were located in the ischemic area, as shown by Roland et al.[10]. However, in our study, we confirmed, using Evans blue perfusion at the end of each experiment, that the electrodes were within the normal zone during ischemia. Fisher et al.[11] have shown the VFT increases with worsening ischemia. Thus, it is likely that the degree of ischemia progressed more rapidly and severely in hypertrophied hearts than in normal hearts.

Many factors are known to influence VFT including the activity of the sympathetic and parasympathetic autonomic nervous system[12,13]. Although such neural activity is excluded from the present study in which isolated perfused hearts were used, the role of endogenous stores of catecholamine in nerve endings is unclear. Coulson et al.[14] report that catecholamine is depleted in pressure overloaded hypertrophied cat hearts. Thus, the lower VFT in hypertrophied hearts cannot be explained by increased myocardial catecholamine content. Coronary flow also may influence VFT, and cardiac hypertrophy reduces coronary vasodilator reserve[15,16]. However, in our study we adjusted perfusion pressure to achieve similar coronary flow in normal and hypertrophied hearts, and coronary efflux did not differ between the two groups even after coronary occlusion. The risk area was not different in the two groups, and the hearts were paced at a constant rate.

It has been reported that VFT reflects the degree of inhomogeneity of the excitability and recovery properties of the myocardium[17,18]. These inhomogeneities, which tend to enhance reentrant activity, reflect differences in the transmembrane potentials, including differences in the rate, amplitude, and length of depolarization. In this regard, it is noteworthy that Aronson[19] has reported that action potential duration is significantly longer in hypertrophied rat heart cells due to renal hypertension than in normal cells. Furthermore, Keung and Aronson[20] showed that action potential prolongation in such renal hypertension-induced hypertrophied heart cells is not uniform at various recording sites. These studies suggest that hypertrophied ventricles are more likely to suffer a greater risk of reentrant tachyarrhythmias. Furthermore, considering that ischemia per se produces dispersion of action potential duration and refractoriness, it is conceivable that electrical inhomogeneities during ischemia are even greater in hypertrophied hearts than in normal hearts.

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Feeding induced by blockade of histamine H_1-receptor in rat brain

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Summary. Histamine antagonists were infused into the third ventricle of the cerebrum in rats. All the H_1-, but none of the H_2-antagonists tested, induced initial feeding during the early portion of the light phase when histamine level was highest. No periprandial drinking was observed. Ambulation increased during feeding. The effect on feeding was attenuated when brain histamine was normally low during the early portion of the dark phase, or was decreased by α-fluoromethylhistidine. Hypothalamic neuronal histamine may suppress food intake through H_1-receptors, and diurnal fluctuations of food intake may mirror neuronal histamine levels.
Key words. Antihistamine; H_1-receptor; feeding elicitation; α-fluoromethylhistidine; hypothalamic neuronal histamine.

Histamine and the activity of its specific synthesizing and catabolizing enzymes are unevenly distributed in the brain. The highest levels are in the hypothalamic nuclei[1], the subcellular location is predominantly synaptosomal[2]. The regional distribution of histamine H_1-receptors is also uneven[3]. These receptors are relatively dense on discrete neurons in the hypothalamus[3], including areas related to food intake, such as the ventromedial hypothalamus (VMH) and the paraventricular nucleus[3]. It has been reported that histamine or its precursor amino acid, histidine, reduced or increased food intake[4,5]. However, exogenous histamine did not mimick the physiological role of endogenous histamine,

because the amine induces variable modification of synaptic transmission and auto-inhibition of its endogeneous release via histamine H_3-receptors [6]. Exogenous histamine can neither be used to distinguish between the effect of neuronal and extraneuronal histamine on feeding, nor to detect the effect on H_1- and H_2-receptors. The effect of blockade of rat brain H_1-receptors on food intake was examined, and it was found that neuronal histamine modulates physiological feeding through H_1-receptors in the hypothalamus.

Male Wistar King A rats, 270–300 g, were housed in a soundproof room illuminated daily from 8.00–20.00 h (12:12 h light-dark cycle) and maintained at 21 ± 1 °C. The rats were allowed free access to standard pellet rat chow (Kanae Inc., Japan, mean pellet weight, 49.8 ± 0.4 mg), and tap water (mean droplet volume, 35.2 ± 0.6 µl). Under pentobarbital sodium anesthesia (50 mg/kg i.p.), each rat was chronically implanted one week before testing with a cannula into the right atrium through the jugular vein or the third ventricle of the cerebrum. 10 µl of test solutions were infused at 1 µl/min [7, 8]. Infusion was carried out between 11.00 and 11.10 h, except where otherwise described. Each rat was housed in a 30 × 25 × 25 cm test chamber equipped with a pellet sensing eatometer, a photoresistor drinkometer and photosensing counters to measure ambulation (Astec Co. Ltd., Japan) [9]. Behavioral patterns were automatically recorded in a separate room. The meal parameters were defined to accommodate consumption of more than 10 pellets at intervals that exceeded 10 min [9]. Data for incidence (elicited/tested) were evaluated by the Fisher exact probability test. Data for meal size, latency before eating the first meal, meal duration and eating speed (meal size divided by meal duration) were evaluated by the Mann-Whitney U test.

