THERMOREGULATORY RESPONSE IN RATS FOLLOWING ADMINISTRATION OF HISTAMINE IN DIFFERENT CSF COMPARTMENTS

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Summary : Recently histamine is being considered as an important neurotransmitter/ neuromodulator in the central nervous system. This has been supported from the present observations with regard to thermoregulatory responses elicited following histamine administration into different CSF compartments. Administration of histamine into the right lateral cerebral ventricle of rats showed a dose dependent fall in rectal temperature. This hypothermic response was evident only at moderately low or at thermoneutral ambient temperature. Administration of histamine into fourth ventricle produced hypothermic response at low ambient temperature and hyperthermia at thermoneutral ambient temperature, which was no longer observed when the ambient temperature remained above the thermoneutral zone. Infusion of histamine into spinal subarachnoid space produced hyperthermia which devolped very slowly. However, the infusion of histamine into the subarachnoid space around the brain stem did not exhibit any change in rectal temperature. The significance of these observations has been discussed.

Key words : histamine temperature regulation csf ambient temperature hypothermia hyperthermia

INTRODUCTION

Over the last two decades the neurochemical basis for central mechanism of thermoregulation in animals has been developed with special significance to the role of neurotransmitters like 5-HT, NA and Ach (3, 13, 17).

The idea that histamine may be regarded as a potentia, neurotransmitter in the central thermoregulatory pathways has recently gained importance because of (i) the pre-

sence of histamine in rich concentration in rostral hypothalamic thermoregulatory areas (24), (ii) synaptosomal localization of histamine alongwith the enzyme systems (23), (iii) identification of histamine receptors, H_1 and H_2 (22), and (iv) resemblance of the turnover rate of histamine to those of other CNS neurotransmitters (12). Several workers have earlier shown that administration of histamine into lateral cerebral ventricle or microinjection into hypothalamic region in laboratory animals produces fall in rectal temperature (1, 3, 5, 8, 9). These investigations were carried out at an ambient temperature range between 4°C and 23°C i.e. below the thermoneutral zone.

It is already established that the alteration of peripheral thermal drive arising from changes in ambient air temperature profoundly influences the body temperature responses to centrally acting drugs (16, 19 25, 27). Therefore the present paper deals with the pattern of thermoregulatory response following i.c.v. administration of histamine at different ambient temperature range.

MATERIAL AND METHODS

Experiments were carried out on inbred male albino rats (CF strain, 180-320 *g*). For infusion of histamine (Histamine dihydrochloride, Sigma Chemical Co., U.S.A.) into the different liquor spaces in brain, a stainless steel guide cannula (21G), with a stylet inserted into its shaft, was chronically implanted in an aseptic preparation under pentobarbitone anaesthesia (40 *mg/kg*, ip) with the rat's head fixed in stereotaxic instrument (INCO, INDIA). After a week following operation, histamine was administered in conscious rats through the implanted cannula in volume of 10 μl with a microinfusion pump which delivered this volume from a 50 μl Hamilton Syringe in 10 min. For such administration of histamine the stylet was removed and a hollow stainless steel needle (26 G) was inserted which was already connected to the Hamilton syringe by a length of polythene tubing filled with histamine solution to be infused. In case of a cannula implanted into the lateral ventricle or IVth ventricle, the hollow needle was inserted through the entire length of the shaft and was extended 1 mm beyond the tip of the guide cannula. The rectal temperature was recorded from Aplab 6 channel Telethermometer through a thermistor probe (Yellow Spring Co., U.S.A.). The probe was inserted 6 cm deep inside the rectum and was held in place by wrapping adhesive leucoplast around the base of the tail of the animal. Temperature was noted at every 5-10 min. intervals. The drug solution (histamine dissolved in sterile normal saline) was administered when the basal rectal temperature of the rat became stabilized, which generally occured within 30 minutes.

Confirmation of the spread of drug solution into ventricular space : After each experiment, the animal was anaesthetized with pentobarbitone, and Evans blue dye (2%) was infused following the same procedure as for that of histamine. After 5 min the brain was perfused with buffered formalin solution and the brain was removed for confirmation of placement of the cannula and mapping of the spread of the dye in the liquor space was carried out through naked eye examination.

