed (Fig. 2).

Metoprine treatment more than doubled urine volume during the first 10-h dark period of the experiment ($p < 0.01$) (Tables 1 and 2). It tended to increase water consumption especially during the dark period, but the changes were not as pronounced as those seen with urine excretion. Although the H_1 receptor blocker mepyramine at the dose of 20 mg/kg IP increased water consumption ($p < 0.01$), it decreased the diuresis induced by metoprine ($p < 0.05$). It caused no change in water consumption in metoprine-treated rats (Table 1). The H_2 receptor blocker ranitidine alone or combined with metoprine caused no significant changes in water consumption or urine volume (Table 1). The blockade of H_3 receptors by thioperamide did not influence water intake or urine flow in vehicle or metoprine rats (Table 2).

DISCUSSION

The present study shows that metoprine, which blocks the conversion of histamine to methylhistamine and thus raises the concentration of endogenous histamine in the brain, suppresses food consumption, and this appetite-suppressing effect of metoprine is attenuated by pretreatment with antihistaminic drugs. The results are in agreement with earlier findings (3,17). Histamine, when injected into the lateral cerebroventricle, causes a profound suppression of food intake (3). This suppression of ingestive behavior after histamine injection as well as after metoprine administration is related to the elevated brain histamine concentration and not to the changes in the levels of histamine catabolites. In fact, methylhistamine and methylimidazole acetic acid, which are the main catabolites of histamine in the brain, do not influence food intake (3). An increase in the release and synthesis of histamine due to the blockade of presynaptic H_3 receptors has been reported to suppress food intake in rats (17,24). On the other hand, a depletion of brain histamine due to α-fluoromethylhistidine (α-FMH), a selective inhibitor of histidine decarboxylase, results in increased food consumption (4,20,32). These findings indicate that different manipulations of the brain histaminergic neuronal activity cause changes in food intake of laboratory animals and point to a role for histamine in the control of feeding behavior.

