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Review Article

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REGULATION OF FEEDING BEHAVIOR, WITH SPECIAL REFERENCE TO HISTAMINE

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Treatment with psychotropic or antiallergic drugs which block histamine H_1-receptors is known to be connected with weight gain. Also in experimental animals food intake is changed after manipulation of the histaminergic system, food intake may be decreased by various treatments with increase histaminergic activity and increased if histaminergic activity is reduced. Recent studies are reviewed illustrating the potential role of brain histaminergic system in the fascinating and complicated regulation of feeding.

Key words: *histamine, metabolism, metoprine, food intake, feeding behavior.*

INTRODUCTION

The regulatory mechanisms controling eating, obesity and the body's energy balance are far more complex than once was thought (1, 2). It is actually amazing that most adults maintain a remarkably stable body weight which fluctuates by only small amounts over many years. To maintain a stable body weight the regulatory system must be extraordinary precise. It has been calculated that a small, less than one gram excess in daily food intake will produce more than 10 kg of excess weight during an adult's life.

In principle it should be very simple to keep energy in balance. In adults the intake of energy must be equal to the amount of energy used. However, the mechanisms regulating this do not always operate flawlessly, leading to disorders of food intake such as anorexia and bulimia or excessive eating leading to obesity. In the USA more than a quarter of the population

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is categorized as overweight or obese (1). Large commercial interests successfully market so called weight watcher's products. The sad fact is, however, that neither they nor the current medical practice have been able to treat adequately these people and prevent the complicating diseases of obesity, such as diabetes, cardiovascular diseases, certain types of cancer etc. The main reason for this is that we do not know enough about the regulatory mechanisms which lie behind the simple energy-balance equation.

There is evidence that the body weight maintenance is governed by a combination of short term and long term mechanisms. In order to adapt to changing conditions, the energy intake is controlled on a different time scale from that of energy balance. Food intake has to be controlled on a daily basis, but it correlates to energy expenditure only over longer periods of time e.g. a week (3).

Most hypotheses are based on the assumption that food intake is modified to compensate for energy requirements, but the body has also been observed to reduce metabolic rate when food is restricted in order to maintain a steady weight. This is one reason why it is so difficult for humans to reduce weight only by dieting.

So it seems that for each individual there is a certain preset body size or weight which is recovered after temporary changes to one direction or the other. As yet it is not understood how this is accomplished. Once it was thought that the ventromedial hypothalamic nucleus serves as a satiety center, and lateral hypothalamus as a hunger center. The theory of central hunger and satiety centers has proved too simplistic. In addition to regulation of the neurotransmitter activity in several brain areas, also afferent signals from the peripheral organs are of utmost importance. As a whole much more is known about the short term regulation of food intake than about the mechanisms of long term maintenance of body weight. In addition to classical neurotransmitters, a number of peptides are involved in the regulation (4).

Clues to the role of histamine

Histamine is phylogenetically an old amine existing in the nervous structures of very simple living organisms. Therefore it is reasonable to suppose that at least some of its functions are crucial for life. One such function is regulation of feeding behavior. This kind of function has been shown to exist even with an identified neuron of the primitive aplasia (5, 6).

It has been known since the 1960's that long term treatment with antidepressive and psychotropic drugs as well as with antihistaminics is connected with weight gain. All these drugs have among other effects, histamine H_1-receptor blocking activities and could thus induce feeding through this mechanism, although e.g. in case of antidepressive drugs also

other mechanisms such as the stimulation of noradrenergic system *via* α_2-receptors could induce feeding.

When studying the effects of i.c.v. infused histamine and H_1-agonists on conscious goats we noticed that they stopped eating hay which was freely available during the experiment. They also refused to eat molasses which was their favorite treat (7). This stimulated us to examine the possible role of histamine in the regulation of food intake.

An inhibitory role for histamine in food intake was further suggested by the fact that an extra load of its precursor amino acid histidine was found to reduce food intake (8, 9).