Chronic implantation of cannula into different CSF compartments :

(i) Lateral ventricle : The cannula (21 G) having a shaft length of 4 *mm* was chronically implanted into the anterior right horn of the lateral ventricle. The cannula was placed 1 *mm* posterior to the bregma and 2.5 *mm* lateral from the mid sagittal iine The detailed procedure has already been described by Feldberg and Lotti (14).

(ii) Fourth ventricle : The cannula (21 G) having a shaft length of 6 *mm* was implanted in the midsagittal line 1 *mm* caudal to the lamda at an angle of 8° directed posteriorly so that the tip of the cannula lay in the middle of the fourth ventricle.

(iii) Subarachnoid space : A polythene cannula was inserted into the spinal subarachnoid space after piercing through the atianto-occipital membrane The length of the cannula inside the spinal subarachnoid space was between 4-6 *cm* so that the tip of the cannula lay between lower cervical and upper thoracic levels of spinal cord (C_6-T_1) usually. The detailed procedure of the chronic catheterization of the spinal subarachnoid space was followed according to Yaksh & Rudy (26).

Acute implantation of cannula into cisterna magna : For infusion of histamine into the cisterna magna, the animal was anaesthetized with ether and was mounted in a stereotaxic instrument.

The atlanto-occipital membrane was exposed according to the method of Yaksh & Rudy (26). Then a sharp hollow stainless steel needle (26 G), connected to a polythene tubing filled with artificial C.S.F. was inserted into the cisterna magna by piercing the membrane carefully so as not to injure the floor of the fourth ventricle. The correct placement of the needle was confirmed by the free flow of CSF through the tubing. Following this, histamine solution (10 μl) was delivered by connecting the polythene tubing to a 50 μl Hamilton syringe already filled with the drug solution. After the infusion

was over, the needle was removed and the wound was quickly closed. The ether anaesthesia was withdrawn and the animal recovered within 10 min. After recovery rectal temperature was recorded. The whole experimentale procedures were generally completed within 15-20 min.

Statistical analysis of data : The paired student's 't' test was applied to evaluate the statistical significance of the data obtained.

RESULTS

Infusion of histamine into right lateral ventricle : The results are shown in fig. 1. The effects of administration of 18 *mM* (20 μg), 45 *mM* (50 μg), 90 *mM* (100 μg) and 180 *mM* (200 μg) of histamine (as free base) in a volume of 10 μl into lateral ventricle on core body temperature were examined at an ambient temperature ranging between 12.5°C and 22°C, i.e., below the thermoneutral zone.

It was observed that all the doses of histamine produced a fall in rectal temperature and the degree of hypothermic response was more or less dose-dependent. Thus a mean fall of 0.9°, 1.35°, 1.77° and 2.3°C was recorded respectively with 18, 45, 90 and 180 *mM* of histamine. It was further noted that the rats remained calm and quiet during the period of hypothermia. Postmortem examination of these rats revealed that the drug had spread from the lateral ventricle into III and IV ventricle. In two rats, there was no hypothermic response following i.c.v. administration of 18 *mM* of histamine, and postmortem examination in these two rats showed that the spread of the drug was confined only to the right lateral ventricle. The mean time taken to reach maximum fall in rectal temperature with different doses of histamine varied between 25 and 36.25 min. and the period taken for returning to euthermic level varied between 187.50 and 302.50 min.

The rate of fall in rectal temperature (as calculated from time taken to exhibit 50% fall of rectal temperature) showed an apparent increase in rate of fall with the increasing doses of histamine (Fig. 1). But when statistical significance was calculated between 18 *mM* (20 μg) and other three higher doses of histamine in terms of rate of fall in rectal temperature, they were not found to be significant.

Therefore, the comparison of the thermoregulatory response elicited from lateral ventricle and IV ventricle was made with i.c.v. administration of 18 *mM* of histamine.

Infusion of 18 mM histamine into lateral ventricle at different ambient temperature : It would appear from the results (Table-I) that the degree of mean hypothermic

response following 18 mM of histamine infusion in animals exposed at ambient temperatures of 11°C, 21°—22°C and 26°—27.5°C remained more or less same which indicated that the effect of histamine on core body temperature at or below the thermoneutral zone was mainly hypothermic. This hypothermic response was associated with mild sedation of the animals.