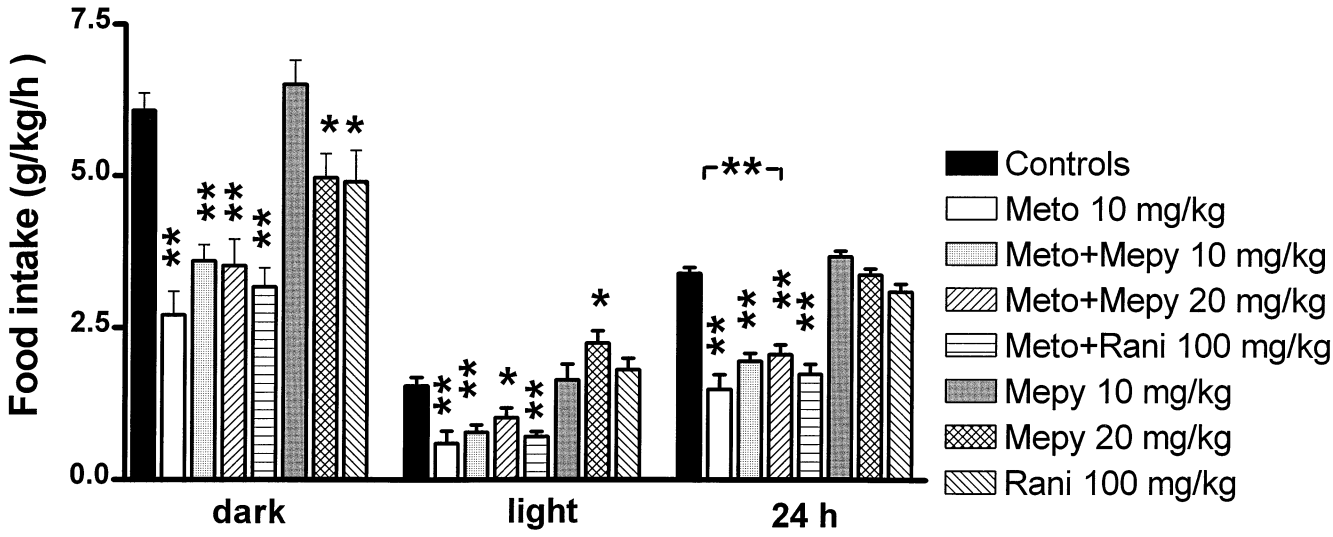

FIG. 1. The effect of mepyramine (mepy, 10–20 mg/kg) and ranitidine (rani, 100 mg/kg) on food intake in metoprine (meto, 10 mg/kg) and vehicle-treated rats during 10-h dark (dark) and 14-h light (light) phases and on total 24-h food consumption (24 h). Food intake (mean ± SEM, $n = 7$ per group) is calculated per rat body weight per hour. Statistical differences between groups were determined by the test of Duncan: $^{*}p < 0.05$, $^{**}p < 0.01$.

To our knowledge, only one study (3) has examined which receptor mediates the HA-induced suppression of feeding. In agreement with our results, it was found that the H_1 receptor blockers antagonized the effects of ICV administered histamine on food intake. Pretreatment with the H_1 blockers, chlorpheniramine and tripelennamine, at the dose of 1 mg/kg PO was sufficient to result in a significant antagonism in a 3-h feeding test (3). In the present study, higher doses (mepyramine 10 mg/kg given twice) were needed before a statistically significant attenuation of metoprine-induced suppression of feeding was reached. The use of higher doses can be explained by the different time schedule and by the chemical properties of metoprine. Metoprine has a long half-life (5) and causes a gradual but prolonged elevation of brain histamine levels (30) compared to ICV infusion of histamine. Metoprine produces also a long-lasting and marked suppression of feeding, which is difficult to abolish with the "old" brain-penetrating antihistamines that usually have a short duration of action. This was seen in the present experiment.

Antihistamines, when infused either into the third cerebroventricle or directly into the VMH or the PVN, cause a temporary stimulation of feeding (18,23). This type of drug administration probably causes relatively transient and local effects in the hypothalamus, the brain area rich in endogenous histamine, histaminergic axons, and H_1 receptors and with moderate density of H_3 receptors (25). Because H_1 receptor blockers do not stimulate feeding when administered into lateral hypothalamus or other hypothalamic nuclei (18,23), it has

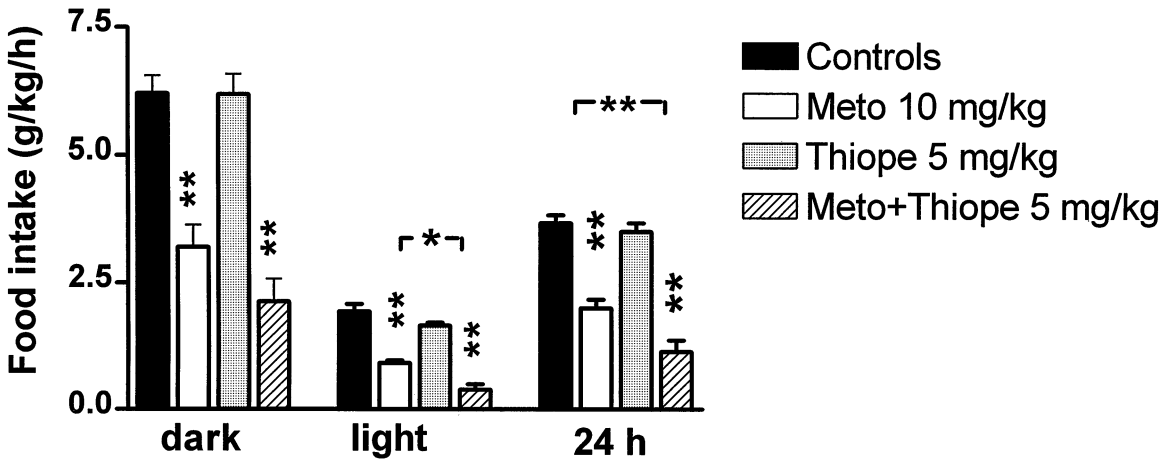

FIG. 2. The effect of thioperamide (thiope, 5 mg/kg) on food intake in metoprine (meto, 10 mg/kg) and vehicle-treated rats during 10-h dark (dark) and 14-h light (light) phases and on total 24-h food consumption (24 h). Food intake (mean ± SEM, $n = 6$–7 per group) is calculated per rat body weight per hour. Statistical differences between groups were determined by the test of Duncan: $^{*}p < 0.05$, $^{**}p < 0.01$.