Infusion of the histamine H_1-receptor antagonists, chlorpheniramine maleate, mepyramine and promethazine hydrochloride, into the third ventricle of the cerebrum, dose-dependently ($p < 0.01$) induced feeding (table 1). Rats treated with chlorpheniramine at a maximal effective dose of 0.26 µmol ate meals (meal size, 39.2 ± 9.1 pellets) most frequently ($p < 0.01$) and persistently ($p < 0.01$). There was no significant difference in the potency of the 0.26 µmol doses of the three H_1-antagonists reported here, nor between the 0.26 and 0.52 µmol doses (not listed in table 1). Feeding after infusion of chlorpheniramine into the third ventricle of the cerebrum may not have been caused by leakage of chlorpheniramine into the general circulation, since equimolar injections of chlorpheniramine into the jugular vein had no effects on ingestive or exploratory behavior. No periprandial drinking was observed after injection of the H_1-antagonists tested (table 1). Ambulatory activity increased concomitantly with feeding after the infusions and no sedation was observed (table 1). The increased ambulation did not exceed the activity associated with one meal. H_2-Antagonists, cimetidine and famotidine, did not affect ingestive behavior or ambulation (table 1).

To verify that the effect on feeding depended on endogenous histamine, and not on unperceived pharmacological effects of the H_1-antihistamines themselves, chlorpheniramine-induced feeding was evaluated during decrease of brain histamine by pretreatment with α-fluoromethylhistidine (α-FMH), a 'suicide' inhibitor of histidine decarboxylase (HDC) [10]. This was done in the early light period when endogenous histamine would otherwise have been high [11], and the effects of chlorpheniramine most noticeable. The production of neuronal histamine in the hypothalamus is almost completely inhibited by α-FMH for 2 to 12 h after i.p. injection (100 mg/kg) [12]. Incidence of feeding induced by 0.26 µmol chlorpheniramine decreased significantly to 33.3% in 2 out of 6 rats 6 h after i.p. pretreatment with α-FMH ($p < 0.05$). Latency until the first meal eaten by the 2 rats in the α-FMH group was also prolonged ($p < 0.05$) and meal duration was shortened ($p < 0.05$), compared to controls (table 1).

Table 1. Changes in feeding due to antagonism of histamine H_1- or H_2-receptors after injection in the early light. Values are mean ± SEM. ND, not detected; icv, infusion into third ventricle of the cerebrum; iv, infusion into jugular vein; ip, infusion into peritoneum.

Treatment[a]	Meal			Drinking (incidence)	Ambulation[b]
	Feeding (incidence)	Latency (min)	Duration (min)		
Chlorpheniramine maleate (icv)					
0.03 µmol	0/6	ND	ND	0/6	±
0.06 µmol	1/6	39.0	1.5	0/6	+
0.12 µmol	3/6*	42.5 ± 2.8	3.0 ± 0.2	0/6	++
0.26 µmol	6/6**	39.2 ± 2.4	14.9 ± 3.6**	0/6	++
Chlorpheniramine maleate (iv)					
0.26 µmol	0/3	ND	ND	0/3	–
Mepyramine (icv)					
0.12 µmol	1/3	47.3	1.5	0/3	+
0.26 µmol	2/3	36.5 ± 0.3	3.6 ± 1.8	0/3	++
Promethazine hydrochloride (icv)					
0.12 µmol	1/3	39.3	1.0	0/3	+
0.26 µmol	2/3	39.4 ± 3.6	5.1 ± 0.4	0/3	++
Cimetidine (icv)					
0.15 µmol	0/3	ND	ND	0/3	–
0.30 µmol	0/3	ND	ND	0/3	–
Famotidine (icv)					
1.5 nmol	0/3	ND	ND	0/3	–
3.0 nmol	0/3	ND	ND	0/3	–
Saline (icv)					
1.5 µmol	0/10	ND	ND	0/10	–
α-Fluoromethylhistidine (100 mg/kg, ip) plus chlorpheniramine maleate (0.26 µmol, icv)					
	2/6*	44.4 ± 6.2*	8.9 ± 1.0*	0/6	+
Saline (0.15 mmol, ip) plus chlorpheniramine maleate (0.26 µmol, icv)					
	6/6	34.5 ± 2.2	14.8 ± 3.6	0/6	++

