INVOLVEMENT OF HISTAMINE RECEPTORS IN MEDIATION OF HISTAMINE INDUCED THERMO-REGULATORY RESPONSE IN RATS

P. K. DEY AND NITIS MUKHOPADHAYA

Neurophysiology Research Unit, Department of Physiology, Institute of Medical Sciences, Banaras Hindu University, Varanasi - 221 005

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Summary : At there ambient air temperature range, the rectal temperature changes following infusion of histamine either into lateral ventricle (L.V.) or IVth ventricle (IVth V) were studied. At an ambient temperature range of 19-22°C, hypothermia occurred following histamine infusion either into L.V. or IVth V. Hypothermia elicited from infusion of histamine into L.V. was prevented with pretreatment of H_1-receptor blocker (mepyramine), but in case of IVth V, it was prevented with H_2-receptor blocker(cimetidine). These H_1 and H_2-receptor antagonists were ineffective in preventing hypothermia following histamine infusion into either L.V. or IVth V, when the ambient air temperature was maintained low (11-13°C).

At thermoneutral zone (25-27.5°C), infusion of histamine in L. V. also produces hypothermia, but in case of IVth V, the same produces hyperthermia which is considerably antagonised by H_1-receptor blocker (mepyramine). The significance of all the above observations are discussed.

Key words : hypothermia, histamine, H_1-receptor blocker, H_2-receptor blocker, hyperthermia, thermoregulation

INTRODUCTION

Recent histochemical findings strongly suggest that histamine may play a role as neurotransmitter in the Central nervous system (18, 19). In our previous paper (13), we have shown that administration of histamine into different C.S.F. compartments in rat brain produces an alteration of core body temperature. It was further noted that the direction and magnitude of changes in core temprature following i.c.v. administration of histamine is dependent on the ambient air temperature.

With the establishment of the presence of H_1 and H_2-receptors on neurons, as well as the mapping of the distribution of these two sub-types of receptors at different regions of the brain (specially in hypothalamus and brainstem region), the present study was undertaken for further analysis of thermoregulatory response of histamine with the use of appropriate antagonists for H_1 and H_2-receptors.

MATERIAL AND METHODS

Experiments were carried out in inbred male albino rats (CF strain, 205-320 g). The detailed procedures for chronic implantation of stainless steel guide cannula either into right L.V. or IVth V, as well as the infusion of drug solutions into C.S.F. compartments have been described earlier (13). All drug solution were administererd in a volume of 10 μl. The rectal temperature was recorded from Aplab 6 channel Telethermometer through a thermistor probe (Yellow Spring Co., USA) as described earlier (13).

After each experiment, the animal was anaesthetised with pentobarbitone, and 10 μl Evans Blue dye (2%) was infused following the same procedure as for the drug solutions. After 5 min the brain was perfused with buffered formalin solution and was removed for confirmation of placement of the cannula. The mapping of the spread of the dye in the liquor space was carried out through naked eye observation.

Drugs: Histamine dihydrochloride, Sigma Chemical Co., U.S.A. cimetidine, Sigma Chemical Co. USA and Mepyramine maleate, May & Baker, India, were used. The drugs were dissolved in sterile 0.9% saline solution (pH adjusted to 7.4) for infusion into either lateral ventricle or IVth ventricle.

RESULTS

The histamine receptor blocking drugs, mepyramine (H_1-receptor blocker) and cimetidine (H_2-receptor blocker), were administered in a dose of 20 μg into L.V. of rat, 60 min prior to infusion of 20 μg histamine through the same route. The results are shown in Table I.

A significant fall in rectal temperature ranging between 0.8° and 0.9° was observed following histamine infusion into L.V., when the experiments were carried out at an ambient temperature of 21-21.5°C. This hypothermic response of histamine was prevented completely by prior administration of mepyramine (H_1-receptor blocker), however, a delayed hyperthermia of about 1° was noted over 70 min after histamine infusion. This late hyperthermia was not associated with spreading of saliva on the fur or wetting of the snouts in the animals. While administration of cimetidine (H_2-blocker) could not prevent the hyperthermic response of histamine. This suggests that histamine induced hypothermia may be

mediated through H_1-receptor bearing neurones located in hypothalamic thermoregulatory system.

TABLE I : Shows effects of mepyramine and cimetidine on histamine induced changes in rectal temperature. All drugs were administered in a dose of 20 μg into lateral venticle. Mepyramine and cimetidine were infused 90 min prior to histamine administration.