TABLE 1

WATER INTAKE AND URINE VOLUME AFTER ADMINISTRATION OF MEPYRAMINE (10–20 mg/kg) AND RANITIDINE (100 mg/kg) IN METOPRINE (10 mg/kg) OR VEHICLE-TREATED RATS

	Water Intake (ml/kg/h)		Urine Volume (ml/kg/h)	
	Dark Hours	Light Hours	Dark Hours	Light Hours
Controls	7.5 ± 0.2	1.5 ± 0.1	2.4 ± 0.2	1.6 ± 0.2
Metoprine 10 mg/kg	9.7 ± 1.9	2.0 ± 0.5	6.9 ± 1.5*	1.7 ± 0.4
Mepyramine 10 mg/kg	7.1 ± 0.4	2.1 ± 0.4	2.0 ± 0.1	1.8 ± 0.1
Mepyramine 20 mg/kg	7.0 ± 0.4	3.3 ± 0.2*	2.7 ± 0.1	1.6 ± 0.1
Ranitidine 100 mg/kg	6.7 ± 0.6	2.0 ± 0.3	2.2 ± 0.7	1.5 ± 0.1
Metoprine + mepyramine 10 mg/kg	8.6 ± 2.2	2.5 ± 0.6	5.4 ± 1.9	2.3 ± 0.5
Metoprine + mepyramine 20 mg/kg	6.2 ± 0.8	3.6 ± 0.4†*	2.8 ± 0.7†	2.2 ± 0.6
Metoprine + ranitidine 100 mg/kg	8.7 ± 2.1	2.6 ± 0.8	5.7 ± 2.0	2.3 ± 0.6

Values are mean ± SEM ($n = 7$) calculated per rat body weight per hour during 10-h dark and 14-h light hours of the experiment. Values marked with * symbol differ significantly from the controls: $*p < 0.01$ and those marked with † differ from metoprine treated group: $\dagger p < 0.05$ (Mann-Whitney *U*-test).

been suggested that endogenous histamine is a satiety modulating agent in the VMH and the PVN (18). On the other hand, chronic ICV infusion of H_1 blockers stimulates daytime feeding, but it does not increase 24-h food consumption in rats. It was suggested that neuronal histamine is involved in the regulation of circadian rhythms, and that antihistamines and α-FMH, by abolishing the effect of endogenous histamine, disrupt circadian rhythms, which is, in turn, reflected in inappropriate feeding behavior (4). In another investigation (19), where the H_1 receptor antagonists, cyproheptadine and promethazine, were injected intraperitoneally to rats, they produced significant increases in the intake of a liquid diet. Some appetite stimulation was observed also with solid food, but this stimulation only occurred at extremely low doses. Because sedation is a common side effect of antihistamine treatment, this side effect may mask possible appetite-stimulating effects of higher doses. In those rats receiving 20 mg/kg of mepyramine, drowsiness is the most likely explanation for their decreased food intake during the dark period of the study.

An increase in the brain histaminergic neuron activity induced by ICV infusion of thioperamide has been shown to suppress food intake (4,17,24), but in our study its IP administration caused no changes in food consumption. Thioperamide readily penetrates the blood–brain barrier (28), and at a dose of 5 mg/kg causes a marked increase in the histamine turnover in the brain already 30 min after its systemic administration. This increase lasts for at least 6 h, with levels returning to normal at 18 h (7,28). Therefore, it is possible that such a relatively brief increase in the turnover of histamine does not suppress eating so markedly that this could be detected with a test system measuring food intake 10 h after the drug administration. Also, compensatory changes occurring during the 10-h measurement may have masked the effect of thioperamide. A systemic administration of either thioperamide 5 mg/kg or metoprine 10 mg/kg has been shown to cause a twofold increase in the content of histamine in the hypothalamus in urethane anesthetized rats, but the combined treatment with the drugs results in an approximately 6.5-fold increase in the hypothalamic extracellular histamine concentration (10). Here, increased release of histamine under conditions where its catabolism was inhibited resulted a profound and long-lasting suppression of feeding behavior. This major suppression in food intake in rats treated with thioperamide and metoprine shows that the loss of appetite is directly related to increased histaminergic activity in the brain. The observation that the suppression of feeding induced by ICV infused thioperamide can be abolished by the tretreatment of the H_1 blockers (24), together with our present findings, are evidence for the involvement of the H_1 receptor activation in the suppression of feeding induced by compounds that increase brain histaminergic activity.