[a] Saline or α-fluoromethylhistidine injected 6 h before infusion of chlorpheniramine. [b] Ambulation determined from differences between photobeam crossings during 1 h before and after injection, $-40 < - \leq +40$, $40 < \pm \leq 80$, $80 < + \leq 160$, $++ > 160$ (after minus before). * = $p < 0.05$, ** = $p < 0.01$

Since feeding due to H_1-antagonists was closely related to neuronal histamine content, the effect was further evaluated under the physiological condition of decreased histamine concentrations and HDC activity in the hypothalamus during the early dark [11]. When 0.26 µmol chlorpheniramine was infused from 19.40 to 19.50 h, immediately before the dark period, its potency in inducing feeding was attenuated. Namely, meal size, latency before eating the first meal and eating speed, observed during 1 h after chlorpheniramine infusion, were found not to differ significantly either from results for the same animals during the corresponding 1-h period in the 2 days before injection, or from those for saline controls during the corresponding 1-h periods on the day of infusion and the day prior to infusion (table 2).

Feeding was elicited by all the H_1-antagonists tested, but not by H_2-antagonists infused directly into the third ventricle of the cerebrum. In addition, absence of periprandial drinking shows that feeding induced by antagonism of H_1-receptors was not a secondary effect, since both spontaneous periprandial and histamine-induced drinking are specifically blocked by H_1-antihistamines [13]. Moreover, H_1-antihistamines are known to have a high specificity and affinity for H_1-receptors in mammalian brain without altering endogeneous histamine content or activity of either HDC or histamine N-methyltransferase (HMT) [6, 14, 15].

These findings indicate that elicitation of feeding may be derived from specific blocking of hypothalamic H_1-recep-

Table 2. Effect of chlorpheniramine and saline on meal parameters during 1 h after injection immediately before the dark. Mean ± SEM.

Treatment	Meal size (No. of pellets)	Latency (min)	Eating speed (No. of pellets/min)
Chlorpheniramine maleate (0.26 μmol) (n = 4)			
1st and 2nd days before	37.7 ± 4.7	37.7 ± 6.1	3.2 ± 0.3
Day of injection	38.8 ± 10.6	37.8 ± 8.1	3.0 ± 0.2
Saline (1.5 μmol) (n = 4)			
1st and 2nd days before	38.2 ± 5.4	39.0 ± 6.2	3.2 ± 0.2
Day of injection	39.6 ± 3.3	38.2 ± 4.6	3.1 ± 0.2

Meal parameters were analyzed for 1 h after injection of chlorpheniramine and compared to corresponding periods 1 and 2 days before infusion in the same rat and at corresponding periods 1 h before and after saline injections. Meals after treatment with chlorpheniramine did not differ from those in other corresponding periods. n, number of rats used.

tors, which receive neuronal inputs from histaminergic pathways and are related to control of food intake[3]. This may ultimately block inhibitory effects of neuronal histamine on feeding behavior. We also found that iontophoretic application of H_1-antagonists, which had no effect of altering body temperature, specifically inhibited the activity of glucose-receptive neurons, but no others in the VMH, and facilitated neuronal activity in the lateral hypothalamus (unreported results).

The question can be raised as to whether this antihistamine-induced feeding might be attributed to complex pharmacological effects, such as local anesthesia, atropine-like anticholinergic or antiadrenergic activity[16,17]. In fact, these possibilities cannot be definitely excluded, because the effects of H_1-antagonists may occur at doses that are possibly greater than those required to saturate H_1-receptor sites of action in the hypothalamus[18]. The following facts, however, support the concept that H_1-antihistamines readily oppose the suppressive effects of endogenous histamine to induce transient feeding elicitation: 1) The α- and β-adrenoreceptor responses are involved reciprocally in the modulation of feeding, and cholinergic synapses are also linked in neural feeding control circuits. Antagonists of these transmitters, however, do not affect (slightly suppress) feeding[19,20]. 2) Preliminary electrophysiological results that chlorpheniramine, as mentioned previously, selectively suppressed or enhanced hypothalamic discrete neurons may exclude the possibility of local anesthetic action. 3) Furthermore, we found that feeding induced by an H_1-antagonist was attenuated under both a physiological condition, in which endogenous histamine was naturally low, and a non-physiological condition in which it was low due to treatment with α-FMH, which left the activity of HMT and other pyridoxal-dependent amino acid decarboxylases unaffected[21].

Previous evidence[3,11] and our present results lead to the conclusion that neuronal histamine in the hypothalamus may suppress feeding through H_1-receptors and, at least in part, be involved in diurnal fluctuations of food consumption.

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