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Relationship Between Histamine Receptors in the Brain and Diazepam-Induced Hyperphagia in Rats

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NARUSE, T. AND R. ISHII. *Relationship between histamine receptors in the brain and diazepam-induced hyperphagia in rats.* PHARMACOL BIOCHEM BEHAV **51**(4) 923-927, 1995.—We investigated whether histaminergic neurons in the brain are involved in diazepam-induced hyperphagia in rats. Pretreatment with intracerebroventricular (ICV) injection of either histamine H_1-receptor antagonist, pyrilamine (10 and 30 μg) or histamine H_2-receptor antagonist, famotidine (3 and 10 μg) did not affect only diazepam (1 mg/kg, subcutaneous, SC)-induced hyperphagia in nondeprived rats, but also spontaneous feeding in food-deprived rats. In addition, pretreatment with ICV injection of histamine H_3-receptor antagonist, thioperamide, and histamine H_3-receptor agonist, (R) alpha methylhistamine, enhanced and inhibited diazepam-induced hyperphagia (1 mg/kg, SC) in nondeprived rats, respectively. However, thioperamide and (R) alpha methylhistamine did not affect spontaneous feeding in food-deprived rats. These findings suggest that histaminergic neurons are not directly involved in diazepam-induced hyperphagia in rats. Furthermore, enhancement or inhibition of diazepam-induced hyperphagia by histamine H_3-receptor antagonist or agonist may occur via histamine H_3-receptors localized in the other neurons in the rat brain.

Histamine H_1-, H_2-, and H_3-receptors Diazepam Hyperphagia Rat

IT IS well known that benzodiazepines produce hyperphagia. Some evidence suggest that hyperphagia induced by benzodiazepines is mediated by gamma-aminobutylic acid (GABA) (3,10) and endogenous opioids (4,6,10,20). However, the precise neuronal mechanisms underlying benzodiazepines-induced hyperphagia are not fully understood.

Since Clineschmidt and Lotti (5) reported that histamine plays, at least partly, a suppressive role in feeding behavior in cats, the neuronal role of histamine on feeding behavior has been increasingly focused. Recently, Ookuma et al. (13) and Sakata et al. (16,17) reported that histamine H_1-receptor antagonists infused into the third ventricle elicited feeding behavior in rats. Furthermore, Sakata et al. (18) also demonstrated that neuronal histamine plays a suppressive role in feeding behavior. On the other hand, Oishi et al. (12) reported that a benzodiazepine, diazepam, inhibits histamine turnover rate. Taken together, there is a possibility that diazepam-induced hyperphagia is due to the inhibitory effect on histaminergic neurons by diazepam. However, there are few reports studying the relationship between diazepam-induced hyperphagia and histaminergic neurons. Thus, we are tempted to speculate whether histaminergic neurons are involved in diazepam-induced hyperphagia.

First, the present study is carried out to clarify which subtypes of histamine H_1- or H_2-receptors are involved in diazepam-induced hyperphagia if histaminergic neurons are involved in the hyperphagia. Thus, we used pyrilamine (8) and famotidine (15) as histamine H_1- and H_2- receptor antagonists, respectively. Second, to determine the effects of neuronal histamine on this hyperphagia, we also used thioperamide and (R) alpha methylhistamine (7) as a histamine H_3-receptor antagonist and agonist, respectively. We previously confirmed that the significant hyperphagia induced by diazepam was observed from over doses of 1 mg/kg (subcutaneous, SC) in nondeprived rats (11). Therefore, in the present study, we investigate the interaction with histamine H_1-, H_2-, and H_3-receptor antagonists or H_3-receptor agonist and diazepam (1 mg/kg, SC)-induced hyperphagia.

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METHOD

Animals

Male Sprague-Dawley rats, weighing 320–380 g, were used in this experiment. Animals were allowed free access to water and food before the experiment, except where stated. The animals were housed at a room temperature of 23 ± 2°C with humidity at 55 ± 10% on a 12 L : 12 D cycle (lights on at 0600 h). To prepare intracerebroventricular (ICV) injection, under pentobarbital (40 mg/kg, IP) anesthesia, a stainless guide cannula (21 gauge) was implanted into the lateral ventricle (A: −1.0, L: 0.9, H: 2.0 mm from bregma) in each rat according to the rat brain in stereotaxic coordinates (14). After 1 week, each rat was used in the experiment. All experiments were performed between 1000 and 1500 h.