Histamine is a potent dipsogen when administered centrally (16). Peripheral mechanisms also seem to play a role in

TABLE 2

WATER INTAKE AND URINE VOLUME AFTER ADMINISTRATION OF THIOPERAMIDE (5 mg/kg) IN METOPRINE (10 mg/kg) OR VEHICLE-TREATED RATS

	Water Intake (ml/kg/h)		Urine Volume (ml/kg/h)	
	Dark Hours	Light Hours	Dark Hours	Light Hours
Controls	7.2 ± 0.5	1.7 ± 0.2	2.5 ± 0.2	1.4 ± 0.2
Thioperamide 5 mg/kg	5.6 ± 1.1	1.8 ± 0.3	2.3 ± 0.6	1.6 ± 0.2
Metoprine 10 mg/kg	9.8 ± 1.2	3.6 ± 1.3	6.4 ± 1.1†	2.5 ± 0.7
Metoprine + thioperamide 5 mg/kg	7.9 ± 0.5	2.7 ± 0.8	5.6 ± 0.7†	2.5 ± 0.5*

Values are mean ± SEM ($n = 6$–7) calculated per rat body weight per hour during 10-h dark and 14-h light hours of the experiment. Values marked with symbols differ significantly from the controls: $*p < 0.05$, $\dagger p < 0.01$ (Mann-Whitney *U*-test).

this effect, because histamine increases drinking even after systemic administration (2,9,11,27). An IP injection of 1–20 mg/kg (R)-α-methyl-histamine (RAMH), which reduces the release and synthesis by activation of H_3 autoreceptors, has been shown to increase water consumption. The drinking response to RAMH can be antagonised by the H_3 receptor antagonist, thioperamide (2,12). Thioperamide also attenuates the drinking response to SC-injected histamine (2). These findings suggest that the dipsogenic effect of histamine may be mediated through H_3 receptors. Therefore, metoprine, which elevates brain histamine levels by blocking the catabolism of histamine, would be expected to stimulate drinking behavior through H_3 receptors. The present findings suggest, however, that the effects of metoprine on water balance cannot be explained simply in terms of H_3 receptors. First, although administration of metoprine tends to increase water consumption, it causes more pronounced increases in urine flow. This may indicate that metoprine primarily affects urine excretion and the changes in drinking behavior are secondary to urine loss. Second, thioperamide does not abolish the effect of metoprine on drinking, although a tendency towards decreased water intake during the dark phase can be seen in both thioperamide treated groups. Third, increase in urine flow induced by metoprine can be abolished by pretreatment an H_1 antagonist.

Previously it has been reported that the H_1 blocker, dexbrompheniramine, or the H_2 blocker, cimetidine, partially attenuate the drinking response to SC histamine in rats. This response could be totally blocked by a combination of the H_1 and H_2 blockers (11,27). In swine, cimetidine alone was able to inhibit the increase in the water intake seen after histamine (9). Large doses of histamine administered peripherally may elicit drinking and possibly induce changes in urine flow indirectly by producing vasodilatation and hypotension, and typically the effects of histamine on the vascular bed can be completely blocked only by a combination of H_1 and H_2 blockers. Metoprine is a widely used tool to elevate brain histamine levels, but it also increases histamine content of the periphery. Therefore, it may increase urine excretion indirectly through circulatory system or directly by activating H_1 and H_2 receptors in the kidney. Histamine-induced diuresis in the dog has been reported to require equally renal H_1 and H_2 receptors (1,21), but even the large dose of ranitidine used in the present experiment did not prevent metoprine-induced diuresis in rats, and thus our data do not point to any involvement of peripheral H_2 receptors. The discrepancy between the present and the previous (1,21) studies is not clear, but might be due to differences in animal species, and further studies are clearly needed to understand the mechanisms that mediate the effects of histamine on drinking behavior and urine excretion in different animal species.