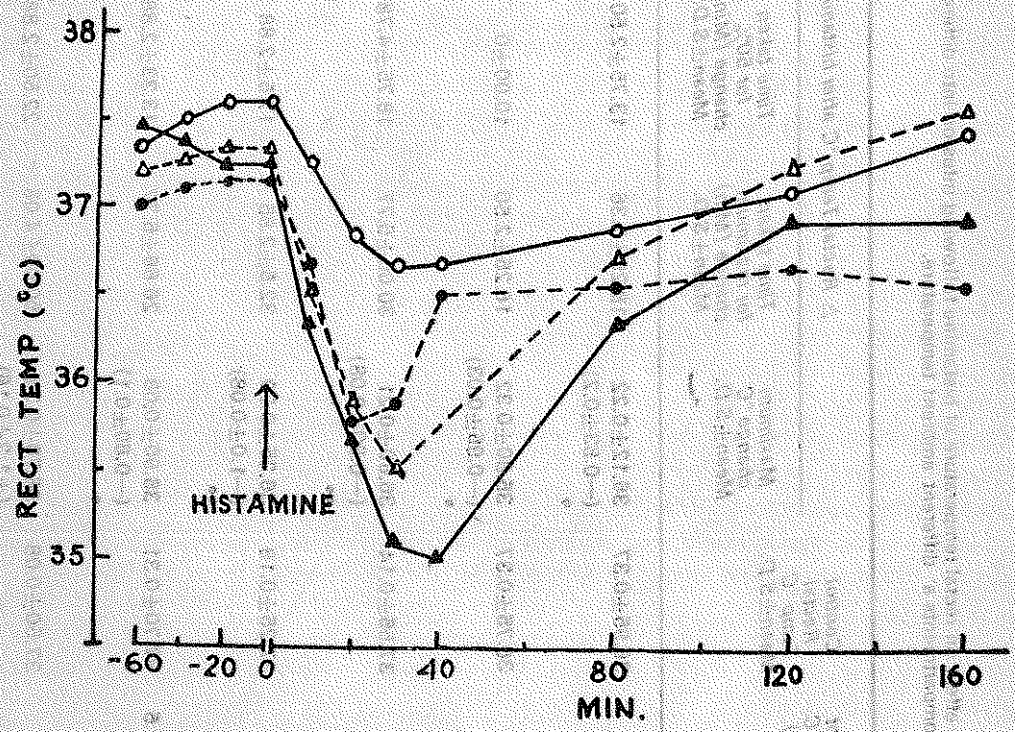

Fig. 1 : Shows the pattern of hypothermic response following infusion of histamine in right lateral ventricle of rat at 20 μg (○——○), 50 μg (●——●), 100 μg (△——△) and 200 μg (▲——▲). The data represent the mean values obtained from four animals. Only in case of 200 μg dose, the data represent the mean values obtained from 3 animals.

However, there was a moderate delay in showing maximum fall of core temperature observed at 21°—22°C and 26°—27.5°C as compared to that 11°C. On the other hand, no significant difference was observed in the time taken for 50% fall in rectal temperature either below or at the thermoneutral zone.

TABLE I : Shows effect on rectal temperature of histamine following infusion into different CSF compartments a' different ambient temperature.

Histamine (route, dose)		*Ambient Temp °C (range)*	*Control Rectal Temp °C Mean±S.D.*	*△ Rectal Temp °C after histamine*			
				Maximum change °C Mean±S.D.	*Time taken for maximum change (Min) Mean±S.D.*	*Time taken for 50% change (Min) Mean±S.D.*	*Recovery period (Min) Mean±S.D.*
Lateral ventricle (n=4)	20 μg	11	36.95±0.37	36.12±0.22 (—0.83±0.2) *	18.25±2.36	13.75±2.50	213.33±33.03
Fourth ventricle (n=4)	20 μg	11-13	36.75±0.37	35.80±0.32 (—0.95±0.03) *	16.25±2.50	10.00±0	175.00±85.04
Lateral ventricle (n=4)	20 μg	21-22	37.55±0.14	36.60±0.21 (—0.90±0.08) **	30.00±5.77	18.75±4.78	187.50±9.50
Fourth ventricle (n=4)	20 μg	19-21	37.25±0.19	36.25±0.20 (—1.0±0.08) **	32.5±2.85	17.5±2.88	150.0±25.80
Lateral ventricle (n=3)	20 μg	26-27.5	37.70±0.31	36.90±0:08 (—0.80±0.1) *	26.66±5.77	13.33±2.88	200.00±17.32
Fourth ventricle (n=4)	20 μg	26	37.50±0.08	38.70±0.24 (+1.2±0.16) ***	50.00±4.08	22.50±2.88	244.00±0