Drugs

Diazepam (Dott Bonapace and Co., Italy), pyrilamine maleate (Sigma, St. Louis, MO), famotidine (Gaster Injection, Yamanouchi, Japan), thioperamide maleate and (R) alpha methylhistamine dihydrochloride (Research Biochemicals International, USA) were used in this experiment. Diazepam was dissolved in propylene glycol : ethanol : distilled water (4 : 1 : 5, v/v) solution. Pyrilamine, famotidine, thioperamide, and (R) alpha methylhistamine were dissolved in 0.9% saline solution. Diazepam was administered SC in a volume of 1 ml/kg. Pyrilamine, famotidine, thioperamide, and (R) alpha methylhistamine were injected ICV in a volume of 10 μl/rat. Doses of all drugs are expressed as the free base.

METHODS

Effects of Pretreatment With Centrally Administered Pyrilamine and Famotidine on Diazepam-Induced Hyperphagia in Rats

To determine the involvement of histamine H_1- and H_2-receptors in the brain in diazepam-induced hyperphagia, effects of centrally administered pyrilamine and famotidine on diazepam-induced hyperphagia were determined in nondeprived rats. Pyrilamine (0, 10, and 30 μg, n = 8–12 for each group) and famotidine (0, 3, and 10 μg, n = 8–10 for each group) were injected ICV to each rat using a stainless injector (25 gauge) 10 min prior to diazepam (1 mg/kg, SC) and vehicle administration (1 ml/kg, SC). After diazepam administration, a preweighed amount of food pellets was placed into the individual cage. Food intake (g) was measured for 60 min and calculated by weighing uneaten food and crumbs. During the test, rats were allowed free access to water.

Effects of Pretreatment With Centrally Administered Thioperamide or (R) Alpha Methylhistamine on Diazepam-Induced Hyperphagia in Rats

To determine the effects of increased or decreased neuronal histamine in the brain, thioperamide, or (R) alpha methylhistamine at doses of 0, 2, 10, and 50 μg were injected ICV to each rat using a stainless injector (25 gauge) 10 min prior to diazepam (1 mg/kg, SC) and vehicle administration (1 ml/kg, SC, n = 6 to 15 for each group). After diazepam administration, food intake was measured for 60 min as described above.

Effects of Pretreatment with Centrally Administered Pyrilamine, Famotidine, Thioperamide, and (R) Alpha Methylhistamine on Spontaneous Feeding in Food-Deprived Rats

To determine the effects of both histamine H_1-, H_2-, and H_3-receptor antaginists and H_3-receptor agonist on spontaneous feeding, rats deprived of food for 24 h with free access to water were used. All rats were prepared the guide cannula for ICV injection as stated above. After ICV injection of pyrilamine (10 and 30 μg, n = 6 for each group) and famotidine (3 and 10 μg, n = 6 for each group), thioperamide (2, 10, and 50 μg, n = 8 for each group) and (R) alpha methylhistamine (2, 10 and 50 μg, n = 6 for each group), food intake was measured for 60 min as described above. Two control groups ICV injected with saline (10 μl/rat, n = 10 and n = 14 for each group) were prepared for both pyrilamine and famotidine or both thioperamide and (R) alpha methylhistamine, respectively.

Statistical Analysis

Differences between the groups were determined by analysis of variance followed by Ryan multiple range test. Differences with p-value less than 0.05 were considered significant. Results are shown as the mean ± SE.

RESULTS

Effects of Pretreatment With Centrally Administered Pyrilamine and Famotidine on Diazepam-Induced Hyperphagia in Rats

Results are shown in Figs. 1 and 2. Analysis of variance indicated significant effects on food intake following treatments [$F(5, 55) = 8.42$, $p < 0.05$, for pyrilamine + diazepam, $F(5, 50) = 7.58$, $p < 0.05$, for famotidine + diazepam]. Multiple range test (Ryan test) indicated that food intake was increased significantly ($p < 0.05$) following diazepam (1 mg/kg, SC) administration. However, pretreatment with pyrilamine (10 and 30 μg, ICV) and famotidine (3 and 10 μg, ICV) did not affect diazepam-induced hyperphagia. In addition, both pyrilamine (10 and 30 μg, ICV) and famotidine (3 and 10 μg, ICV) did not affect spontaneous feeding behavior following vehicle administration.