Manipulations of histaminergic activity

One way to study the influence of the histaminergic system on histamine concentration is by preventing its metabolism. Metoprine which inhibits histamine N-methyltransferase almost doubles brain histamine concentration at a dose of 20 mg/kg i.p. and the effect lasts for at least hours (10). When food intake was monitored in rats after this dose of metoprine, a clear decrease was seen, the inhibition was evident also in rats already having reduced food intake due to water deprivation (11, 12).

The inhibitory effect of metoprine on food intake was dose-dependent and it was seen during the night which is the main period of food intake for rats but also occurred during the day (13, in preparation). The suppression of feeding behavior by metoprine was quite remarkable since reduced food intake was observed even after 72 hours of food deprivation (in preparation). Experiments aimed at defining the receptor specificity of the inhibition are currently underway.

Several studies have been done by applying exogenous histamine receptor antagonists either by infusion into the 3rd ventricle or directly into hypothalamic nuclei (14—16). These studies are in favor of the participation of H_1-receptors in the control of food intake. However, only rather short-lasting effects of some minutes were seen and these short-term increases did not seem to effect the gross daily food intake. In these studies a number of brain nuclei have been studied, VMH, LHA, PVN, DMH and POAH, but only bilateral infusion of H_1-antagonists into VMH or PVN induced feeding.

An opposite approach is to reduce histaminergic activity by α-fluoromethylhistidine (FMH), an irreversible inhibitor of histamine synthesis (17), which inhibits the histaminergic system for more than a day. Daily food intake increased clearly in rats given (60 μg/day of) FMH i.c.v. with an osmotic minipump (18). Also acute application of FMH into the 3rd ventricle or into VMH or PVN has been shown by Wada's group to transiently increase food intake during the light hours (19).

An interesting finding suggesting a physiological importance for the histaminergic regulation of feeding behavior was that also the body weight increased significantly more in our FMH-treated rats than in the controls during the follow-up period of one week (18). This implies that at least within this time frame no compensatory mechanisms appeared to counteract the increased feed intake due to the loss of histaminergic tone. Similar findings after peripheral application of FMH have been reported by another group (20).

Analogously, food intake decreases when the release of endogenous histamine is stimulated by i.c.v. application of thioperamide, an H_3-receptor antagonist blocking the autoinhibition of histamine release. The ultimate anorectic effect of histamine is thought to be mediated through H_1-receptors also in this case as it could be prevented by pretreatment with chlorpheniramine (19).

A general feature in the studies on the histaminergic neuronal system and food intake seems to be the involvement of circadian variation. This has been reported in connection with the effects of the precursor, synthesis inhibitor and differrent antagonists. Also histamine infused into the SCN has been shown to change the feeding pattern, to flatten the rhythm (21).

Recently it has been suggested that histamine may mediate also the modulatory effects of sensory stimuli, such as food consistency, on eating volume and speed in the rat (22).

Effect of eating on histamine release

By using the microdialysis technique it has been possible to follow the release of endogenous histamine while the animal is eating. In the medial hypothalamus, an increased release has been shown within minutes after eating (23). Since stimulation of this hypothalamic area is considered to be connected with the feeling of satiety, one may speculate that the periprandial release of this transmitter could be part of a negative feedback system controlling the amount of food to be eaten.

It is of interest that the circadian variation in methylhistamine concentrations has been reported to disappear during fasting (24). This finding is consistent with the increased release of histamine during feeding but it opens a number of questions as to the relationships of eating-induced histamine turnover with other activities of the histaminergic neurons.

What could be the mechanism of action of histamine in inhibiting food intake?

Since there was some *in vitro* evidence that histamine could be connected to the glucose regulating system (25—28), we studied the effect of metoprine on the glucoprivic feeding response induced by 2-DG. This substance acts

kinetically as glucose but is not metabolized. By inducing intracellular hypoglycemia it stimulates feeding behavior. Although metoprine decreased eating after 2-DG, it did not prevent the entire feeding response, suggesting that the mechanism of action of metoprine, and possibly of histamine, is not via inhibiting the glucoprivic feeding signal but on a higher modulatory level (29, 30).