Treatment	*Ambient Temp. (°C)*	*Basal/Rectal Temp. (°C) Mean±SD*	*Rect. Temp. Mean±SD*	*Time taken for maxim. change (min) Mean±SD*	*Time taken for 50% change (min) Mean±SD*	*Recovery period (min) Mean±SD*
Histamine (n=4)	11°	36.95±0 37	−0.83±0.2	18.25±2.36	13.75±2.50	213.33±23.03
Mepyr.+Histamine (n=3)	11°	37.16±0.40	−0.63±0.15	16.66±2.88	10.00±2.50	71.66±10.40
Cimet.+Histamine (n=3)	13°	36.50±0.6	−0.6±0.0	15.0±2.50	10.50±1.50	170.0±17.32
Histamine (n=4)	21-22°	37.55±0.14	−0.90±0.05	30.0±5.77	18.75±4.78	187.50±9.50
Mepyr.+Histamine (n=2)	21°	36.90±0.50	+1.0±0.0	70.50±0.50	50.0±2.50	165.0±12.50
Cimet.+Histamine (n=4)	21-21.5°	37.21±0.38	−1.02±0.09	30.0±4.08	15.0±3.80	177.50±25.0
Histamine (n=3)	26-27.5°	37.70±0.31	−0.80±0.1	26.66±5.77	13.33±2.88	200.0±17.32
Mepyr.+Histamine (n=4)	27-27.5°	37.70±0.53	+0.85±0.12	103.75±50.72	41.25±9.46	252.50±37.74
Cimet.+Histamine (n=4)	27°	37.35±0.4	−0.90±0.0	28.0±2.80	10.0±0.0	150.0±14.14

\+ Increase
— Decrease

Table II shows the results following either administration of mepyramine or cimetidine in a dose of 20 μg into IVth V 60 min prior to infusion of 20 μg histamine. A significant fall in rectal temperature of 1°C was observed following infusion of histamine into IVth V at an ambient temperature of 19-21°C, which is similar to observed in case of L.V. under similar ambient temperature. However, this hypothermic response was prevented with cimetidine, but not with mepyramine. This indicates, that in case of IVth V, the hypothermic response of histamine was mediated through H_2-receptors, which is in contrast to the observed involvement of H_1-receptors in case of L.V.

Unlike the hypothermia observed in case of L.V. route, the administration of histamine into IVth V at near thermoneutral ambient temperature (26°C) produced hypothermia of about 1.2°C. And this hyperthermic response was significantly attenuated following prior administration of mepyramine and not with cimetidine, indicating the role of H_1-receptors in such hyperthermic response from IVth V.

It was interesting to observe that when the experiments were carried out at an

ambient air temperature of 11-13°C, infusion of histamine either into L.V.or IVth V produced a fall in rectal temperature of 0.9-1°C, but this hypothermia occuring at such low ambient temperature range, remained unaffected by prior administration of H_1-receptor antagonist (mepyramine) or H_2-receptor antagonist (cimetidine).

TABLE II : Shows the effects of Mepyramine and Cimetidine on histamine incduced changes in rectal temp. All drugs were administered in a dose of 20 μg into IVth ventricle. Mepyramine and Cimetidine were infused 60 min prior to histamine administration.

Treatment	*T amb.* (°C)	*Basal Rectal Temp.* (°C) *Mean±SD*	*△ Rect. Temp. Mean±SD*	*Time taken for maxim. change (min)*	*Time taken for 50% change (min) Mean±SD*	*Recovery period (min) Mean±SD*
Histamine (n=4)	11-13	36.75±0.37	−0.95±0.03	16 25±2.50	10.50±2.50	175.0±85.04
Mepyr.+Histamine (n=3)	11-13	36.60±0.12	−0.87±0.01	15 20±2.80	12 0±1.0	152.0±14 26
Cimet.+Histamine (n=3)	13	37,0±0.0	−1.06±0.11	23.33±2.88	13.33±2.88	186.66±50.33
Histamine (n=4)	19-21	37.25±0.19	−1.0±0.08	32.50±2.85	17.50±2.88	150.0±25 80
Mepyr.+Histamine (n=3)	19-21	37.06±0.11	−0.96.±0.05	26.66±2.88	13.33±2.88	126 66±30.55
Cimet.+Histamine (n=3)	19-20	37.06±0.21	−0.20±0.0	10.0±0.0	—	—
Histamine (n=4)	26	37.50±0.08	+1.20±0.16	50.0±4.08	22.50±2 83	240.0±0.0
Mepyr.+Histamine (n=3)	25-27	38.0±0.21	+0.40±0.17	56.66±11.54	40.0±10.0	186.66±30 55
Cimet.+Histamine (n=2)	27-27.5	37.35±0.07	+1.10±0.14	40.0±0.0	22.50±3 50	235.0±21.20

\+ Increase
— Decrease

DISCUSSION

The observation that mepyramine (H_1-receptor blocker), but not cimetidine (H_2-receptor blocker), was very effective in antagonising the hypothermic response of histamine administered into L.V., indicates that such hypothermic effect of histamine is mediated through involvement of H_1-receptors located at hypothalamic region. Several workers have earlier reported that administration of histamine into L.V. or micro-infusion into rostral hypothalamus causes lowering of core body temperature in various species of animals and such hypothermic response was abolished by pretreatment with H_1-receptor blocking drugs (2,7,9,21). This view is strengthened with the observation made by Chang *et al* (6) who have shown through radioligand binding studies. that most of the histamihe receptors in hypothalamus of rat are of H_1 type. However the involvement of H_2-receptors in hypothermia has also been suggested (8,14). Identification and localization of histamine H_2-receptors in brain by radioligand binding studies (3) further suggest that there are both sets of histamine receptors (H_1 and H_2) in the central thermoregulatory pathways in rat. Following its central administration, histamine is expected