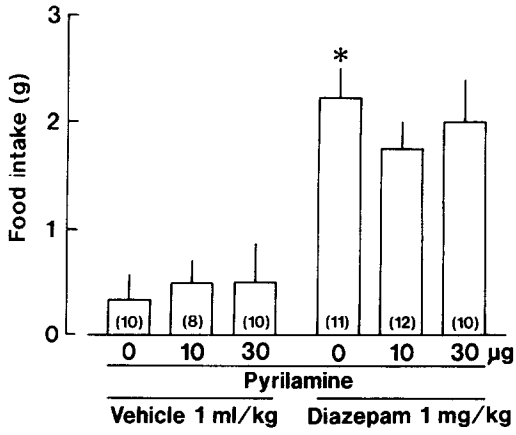

FIG. 1. Effects of centrally administered pyrilamine on diazepam-induced hyperphagia in nondeprived rats. Pyrilamine was administered intraventricularly 10 min prior to diazepam (1 mg/kg, SC) and vehicle administration. Following diazepam administration, food intake was measured for 60 min. Parentheses indicate number of rats used in the experiment. Each column and each vertical bar represent mean ± SE. *Significantly different from control, $p < 0.05$.

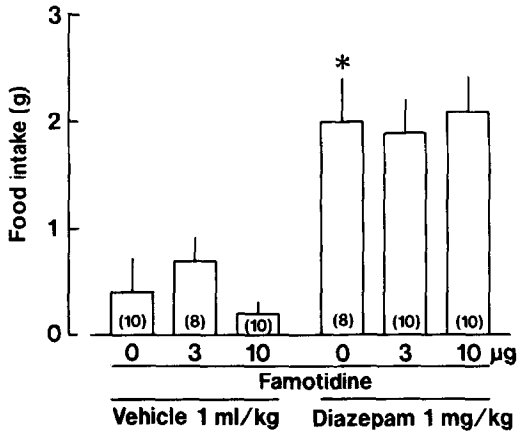

FIG. 2. Effects of centrally administered famotidine on diazepam-induced hyperphagia in nondeprived rats. Famotidine was administered intraventricularly 10 min prior to diazepam (1 mg/kg, SC) and vehicle administration. Following diazepam administration, food intake was measured for 60 min. Parentheses indicate number of rats used in the experiment. Each column and each vertical bar represent mean ± SE. *Significantly different from control, $p < 0.05$.

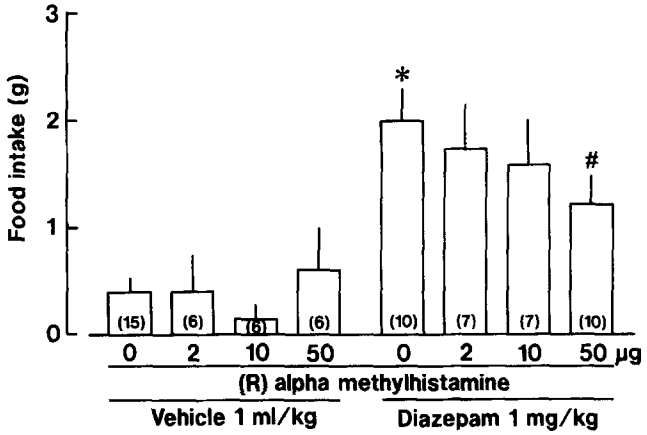

FIG. 4. Effects of centrally administered (R) alpha methylhistamine on diazepam-induced hyperphagia in nondeprived rats. (R) alpha methylhistamine was administered intraventricularly 10 min prior to diazepam (1 mg/kg, SC) and vehicle administration. Following diazepam administration, food intake was measured for 60 min. Parentheses indicate number of rats used in the experiment. Each colum and each vertical bar represent mean ± SE. *Significantly different from control, $p < 0.05$. #Significantly different from the group treated with vehicle and diazepam, $p < 0.05$.

