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Invited review

The histaminergic system as a target for the prevention of obesity and metabolic syndrome

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ABSTRACT

The control of food intake and body weight is very complex. Key factors driving eating behavior are hunger and satiety that are controlled by an interplay of several central and peripheral neuroendocrine systems, environmental factors, the behavioral state and circadian rhythm, which all concur to alter homeostatic aspects of appetite and energy expenditure. Brain histamine plays a fundamental role in eating behavior as it induces loss of appetite and has long been considered a satiety signal that is released during food intake (Sakata et al., 1997). Animal studies have shown that brain histamine is released during the appetitive phase to provide a high level of arousal preparatory to feeding, but also mediates satiety. Furthermore, histamine regulates peripheral mechanisms such as glucose uptake and insulin function. Preclinical research indicates that activation of H_1 and H_3 receptors is crucial for the regulation of the diurnal rhythm of food consumption; furthermore, these receptors have been specifically recognized as mediators of energy intake and expenditure. Despite encouraging preclinical data, though, no brain penetrating H_1 receptor agonists have been identified that would have anti-obesity effects. The potential role of the H_3 receptor as a target of anti-obesity therapeutics was explored in clinical trials that did not meet up to the expectations or were interrupted (clinicaltrials.gov). Nonetheless, interesting results are emerging from clinical trials that evaluated the attenuating effect of betahistine (an H_1 agonist/H_3 antagonist) on metabolic side effects associated with chronic antipsychotics treatment. Aim of this review is to summarize recent results that suggest the clinical relevance of the histaminergic system for the treatment of feeding disorders and provide an up-to-date summary of preclinical research.

This article is part of the Special Issue entitled 'Histamine Receptors'.

1. Histamine and feeding behavior: preclinical studies

The first evidence of the inverse relationship between brain histaminergic activity and appetite dates back to the seminal paper by Clineschmidt and Lotti (Clineschmidt and Lotti, 1973) who administered histamine that does not cross the blood brain barrier, into the lateral ventricle of cats, and observed a long-term suppression of food intake. Similarly, continuous histamine infusion into the suprachiasmatic nucleus of the hypothalamus (Itowi, 1988) or acute injection into the lateral ventricles (Lecklin and Tuomisto, 1998) reduced food intake in rats. Similar effects were observed after systemic administration of the histamine precursor, L-histidine (Kasaoka et al., 2004; Orthen-Gambill, 1988; Sheiner et al., 1985; Vaziri et al., 1997; Yoshimatsu et al., 2002) or the inhibitor of histamine catabolism, metoprine (Lecklin et al., 1995). Subsequent studies demonstrated that H_1 receptor activation in the hypothalamic paraventricular nucleus (PVN) and ventromedial nucleus (VMH) induced satiety (reviewed in Masaki and Yoshimatsu, 2006), whereas blockade of brain H_3 autoreceptors, that increase the release of histamine and other neurotransmitters, appear to have beneficial effects in several behavioral and metabolic parameters associated with food intake. Results obtained in animal studies are summarized in the Table 1.

Neuronal histamine affects not only food intake, but also regulates feeding circadian rhythms. Sustained infusion of alpha-fluoromethylhistidine (a-FMHis, a suicide inhibitor of histidine decarboxylase) into the rat third cerebral ventricle disrupted light–dark cycles of feeding, drinking and ambulatory activity in rats fed ad libitum (reviewed in Passani et al., 2011). It is known that food availability is a powerful circadian signal, thus when food

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Table 1
Effect of histaminergic ligands on food intake and body weight.