In conclusion, the present study shows that an increase in the brain histaminergic neuronal activity due to inhibited histamine catabolism leads to a suppression of food intake in rats, this effect being mediated through H_1 receptors, because it can be abolished by pretreatment with H_1 blockers. Thus, the findings also suggest that brain histaminergic systems, similarly to many other neuronal systems, may participate in the control of feeding behavior. In addition to its effects on feeding, metoprine induces diuresis and elicits drinking. Although the blockade of H_1 receptors decreases the effect of metoprine on urine flow, further studies are required to clarify the mechanisms that mediate the effects of histamine on water balance.

REFERENCES

1. Bhargava, K. P.; Palit, G.; Dixit, K. S.: Behavioral effects of intracerebroventricular injection of histamine in dogs. In: Uväs, B.; Tasaka, K., eds. Advances in histamine research. Oxford: Pergamon Press; 1982:115–126.
2. Clapham, J.; Kilpatrick, G. J.: Histamine H_3 receptor-mediated modulation of water consumption in the rat. Eur. J. Pharmacol. 232:99–103; 1993.
3. Clineschmidt, B. V.; Lotti, V. J.: Histamine: Intraventricular injection suppresses ingestive behavior of the cat. Arch. Int. Pharmacodyn. Ther. 206:288–298; 1973.
4. Doi, T.; Sakata, T.; Yoshimatsu, H.; Machidori, H.; Kurokawa, M.; Jayasekara, L. A. L. W.; Niki, N.: Hypothalamic neuronal histamine regulates feeding circadian rhythm in rats. Brain Res. 641:311–318; 1994.
5. Duch, D. S.; Bowers, S.; Edelstein, M.; Nichol, C. A.: Histamine: Elevation of brain levels by inhibition of histamine *N*-methyltransferase. In: Usdin, E.; Borchardt, R. T.; Creveling, C. R., eds. Transmethylation. New York; Elsevier; 1979:287–295.
6. Fukagawa, K.; Sakata, T.; Shiraishi, T.; Yoshimatsu, H.; Fujimoto, K.; Ookuma, K.; Wada, H.: Neuronal histamine modulates feeding behavior through H_1-receptor in rat hypothalamus. Am. J. Physiol. 256:R605–R611; 1989.
7. Garbarg, M.; Trung Tuong, M. D.; Gros, C.; Schwartz, J. C.: Effects of histamine H_3-receptor ligands on various biochemical indices of histaminergic neuron activity in rat brain. Eur. J. Pharmacol. 164:1–11; 1989.
8. Hough, L. B.; Khandelwal, J. K.; Green, J. P.: Inhibition of brain histamine metabolism by metoprine. Biochem. Pharmacol. 35:307–310; 1986.
9. Houpt, T. R.; Weixler, L. C.; Troy, D. W.: Water drinking induced by gastric secretagogues in pigs. Am. J. Physiol. 251:R157–R164; 1986.
10. Itoh, Y.; Oishi, R.; Nishibori, M.; Saeki, K.: Characterization of histamine release from the rat hypothalamus as measured by in vivo microdialysis. J. Neurochem. 56:769–773; 1991.
11. Kraly, F. S.; Arias, R. L.: Histamine in brain may have no role for histaminergic control of food-related drinking in the rat. Physiol. Behav. 47:5–9; 1990.
12. Kraly, F. S.; Tribuzio, R. A.; Kim, Y.-M.; Keefe, M. E.; Finkell, J.: Histamine H_3 receptors contribute to drinking elicited by eating in rats. Physiol. Behav. 58:1091–1097; 1995.
13. Lecklin, A.; Tuomisto, L.: Fluid balance in rats of three different strains after inhibition of histamine catabolism. Physiol. Behav. 58:861–867; 1995.
14. 14. Lecklin, A.; Järvikylä, M.; Tuomisto, L.: The effect of metoprine on glucoprivic feeding induced by 2-deoxy-D-glucose. Pharmacol. Biochem. Behav. 49:853–857; 1994.
15. Lecklin, A.; Tuomisto, L.; MacDonald, E.: Metoprine, an inhibitor of histamine N-methyl-transferase but not catechol-O-methyltransferase, suppresses feeding in sated and food deprived rats. Methods Find. Clin. Exp. Pharmacol. 17:47–52; 1995.
16. Leibowitz, S. F.: Histamine: A stimulatory effect on drinking behavior in the rat. Brain Res. 63:440–444; 1973.
17. Machidori, H.; Sakata, T.; Yoshimatsu, H.; Ookuma, K.; Fujimoto, K.; Kurokawa, M.; Yamatodani, A.; Wada, H.: Zucker obese rats: Defect in brain histamine control on feeding. Brain Res. 590:180–186; 1992.
18. Ookuma, K.; Yoshimatsu, H.; Sakata, T.; Fujimoto, K.; Fukagawa, K.: Hypothalamic sites of neuronal histamine action on food intake by rats. Brain Res. 490:268–275; 1989.
19. Orthen-Gambill, N.: Antihistaminic drugs increase feeding, while histidine suppresses feeding in rats. Pharmacol. Biochem. Behav. 31:81–86; 1988.
20. Orthen-Gambill, N.; Salomon, M.: FMH-induced decrease in central histamine levels produces increased feeding and body weight in rats. Physiol. Behav. 51:891–893; 1992.