Effects of Pretreatment With Centrally Administered Thioperamide or (R) Alpha Methylhistamine on Diazepam-Induced Hyperphagia in Rats

Results are shown in Figs. 3 and 4. Analysis of variance indicated significant effects in food intake following treatments [$F(13, 100) = 8.55$, $p < 0.05$, for thioperamide and (R) alpha methylhistamine + diazepam]. Multiple range test (Ryan test) indicated that food intake was increased significantly ($p < 0.05$) following diazepam (1 mg/kg, SC) administration. Furthermore, pretreatment with thioperamide (10 µg, ICV) enhanced significantly ($p < 0.05$) diazepam-induced hyperphagia (Fig. 3). On the other hand, pretreatment with (R) alpha methylhistamine (50 µg, ICV) inhibited significantly ($p < 0.05$) diazepam-induced hyperphagia. In addition, both thioperamide (2 to 50 µg, ICV) and (R) alpha methylhistamine (2 to 50 µg, ICV) did not affect spontaneous feeding behavior following vehicle administration.

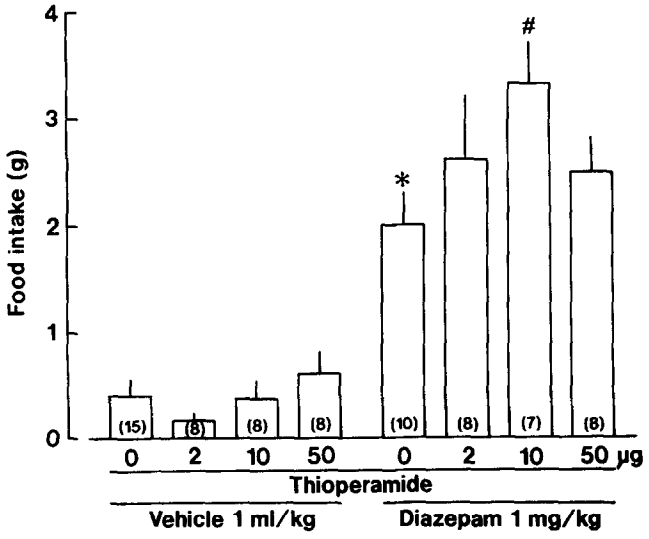

FIG. 3. Effect of centrally administered thioperamide on diazepam-induced hyperphagia in nondeprived rats. Thioperamide was administered intraventricularly 10 min prior to diazepam (1 mg/kg, SC) and vehicle administration. Following diazepam administration, food intake was measured for 60 min. Parentheses indicate number of rats used in the experiment. Each column and each vertical bar represent mean ± SE. *Significantly different from control, $p < 0.05$. #Significantly different from the group treated with vehicle and diazepam, $p < 0.05$.

Effect of Pretreatment With Centrally Administered Pyrilamine, Famotidine, Thioperamide, and (R) Alpha Methylhistamine on Spontaneous Feeding in Food- Deprived Rats

Results are shown in Tables 1 and 2. Analysis of variance indicated no significant effects in food intake following treat-

TABLE 1

EFFECT OF CENTRALLY ADMINISTERED PYRILAMINE OR FAMOTIDINE ON SPONTANEOUS FEEDING BEHAVIOR IN FOOD-DEPRIVED RATS

Treatment	Doses (µg)	No. of Rats	Food intake (g) Mean ± SE
Vehicle	0	10	5.14 ± 0.47
Pyrilamine	10	6	5.65 ± 0.35
	30	6	4.75 ± 0.71
Famotidine	3	6	5.92 ± 0.43
	10	6	6.57 ± 1.39

Pyrilamine or famotidine was administered intracerebroventricularly (ICV) in rats food deprived for 24 h with free access to water. Following ICV injection, all rats were given food. Food intake was measured for 60 min.

ments [$F(4, 29) = 0.89$, NS, for pyrilamine and famotidine, $F(6, 49) = 1.94$, NS, for thioperamide and (R) alpha methylhistamine]. Thus, pyrilamine (10 and 30 μg), famotidine (3 and 10 μg), thioperamide (2, 10, and 50 μg), and (R) alpha methylhistamine (2, 10, and 50 μg) did not affect spontaneous feeding in food-deprived rats.