to activate both the receptors. Green *et al.* (9) have shown that activation of H_1-receptors in the PO/AH region causes a lowering of the core body temperature in rat accompanied by heat avoidance behaviour indicating a lowering of the thermoregulatory set-point. A similar observation has been made by Clark and Cumby (7) in cats. However, a direct activation of efferent heat loss pathways, without altering the setpoint, can also result in a fall of core temperature. By employing thermoregulatory behavioral studies in rat, Green *et al.* (8) have shown that histamine-induced-hypothermia is mediated through H_2-receptors which are located in the efferent heat loss pathways.

Interestingly, the Green *et al.* (8) in their study, failed to show blocking of the hypothermic response following administration of burimamide (H_2-receptor antagonist) into the L.V. However, from our present study, it appears likely the H_2-receptors, instead of being located in the efferent heat loss pathways are possibly concerned with heat production pathways. This assumption would be helpful in explaining occurence of delayed hyperthermia observed following mepyramine pretreatment. In this situation hyperthermia might be due to increased heat production/conservation mediated through H_2-receptors, location of which at distal areas away from the ventricular surface may account for the slow hyperthermic response. This reasoning fits well as to why hypothermic response remains unaltered rather a mild potentiation is observed with cimetidine pretreatment (Table I).

Besides, the hypothalamus and the adjacent preoptic area being known as the principal site of thermoregulation, in recent years it has emerged that other regions of brain including midbrain and lower brain stem are involved in thermoregulation, and in fact, are capable of exhibiting a limited degree of autonomous control (4,12,17). The presence of thermosensitive neurones (both warm and cold sensitive) in brain stem area behaving in the same manner as that of hypothalamus have also been reported (1,10). Moreover, the recent studies related to biochemical mapping of histamine in discrete areas of rat brain, identification of a descending histaminergic tract originating in the posterior hypothalamus and coursing downwards into the brainstem (16) as well as localisation of H_1 and H_2-receptors in the brainstem region (3,6) together suggest that certain thermosensitive brainstem neurones may be histaminergic. This has been supported with electrophysiological studies which revealed that microiontophoresis of histamine causes depression of neuronal firing rate in most of the brain regions except hypothalamus in rat (20) and such depression is mediated through H_2-receptors which are predominant (in comparison to H_1) in the midbrain and brainstem region. All these observations warrant a study of thermal change following administration of histamine into brainstem area; and this has been attempted through administration of histamine into IVth V in view of the suggestion made by Lipton (11) that medulla may be an important thermoregulatory zone in rat outside the hypothalamus.

The results show that administration of histamine into IVth V produced hypothermia at 19-21°C (Ta) and hyperthermia at 26-27.5°C (Ta). It is thus obvious that peripheral thermal drive arising from changes in ambient air temperature is an important factor for determining the thermoregulatory changes brought about by a neurochemical substance. It was observed that cimetidine antagonised the hypothermic effect, whereas, mepyramine blocked the hyperthermic effect of histamine. The above results may be explained on the basis, that at low Ta (19-21°C), where heat gain mechanism is fully operative, histamine infusion results in an inhibition of heat production leading to hypothermia which was blocked by cimetidine. This supports the mediation of H_2-receptors and electrophysiological studies have also revealed inhibitory action of histamine on H_2-receptors bearing neurones (20).

It has recently been reported (16) that, in lower brain stem region of rat, a thermogenic centre is present. This region also consists of high density excitatory H_1-receptors. The hyperthermic effect of histamine (observed at Ta 26-27.5°C) elicited from IVth V may be due to direct excitation of H_1-receptor bearing neurones and this is in confirmity with the ability of H_1-receptor blocker drug (mepyramine) to antagonise the hyperthermia.

One interesting observation made in the present study, was that, at 11-13°C (Ta), infusion of histamine either, into L.V. or IVth V produced hypothermia, which could not be prevented either with mepyramine or cimetidine. It is suggested that at this very low Ta, endogenous histamine released has already occupied most of its receptors and the dose blockers used in this study (20 μg) might have been quantitatively inadequate to compete with histamine for binding with the receptors. The work of Taylor and Snyder (22) may support such a possibility. Alternately, it may be that histamine induced hypothermia at such low Ta may be secondary to release of another neurotransmitter. Recently one such suggestion indicating serotonergic link in the hypothermic action of histamine has been made by Pilic and Nowak (15) though their experiments were carried out at 22°C (Ta).

It would appear from the present investigation that putative histaminergic neurones located in hypothalamus as well as scattered in lower levels of neuraxis might contribute to thermoregulatory control and such control might involve different sets of histaminergic receptors at hypothalamic and brainstem regions. Also, the pattern of thermal changes elicited through such histaminergic neurones following central administration of histamine are dependent on the peripheral thermal drive providing information about ambient air temperature.

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