21. Radke, K. J.; Selkurt, E. E.; Willis, L. R.: The role of histamine H_1 and H_2 receptors in the canine kidney. Renal Physiol. 8:100–111; 1985.
22. Sakata, T.; Fukagawa, K.; Fujimoto, K.; Yoshimatsu, H.; Shiraishi, T.; Wada, H.: Feeding induced by blockade of histamine H_1-receptor in rat brain. Experientia 44:216–218; 1988.
23. Sakata, T.; Ookuma, K.; Fukagawa, K.; Fujimoto, K.; Yoshimatsu, H.; Shiraishi, T.; Wada, H.: Blockade of the histamine H_1-receptor in the rat ventromedial hypothalamus and feeding elicitation. Brain Res. 441:403–407; 1988.
24. Sakata, T.; Fukagawa, K.; Ookuma, K.; Fujimoto, K.; Yoshimatsu, H.; Yamatodani, A.; Wada, H.: Hypothalamic neuronal histamine modulates ad lib feeding in rats. Brain Res. 537:303–306; 1990.
25. Schwartz, J.-C.; Arrang, J.-M.; Garbarg, M.; Pollard, H.; Ruat, M.: Histaminergic transmission in the mammalian brain. Physiol. Rev. 71:2–51; 1991.
26. Sheiner, J. B.; Morris, P.; Anderson, G. H.: Food intake suppression by histidine. Pharmacol. Biochem. Behav. 23:721–726; 1985.
27. Specht, S. M.; Spear, L. P.: Histamine-elicited drinking in weanling and adult rats. Physiol. Behav. 45:63–70; 1989.
28. Taylor, S. J.; Michel, A. D.; Kilpatrick, G. J.: In vivo occupancy of histamine H_3 receptors by thioperamide and (R)-α-methylhistamine measured using histamine turnover and an ex vivo labeling technique. Biochem. Pharmacol. 44:1261–1267; 1992.
29. Tuominen, R. K.; Tuomisto, L.; Männistö, P. T.: Effect of modified brain histamine contents on prolactin and thyrotropin secretion in male rats. Eur. J. Endocrinol. 134:209–214; 1996.
30. Tuomisto, L.; Eriksson, L.: Antidiuresis induced by infusions of histamine into the brain ventricles of conscious hydrated goats. Eur. J. Pharmacol. 54:191–201; 1979.
31. Tuomisto, L.; Tacke, U.: Is histamine anticonvulsive inhibitory transmitter? Neuropharmacology 25:955–958; 1986.
32. Tuomisto, L.; Yamatodani, A.; Jolkkonen, J.; Sainio, E.-L.; Airaksinen, M. M.: Inhibition of brain histamine synthesis increases food intake and attenuates vasopressin response to salt loading in rats. Methods Find. Exp. Clin. Pharmacol. 16:355–359; 1994.