TABLE 2

EFFECT OF CENTRALLY ADMIMISTERED THIOPERAMIDE OR ALPHA METHYLHISTAMINE ON SPONTANEOUS FEEDING IN FOOD-DEPRIVED RATS

Treatment	Doses (μg)	No. of Rats	Food intake (g) Mean ± SE
Vehicle		14	6.63 ± 0.39
Thioperamide	2	8	5.83 ± 0.66
	10	8	7.10 ± 0.43
	50	8	5.20 ± 0.50
(R) Alpha methylhistamine	2	6	7.50 ± 0.50
	10	6	6.87 ± 0.92
	50	6	6.08 ± 0.51

Thioperamide or (R) alpha methylhistamine administered intracerebroventricularly (ICV) in rats food deprived for 24 h with free access to water. Following ICV injection, all rats were given food. Food intake was measured for 60 min.

DISCUSSION

Although we estimate in the present study that diazepam-induced hyperphagia is due to the inhibitory effect on histaminergic neurons by diazepam based on the report by Oishi et al. (12), diazepam-induced hyperphagia was neither potentiated nor inhibited by centrally administered pyrilamine or famotidine. Assuming that decrease of histamine turnover rate by diazepam is related to diazepam-induced hyperphagia, this hyperphagia could be enhanced by these antagonists. Furthermore, Garbarg et al. (7) have reported that blockade of histamine H_1- and H_2-receptors does not result in any significant changes in histamine turnover. Therefore, our results suggest that histaminergic neurons are not directly involved in diazepam-induced hyperphagia.

Interestingly, centrally administered thioperamide (10 μg) and (R) alpha methylhistamine (50 μg) enhanced and inhibited diazepam-induced hyperphagia, respectively. Furthermore, it should be noted that, centrally administered, these drugs did not affect spontaneous feeding in food-deprived rats, suggesting that diazepam-induced hyperphagia is specifically affected by a histamine H_3-receptor antagonist or agonist. Arrang et al. (1) reported that histamine H_3-receptors control not only the release but also synthesis of histamine at the level of nerve endings as autoreceptors, implying that thioperamide increases histamine release from nerve endings and (R) alpha methylhistamine decreases neuronal histamine release. Considering the findings of Arrang et al. (1), our data are contrary to the reports indicating the suppressive role of histamine in feeding (5,18). Although we did not measure neuronal histamine levels following ICV injection of thioperamide or (R) alpha methylhistamine, there is a possibility that neuronal histamine levels did not change following ICV injection of these drugs. Otherwise, changes of neuronal histamine levels may not be related to enhancement or inhibition of diazepam-induced hyperphagia according to our results, indicating that diazepam-induced hyperphagia was not affected by centrally administered pyrilamine and famotidine. Therefore, other neuronal mechanisms on diazepam-induced hyperphagia by both thioperamide and (R) alpha methylhistamine should be controversial.

With regard to this issue, Arrang et al. (2) also reported that histamine H_3-receptors were extensively found in the brain, such as the cerebral cortex, hypothalamus, striatum, hippocampus, lateral septum, and olfactory nuclei. Therefore, histamine H_3-receptors would exist presynaptically in the other neurons. In fact, Schlicker et al. (19) reported that the stimulation of histamine H_3-receptors reduces release of serotonin in the rat barin. According to the findings of Schlicker et al. (19), it is reasonable to propose that other neurons affected by histamine H_3-receptor antagonist or agonist might have influence do diazepam-induced hyperphagia. In the present study, we could not clarify that the precise neurons can be modulated by histamine H_3-receptors. However, because it has demonstrated that serotonin can inhibit feeding (9), the involvement of serotonergic neurons via histamine H_3-receptors as reported by Schlicker et al. (19) may be negligible. As another plausible explanation, we recently reported that dopamine D_1- and D_2-receptors are involved in diazepam-induced hyperphagia, and that supersensitivity of dopaminergic receptors enhanced this hyperphagia (11). Thus, if histamine H_3-receptors could presynaptically exist in dopaminergic neurons in the rat brain, both thioperamide and (R) alpha methylhistamine could affect dopamine release (i.e., facilitation and inhibition of dopamine release) and result in enhancement and inhibition of diazepam-induced hyperphagia, respectively. However, further studies will be required to clarify the relationship between other neurons and diazepam-induced hyperphagia affected by stimulation of histamine H_3-receptors.

