

Central effects of histamine on food intake, and kind of histamine receptors in sheep brain

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Abstract

Histamine is a well known amine which controls many physiological functions of the CNS, including; fluid balance, appetite, thermoregulation, cardiovascular control, learning and stress response. All these functions are done via three membranous H₁, H₂ and H₃ receptors, which in laboratory animals feeding behaviour is under the control of H₁ type. In order to investigate the central effect of histamine on sheep feeding behaviour and characterization of its receptors, a Latin square test was designed using four Iranian Nainee rams which were intra-cerebroventricularly cannulated. In the first stage 12hr fasted (7PM to 7AM) rams in individual cages were infused with 0(control), 100, 400 and 800nM of histamine in turn, which each ram received each dose 4 times in different days. 10 minutes later (7AM) water and food container were put in their cages and the consumed water and food were recorded at 0.5, 1, 3 and 12hr intervals. Results of this stage revealed that histamine significantly ($P<0.01$) suppressed food intake in this species. Using three specific histamine antagonists; chlorpheniramine, ranitidine and thioperamide in the next stage showed this suppressive effect of histamine was significantly ($P<0.01$) blocked by chlorpheniramine. Concluding that feeding behaviour in sheep by histamine is controlled via H₁ receptors.

Key words: histamine, sheep, brain, receptor, feeding

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Introduction

Animal food intake and energy balance in applied physiology is considered seriously. Different mechanisms which control the feeding behaviour have been discovered by particular techniques. All these mechanisms involve molecular signals from peripheral to the central nervous system (CNS) including; glucose, triglycerides, leptin, insulin, amylin, enterostatin, ghrelin and cholecystokinin from different tissues. These signals modulate other molecules in the CNS such as, neuropeptide Y, α MSH, opioids, interleukin 1, galanin, glutamate, dopamine, norepinephrin, serotonin, GABA, acetylcholine and histamine (Costentin, 2004).

Histamine is one of the well known amines which contribute in many physiological functions in the CNS (Brown et al., 2001) as well as feeding behaviour (Cohn et al., 1973; Machidori et al., 1992 and Ookuma et al., 1993). Two sources of this amine in the brain are neurons and mast cells (Garbarg et al., 1976) which the later is

scarce in this tissue. These secretory neurons are almost localized in tuberomammillary nucleus (TMN) of posterior hypothalamus and project to several brain areas (Inagaki et al., 1988). The released histamine affects arousal state, locomotor activity, feeding and drinking functions (Cacabelos, 1990; Wada et al., 1991; Onodera et al., 1994; Doi et al., 1994) via three well known kinds of H_1 , H_2 and H_3 receptors (Hill, 1990).

There are considerable reasons that believe histamine inhibits food intake through H_1 receptors (Sakata et al., 1988; Fukagawa et al., 1989; Ookuma et al., 1993; Doi et al., 1994 and Lecklin et al., 1998). Researches on different species such as rat (Lecklin et al., 1998), cat (Clineschmidt et al., 1973) and goat (Tuomisto and Eriksson, 1979) have shown that histamine is involved in their feeding behaviour. Recent evidences suggest that leptin as an important anti-feeding agent works via histamine mediating (Yoshimatsu et al., 1999 and Itateyama et al., 2003), and even histidine supplementation of food suppresses food intake in rats (Kasaoka et al., 2004). Sheep as a ruminant model and different species from laboratory animals is under the influence of high concentration of different biogenic amines and might be interesting for studying the role of histamine in this species. The present study was conducted to evaluate the central effects of histamine, its dose dependency and its candidate receptors in the sheep brain.