Toxicological tools in anorexia research

Different kind of an approach is to study the efffects of TCDD (2, 3, 7, 8-tetrachlorodibenzo-p-dioxin) which is a very potent anorectic agent on the levels of endogenous histamine. A lethal dose of TCDD causes a drastic reduction of feed intake within one to two days. In a sensitive rat strain (Long-Evans, LE) anorexia is permanent, and the animals will called wasting syndrome in about three weeks. In very resistant rats, the Han/Wistar Kuopio (H/W) strain, the food intake also decreases initially, but in about two weeks the rats start to eat again, and they can survive even a huge dose of TCDD (31).

Different brain neurotransmitters including histamine were studied in LE rats after a large lethal dose to screen for mechanistic explanations for the development of anorexia (32, 33). In catecholamines no meaningful changes were seen. In the serotonergic system the most remarkable change was a late increase in brain tryptophan but the correlation to anorexia was not convincing (33). In hypothalamic histamine a small increase was seen 28 h after the TCDD dosing (32), and by the punch technique, an increase was seen in median eminence (34). These fluctuations might indicate minor disturbances in the regulatory systems of the hypothalamus.

Recently, in a Polish-Finnish collaboration it was possible to study portocaval anastomosed (PCA) rats and their reactions to TCDD. These PCA animals have brain histamine concentrations which are elevated severalfold (35, 36). The animals grew more slowly than controls, but after one to two months their food intake did not differ from sham operated controls.

After TCDD treatment, we were unable to detect any major TCDD related effects in brain concentrations of histamine or methylhistamine of these PCA rats. At a sublethal dose, in LE rats the PCA aggravated the anorexia and significant decrease in body weight, but at a high lethal dose in LE and at two high nonlethal doses in H/W rats the anorectic effect was even somewhat inhibited by PCA (37).

Hence it seems that at least the increased brain histamine after PCA does not systematically lead to an aggravated anorexia after TCDD, but the results with a sublethal dose may require a further examination. By and large, aminergic mechanisms do not seem to be the main mediators of anorexia after TCDD.

Connections between the histaminergic and other neurotransmitter systems

Because food intake is such a crucial activity for living organisms, it is plausible that its proper functioning is protected and maintained by a complicated cascade of events and a whole network of modifying systems.

Some of the effects and sites of action of classical neurotransmitters on food intake are listed in *Table 1*. One can see that noradrenaline, 5-HT and GABA exert effects in the same hypothalamic nuclei where the actions of histamine have been localized. In other systems α-adrenergic stimulation is known to inhibit (38, 39) and 5-HT to stimulate (40, 41) the release of histamine. It would be interesting to study whether similar, apparently logical functional cooperation exists between these substances in PVN and VMH in connection with feeding regulation.

Table 1. The effects of neurotransmitters on food intake

Receptor type	Action	Site of action
α_2-Noradrenergic	Increases	PVN
b-Adrenergic	Decreases	Perifornical hypothalamus
5-HT_{1A}	Increases	Median raphe nucleuses
5-HT_{1B}	Decreases	PVN
Dopamine (low dose)	Increases	Perifornical hypothalamus and VTA
Dopamine (high dose)	Decrease	
GABA (muscimol)	Increases	VMH
	Decreases	Lateral hypothalamus

The histaminergic neurons are functionally associated also with several peptides e.g. galanin (42) and growth hormone releasing hormone (GH-RH) (43) which are involved in the control of food intake (44, 43).

CONCLUSION

Histaminergic regulation of feeding behavior may have applications in basic physiology, pharmacology and toxicology. It is, however, quite clear that our understanding of the complexity of this regulation is still rudimentary. Therefore continued effort is needed to reveal the sites of the crucial synapses, the afferent inputs which make the histaminergic neurons to respond, and the efferent structures on which the histaminergic neurones exert their modifying effect. All of these will provide interesting puzzles for histamine researchers for many years to come.

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