Compound	Species	Administration route	Treatment regimen	Pharmacological effects		Reference
				Food intake	Body weight	
H_1R Agonist						
2-(3-trifluoromethylphenyl) histamine	Rat	i.c.v.	Acute	↓	NI	(Lecklin and Tuomisto, 1998)
H_1R Antagonists						
Cetirizine	Mice (HFD)	i.p.	Chronic	–	↑	(Raveendran et al., 2014a)
Chlorpheniramine	Rat	i.c.v. Intra VMH/PVN	Acute	↑	NI	(Doi et al., 1994; Fukagawa et al., 1989; Sakata et al., 1988a; Sakata et al., 1988b; Sakata et al., 1988c)
	Rat	Intra DMH/LH/POAH	Acute	–	NI	(Ookuma et al., 1989; Sakata et al., 1988b; Sakata et al., 1988c)
	Rat	i.c.v. Intra VMH/PVN	Acute	↑	NI	(Machidori et al., 1992; Sakata, 1991; Sakata et al., 1991; Yoshimatsu et al., 1993)
	Zucker rat	i.c.v. Intra VMH/PVN	Acute	–	NI	(Machidori et al., 1992; Sakata, 1991; Sakata et al., 1991; Yoshimatsu et al., 1993)
	Rat	i.p.	Acute	Block thioperamide effect	NI	(Okuma et al., 1993)
	Rat	i.p.	Acute	↓	NI	(Vaziri et al., 1997)
	Sheep	i.c.v.	Acute	Block HA effect	NI	(Rahmani and Ingram, 2007)
	Chicken	i.c.v.	Acute	Block HA effect	NI	(Meade and Denbow, 2001)
	Rat	i.c.v. Intra VMH	Acute	↑	NI	(Fukagawa et al., 1989; Sakata et al., 1988a; Sakata et al., 1988b; Sakata et al., 1988c)
	Rat	Intra LH/PVN	Acute	–	NI	(Sakata et al., 1988b; Sakata et al., 1988c)
Cyproheptadine	Rat	?	?	↑	NI	(Mercer et al., 1994; Orthen-Gambill, 1988)
	Rat	i.p.	Chronic	↑	↑	
Diphenydramine	Rat	i.p.	Chronic	↑	↑	(Mercer et al., 1994)
Doxepin	Rat	?	?	↑	NI	(Mercer et al., 1994; Orthen-Gambill, 1988)
	rat	i.p.	Chronic	↑	↑	
Fexofenadine	Mice (HFD)	i.p.	Chronic	–	↑	(Raveendran et al., 2014a)
Mepyramine/pyrilamine	Rat	i.c.v. Intra VMH	Acute	↑	NI	(Fukagawa et al., 1989; Sakata et al., 1988a; Sakata et al., 1988b; Sakata et al., 1988c)
	Rat	Intra LH/PVN	Acute	–	NI	(Sakata et al., 1988b; Sakata et al., 1988c)
	Rat	i.p.	Acute	↓ Block metoprine effect	NI	(Lecklin and Tuomisto, 1998)
	Rat	?	?	Block HA effect	NI	(Itowi, 1988)
Promazine	Rat	i.p.	Chronic	↑	↑	(Mercer et al., 1994)
Promethazine	Rat	i.c.v. Intra VMH	Acute	↑	NI	(Fukagawa et al., 1989; Sakata et al., 1988a; Sakata et al., 1988b; Sakata et al., 1988c)
	Rat	Intra LH/PVN	Acute	–	NI	(Sakata et al., 1988b; Sakata et al., 1988c)
	Rat	?	?	↑	NI	(Orthen-Gambill, 1988)
	Chicken	i.p.	Acute	Block HA effect	NI	(Cabrera and Saadoun, 2006)
Tiprolidine	Rat	i.c.v.	Acute	↑	NI	(Kurose and Terashima, 1999)
H_2R Agonist						
Dimaprit	Rat	Icv	Acute	–	NI	(Lecklin and Tuomisto, 1998)
H_2R Antagonists						
Cimetidine	Rat	i.c.v. Intra VMH/LH/PVN	Acute	–	NI	(Fukagawa et al., 1989; Sakata et al., 1988a; Sakata et al., 1988b; Sakata et al., 1988c)
Cimetidine	Chicken	i.c.v.	Acute	Block HA effect	NI	(Meade and Denbow, 2001)
	Chicken	i.p.	Acute	Did not Block HA effect	NI	(Cabrera and Saadoun, 2006)
Famotidine	Rat	i.c.v. Intra VMH/LH/PVN	Acute	–	NI	(Doi et al., 1994; Fukagawa et al., 1989; Sakata et al., 1988a; Sakata et al., 1988b; Sakata et al., 1988c)
Famotidine	Rat	Icv	Acute	↓	NI	(Lecklin and Tuomisto, 1998)
Ranitidine	Rat	Ip	Acute	↓ in the dark phase - no effect on light fase and total 24 ours - did not change metoprine effect	NI	(Lecklin and Tuomisto, 1998)
	Sheep	icv	Acute	Did not Block HA effect	ni	(Rahmani and Ingram, 2007)
H_3R Agonists						
Imetit	Rat	i.c.v./i.p.	Acute	↑	NI	(Clapp and Luckman, 2012)
Immepip	Rat	i.c.v.	Acute	↑	–	(Chiba et al., 2009)
RAMH	Rat	i.c.v.	Acute	–	NI	(Lecklin and Tuomisto, 1998)
	Mouse	i.p.	Acute	↑	NI	(Jørgensen et al., 2005)
	Sheep	i.c.v.	Acute	Did not block HA effect	Ni	(Rahmani and Ingram, 2007)
H_3R Antagonists						
(4,4-Difluoropiperidin-1-yl) [1-isopropyl-5-(1-isopropylpiperidin-4-yloxy)-1*H*-indol-2-yl]methanone	Rat (HFD)	i.p.	Chronic	↓	↓	(Pierson et al., 2009)
A-304121	Rat	i.p.	Chronic	–	–	(Pan et al., 2006)
A-331440	Mice (HFD)	p.o.	Chronic	↓	↓	(Hancock et al., 2004a; Hancock and Brune, 2005)