In conclusion, our data suggest that histaminergic neurons are not directly involved in diazepam-induced hyperphagia in rats. Furthermore, enhancement or inhibition of diazepam-induced hyperphagia by histamine H_3-receptor antagonists or agonists may occur via histamine H_3-receptors localized in the other neurons in rats.

REFERENCES

1. Arrang, J.-M.; Garbarg, M.; Schwartz, J.-C. Autoinhibition of histamine synthesis mediated by presynaptic H_3-receptors. Neuroscience 23:149–157; 1987.
2. Arrang, J.-M.; Garbarg, M.; Lancelot, J.-C.; Lecomte, J.-M.; Pollard, H.; Robba, M.; Schunack, W.; Schwartz, J.-C. Highly potent and selective ligands for histamine H_3-receptors. Nature 327:117–123; 1987.
3. Birk, J.; Nobel, R. G. Bicuculline blocks diazepam-induced feeding in Syrian hamsters. Life Sci. 30:321–325; 1982.
4. Britton, D. R.; Brittonm K. T.; Dalton, D.; Vale, W. Effects of naloxone on anticonflict and hyperphagic actions of diazepam. Life Sci. 29:1297–1302; 1981.
5. Clineschmidt, B. V.; Lotti, V. J. Histamine: Intraventricular injection suppresses ingestive behavior of the cat. Arch. Int. Pharmacodyn. 206:288–298; 1973.
6. Cooper, S. J. Benzodiazepine-opiate antagonist interactions in relation to feeding and drinking behavior. Life Sci. 32:1043–1051; 1983.

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. Garrison, J. C. Histamine, bradykinin, 5-hydroxytryptamine and their antagonists. In: Gilman, A. G.; Theodore, W. R.; Nies, A. S.; Taylor, P., eds. Goodman and Gilman's the pharmacological basis of therapeutics, 8th ed. New York: Pergamon Press; 1990: 586.
9. Leibowitz, S. F.; Shor-Posner, G. Brain serotonin and eating behavior. Appetite 7:1–14; 1986.
10. Naruse, T.; Asami, T.; Koizumi, Y. Effects of naloxone and picrotoxin on diazepam- or pentobarbital-induced hyperphagia in nondeprived rats. Pharmacol. Biochem. Behav. 31:709–711; 1988.
11. Naruse, T.; Amano, H.; Koizumi, Y. Possible involvement of dopamine D_1 and D_2 receptors in diazepam-induced hyperphagia in rats. Fundam. Clin. Pharmacol. 5:677–697; 1991.
12. Oishi, R.; Yoshibori, M.; Ito, Y.; Saeki, K. Diazepam-induced decrease in histamine turnover in mouse brain. Eur. J. Pharmacol. 124:337–342; 1986.
13. Ookuma, K.; Yoshimatsu, H.; Sakata, T.; Fujimoto, K.; Fukagawa, K. Hypothalamic sites of of neuronal histamine action on food intake by rats. Brain Res. 490:268–275; 1989.
14. Paxinos, G.; Watson, C. The rat brain stereotaxic coordinates, 2nd ed. New York: Academic Press; 1986.
15. Pendleton, R. G.; Torchiana, M. L.; Chung, C.; Cook, P.; Wise, S.; Clineschmidt, B. V. Studies on MK-208 (YM-11170) a new, slowly dissociable H_2-receptor antagonist. Arch. Int. Pharmacodyn. 266:4–16; 1983.
16. 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.
17. 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. 441:473–407; 1988.
18. Sakata, T.; Fukagawa, K.; Ookuma, K.; Fujimoto, K.; Yoshimatsu, H.; Yamatodani, A.; Wada, H. Hypothalamic neuronal histamine modulates ad lib feeding by rats. Brain Res. 537:303–306; 1990.
19. Schlicker, E.; Betz, R.; Gothert, M. Histamine H_3 receptor-mediated inhibition of serotonin release in the rat brain cortex. Naunyn Schmiedebergs Arch. Pharmacol. 337:588–590; 1988.
20. Stapleton, J. M.; Lind, M. D.; Merriman, V. J.; Reid, L. D. Naloxone inhibits diazepam-induced feeding in rats. Life Sci. 24: 2421–2426; 1979.