Materials and Methods

1. Animals

Six 12 months old Nainee (fat tailed medium size Iranian breed) male sheep weighing 32 ± 3 Kg after one week complete checking were intracerebroventricularly (ICV) cannulated. The reason for selecting the male sheep is the research which has shown that content of mast cells is changed over the oestrous cycle in rat brain (Aydin et al., 1998). The method for ICV cannulation was similar to the method explained by Keverne and Kendrick (1992); briefly, the sheep were pretreated by xylazin (0.22 mg/Kg) and Ketamin (0.05 mg/kg) via IV injections. Then the endotracheal tube was inserted into the trachea and connected to the anaesthetic machine which controlled the anaesthetic stage with halothane inhalation, and the surgery was done at 3rd stage. The sheep were positioned in sternal recumbency and their head were fixed in a stereotaxic frame (Kopf model UK, for large animals). Under the sterile conditions the skin of the frontal area which were earlier clipped and washed by alcohol and betadine was opened 10cm at midline. Bregma point as a landmark was chosen and $5.4 \pm 0.2 \text{ mm}$ lateral, and $17 \pm 1 \text{ mm}$ cranial and left to this point the frontal bone was drilled. After getting the soft tissue, the needle attached to the manipulator was holding down gradually till the entrance to the ventricle (about $16 \pm 2 \text{ mm}$ ventral) indicated by PBS (phosphate buffer saline) flowing down. The needle number 18 was fixed at this situation by dental cement surrounded by 3 screws and a holding ring. Animals received antibiotic (pen-strep 1+1) for 3 days and a radiographic picture was taken from their skull to check the cannula position, then were kept for one week later. After ten days sheep were separated into individual cages ($1.5 \times 1.5 \text{ m}$) in a 20 m^2 room with natural light (12 ± 1 dark/light period), 50-60% humidity and 17°C controlled temperature. Two of these sheep were kept as the reserve and four of them were used in a Latin square designed test and the experiment was divided in two stages.

2. Experiment 1

In the first stage in order to find out the effective dose of histamine four of these sheep received 0 (control), 100, 400, 800 nM histamine chloride (sigma) dissolved in 100µl of PBS (phosphate buffer saline, pH 7.4), intra-ventricularly at 7AM after 12 hr fasting. After 10-15 minutes they had free access to food in TMR (total mixed ration) form and drinking water. Consumed food and water were measured and recorded 0.5, 1, 3 and 12 hr later, and their container were removed from the cages at 7.15 PM, which sheep were fasted for 12 hr prior to the next injection. Each sheep received different dose of histamine in turn on consecutive day, and finally each sheep at least had received each dose of histamine four times, and totally for each dose of histamine there were 16 recorded food and water intake levels from 4 sheep.

3. Experiment 2.

Results of the first stage showed the effective dose of histamine in sheep brain on feeding behaviour. Using these data in the second stage of the experiment all the conditions were the same as the first stage except the sheep were pre-treated by icv injection of 400nM of histamine selective antagonists; Chloropheniramine (H_1 antagonist), ranitidine (H_2 antagonist) and thioperamide (H_3 antagonist) dissolved in 50µl of PBS, 10 minutes prior to histamine injection, and the rest of the experiment was similar to the first stage except the histamine for pretreated sheep was dissolved in 50µl of PBS in order to keep the infused volume stable over the experiments.

The results of both experiments were analyzed by GLM, and averages compared by Duncan's range test method using the SAS (1999) software.

Results and Discussion

Results of the first experiment are shown in table 1. Mean±SE of water and food intake (ml and gram, respectively) in different interval times after histamine infusion indicate that water consumption is not affected by any dosages of histamine, but the food intake has been significantly ($P<0.01$) reduced, particularly at 400 and 800 nM levels for 3 hours. 100nM of histamine was also effective on food intake level for just 0.5 hour after injection. These results were essential for setting up the second stage of the experiment, because the effective dose of histamine and duration of histamine activity in the brain of this species were not accessible.

Results of the second experiment are shown in Table 2. As Mean±SE of the water and food consumption (ml and gram, respectively) in different interval times (0.5, 1, 3, 12 hr) after histamine, or antagonist pre-treated and histamine illustrate, there are significant differences among some treatments. As table 2 monitors there is no difference for water consumption among treatments. As stated earlier, it seems sheep is not responding to histamine and its antagonists at all in relation with water consumption. But the results show significant differences ($P<0.01$) for food consumption among treatments. Chloropheniramine, ranitidine and thioperamide as specific H_1 , H_2 and H_3 receptor antagonists, respectively demonstrate different results. Pre-treatment sheep with 400nM chloropheniramine at both levels (400 and 800nM) of histamine blocked the suppressive effect of histamine on food intake, but neither ranitidine, nor the thioperamide showed any difference with histamine infused group. The effect of chloropheniramine was

dependent to the dosages of histamine used. When sheep were pre-treated with 400nM chloropheniramine and infused with 400 and 800nM histamine, the later group fed 37% less at half and one hour later, and also the results are comparable with control group of experiment one (Table 1).

The role of histamine in fluid balance have been implicated for a long time. Direct action of histamine on drinking has already been reported (Gerald and Maickel, 1972; Leibowitz, 1973), and also indirect effect of this amine on vasopressin has also been confirmed (Bhargava et al., 1973; Bennet and Pert, 1974; Kjaer et al., 1994). As the results of this study show water consumption in sheep was not influenced by any dosages of histamine. These results are not consistent with several studies done on rat (Leibowitz, 1973; Lecklin et al., 1998). Histamine even as a dipsogenic compound is highly site-specific and elicits drinking where administered, particularly into the anterior, lateral, preoptic and antero-lateral hypothalamus of the rat (Leibowitz, 1973). Lecklin et al., (1998) reported stimulating H_3 receptors is followed by drinking response and is antagonized by thioperamide which confirmed the earlier study (Clapham and Kilpatrick, 1993). One point which should be considered about these reports relates to a specific H_3 receptor agonist (RAMH, R- α -methylhistamine) which has 14 times more affinity than histamine for H_3 receptors (Arrang et al., 1987). Even in rat there are reports which believe injection of histamine into the third ventricle does not affect water intake (Kraly and Arias, 1990), but reconfirming H_3 receptors are involved in this behaviour (Kraly et al., 1995).

Relation between histamine, water intake and diuresis is relatively complicated and seems other neurotransmitters such as vasopressin are also involved in different species (Bennet and Pert, 1974; Bhargava et al., 1973; Tuomisto and Eriksson, 1979; Dogterom et al., 1976 and Tuomisto et al., 1984). It is interesting that couple of these reports is about goat which is a ruminant, and histamine plays an antidiuretic role in this species (Tuomisto and Eriksson, 1979, Tuomisto et al., 1984). Similar results has also been reported about different strains of rats; wistar and Long-Evans, which exhibit different diuretic response to histamine (Lecklin and Tuomisto, 1995). Considering the mentioned articles, it is not very unusual that special Iranian breed did not respond to histamine in relation with water intake. On the other hand the urine volume measuring in this study was really difficult in conscious ram and seems interesting to think about vasopressin level and diuresis in this kind of species which are adapted to hot and dry climate.

The history of histamine involvement in feeding behaviour is related to some antidepressant and antipsychotic drugs which increased weight gain of patients (Kalucy, 1980; Russ and Ackerman, 1988), and researches had confirmed these drugs were H_1 receptor blockers (Hill and Young, 1978; Taylor and Richelson, 1980). All these consider the histamine as an anorectic amine, which is also released in response to many other chemical signals such as Leptin (Ito et al., 2003), Amylin (Mollet et al., 2003), Peptide YY (Itoh et al., 1999). A recent study has monitored even supplementing rat ration with histidine as a histamine precursor inhibits food intake in this species (Kasaoka, et al., 2004). In this study, in contrast to the water intake, food intake was significantly ($P<0.01$) affected by icv histamine infusion. This behaviour was dose dependent that 400 and 800 nM of histamine suppressed feeding for at least three hours. This data are in line with other reports in different species (Clineschmidt and Lotti, 1973; Machidori et al.,

1992; Tuomisto and Eriksson, 1979; Lecklin et al., 1998; Morimoto et al., 2001; Brown et al., 2001). Involvement of histamine in food intake is very consistent, and seems to be an exception. Regarding Table 1 indicates 100, 400 and 800 nM of histamine decreases food intake 17, 77 and 88%, respectively in half an hour after infusion in fasted sheep, and this reduction continued at 58 and 77% levels and, 32 and 40% levels for one and three hours later, respectively. But the total food consumption at twelve hours are similar, which means over the rest nine hours their food intake is improved and the infused histamine is metabolized. Unfortunately there is no reference for half life of histamine in sheep brain, but it is interesting that the turnover time of this amine in this tissue is close to the rat (Lecklin et al., 1998).

Different procedures have demonstrated which histamine as a central amine controls feeding (Cohn et al., 1973; Sheiner et al., 1985; Machidori et al., 1992 and Ookuma et al., 1993), and H₁ antagonists block this suppressive effect of histamine (Sakata et al., 1988; Ookuma et al., 1989 and Eukagawa et al., 1989). Most of these H₁ receptors are located in the ventromedial nucleus (Fukagawa et al., 1989), and a recent study believes that mesencephalic trigeminal nucleus is also considered (Fujise et al., 1998). As stated by Morimoto (2001) about rat the role of histamine in the brain is relatively complicated and this is when enormous researches have been done on laboratory animals, particularly rat. In this condition with limited reports about large animals such as sheep and regarding the species differences, this is just beginning.

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Table 1: Effect of icv infused histamine on water (W, ml) and food (F, gr) intake in sheep

Treatment Histamine (nM)	Time after ICV infusion (hr)							
	0.5		1		3		12	
	W	F	W	F	W	F	W	F
0 (control)	428±50 ^a	316±26 ^a	740±100 ^a	478±60 ^a	1140±120 ^a	690±65 ^a	2541±160 ^a	1249±95 ^a
100	336±73 ^a	261±16 ^b	758±95 ^a	401±84 ^a	1195±170 ^a	601±75 ^a	2597±140 ^a	1335±120 ^a
400	483±84 ^a	73±27 ^c	840±83 ^a	198±23 ^b	1216±90 ^a	465±42 ^b	2610±90 ^a	1344±150 ^a
800	598±88 ^a	38±21 ^c	883±70 ^a	108±31 ^c	1305±110 ^a	416±50 ^b	2809±120 ^a	1405±170 ^a

The numbers are Mean ± SE of 15-16 recorded data. In each column different superscript letter indicate the numbers are statistically different (p<0.01)

Table 2: Effect of icv infused histamine antagonist, and histamine on water (W, ml) and food (F, gr) intake in sheep

Treatment (Antagonist and Histamine)	Time after ICV infusion (hr)							
	0.5		1		3		12	
	W	F	W	F	W	F	W	F
400nM	540±74 ^a	84±33 ^c	822±74 ^a	186±34 ^c	1120±90 ^a	485±56 ^a	2585±86 ^a	1387±146 ^a
Chloropheniramine	435±87 ^a	387±21 ^a	820±60 ^a	506±27 ^a	940±150 ^a	572±53 ^a	2398±180 ^a	1381±30 ^a
Ranitidine	403±110 ^a	81±27 ^c	760±80 ^a	205±25 ^c	975±120 ^a	477±42 ^a	2593±85 ^a	1413±23 ^a
Thioperamide	452±95 ^a	65±25 ^c	751±65 ^a	200±21 ^c	1128±75 ^a	511±24 ^a	2403±90 ^a	1413±31 ^a
800nM	530±76	43±25 ^c	878±76 ^a	99±43 ^d	1312±116 ^a	506±58 ^a	2794±118 ^a	1396±156 ^a
Chloropheniramine	616±70 ^a	245±25 ^b	860±55 ^a	480±63 ^a	1308±60 ^a	480±63 ^a	2825±170 ^a	1401±27 ^a
Ranitidine	534±65 ^a	65±18 ^c	811±95 ^a	106±24 ^d	1113±70 ^a	505±25 ^a	2407±110 ^a	1428±31 ^a
Thioperamide	618±90 ^a	98±20 ^c	825±70 ^a	113±23 ^d	1315±50 ^a	518±26 ^a	2828±80 ^a	1435±25 ^a

The numbers are Mean ± SE of 15-16 recorded data. In each column different superscript letters indicate the numbers are statistically different (p<0.01)