Lateral ventricle	20μg	31	37.45±0.14	37.30±0.11 (−0.15±0)	20.00±2.50	15.00±1.8	Did not recover upto 4 hr.
Fourth ventricle	20μg	30-31	37.53±0.30	37.33±0.28 (−0.20+0.1)	20.66±3.55	14.20±2.1	Did not recover upto 4 hr.
Cisterna magna (n=2)	50μg	26	37.20±0.02	37.09±0.01 (0.2±0)	18.00±2.30		
Cisterna magna (n=2)	100μg	27	37.26±0.05	37.10±0.08 (−0.12±0)	18.50±3.50		
Spinal subarachroid space (n=7)	10μg	25-32	36.9±0.40	38.28±0.57 (+1.25±0.5) **	271.42±93.21	124.28±62.42	6 hr. to more than 8 hr.

Figures in parentheses indicate mean temperature change from control. n=number of animals.
Students paired 't' test employed for calculation of P value.
*, P∠.05, **, P∠.01, ***, P∠.001.

Interestingly, this hypothermic response of histamine was practically no longer observed when the ambient temperature exceeded beyond that of the thermoneutral zone (31°C).

Postmortem examination indicated that the drug had reached from lateral ventricle downwards upto fourth ventricle in all the above experiments.

Infusion of 18 mM of histamine into fourth ventricle at different ambient temperature : The administration of 18 mM of histamine into fourth ventricle produced either hypothermic or hyperthermic response depending on the ambient temperature (Table I). Thus at 11°—13°C (i.e. below the thermoneutral zone), 18 mM of histamine produced a fall in rectal temperature of 0.95° ± 0.03°C within 16.26 ± 2.5 min. which was very similar to the results observed following infusion of the same dose of histamine into lateral ventricle under the same condition. However, the rate of fall of rectal temperature was relatively faster as compared to that of lateral ventricle.

Unlike the hypothermic response observed following infusion of histamine (18 mM) into lateral ventricle at the thermoneutral zone (26°—27.5°C), the infusion 18 *mM* of histamine into fourth ventricle at 26°C ambient temperature led to a significant rise in the rectal temperature of about 1.2°±0.16°C within 50.00±4.08 minutes and time taken for 5% rise of the rectal temperature was about 22.5±2.88 minutes. But this histamine-induced hyperthermia did not occur when the same dose of histamine (18 mM) was infused into the fourth ventricle at 30°—31°C ambient temperature (i.e.) above the thermoneutral zone). Postmortem examination in all above mentioned experiments showed that the dye reached IV ventricle and also onto the ventral surface of brain stem region.

In two rats, there occurred no change in the rectal temperature following infusion of histamine into the fourth ventricle, Postmortem examintion in these rats showed that the dye did not enter into IV ventricle.

Infusion of histamine into spinal subarachnoid space : Infusion of 10 *μg* histamine into spinal subarachnoid space in seven rats resulted in hyperthermia with a mean rise of 1.25°C (Table I). But this hyperthermic response developed very slowly. These experiments were carried out at an ambient temperature of 25°—3 2.5°C.

Postmortem examination showed that the drug had spread from C_6 to T_1 level in five animals and in two, it spread from C_3 to T_1 level.

Infusion of histamine into cisterna magna : The infusion of histamine into cisterna magna, at a dose of 45 mM in two rats, and 90 mM in another two rats, did not exhibit any change in rectal temperature of the animals exposed at the ambient temperature of 26°—27°C (Table I).

Postmortem examination showed that the drug had spread from cisterna magna to the ventral surface of medulla and pons as well as downwards upto upper cervical spinal cord.

DISCUSSION

In the present investigation, a dose-dependent hypothermic response (0.9°C to 2.3°C) was observed following infusion of 18 mM to 180 mM of histame into the lateral ventricle of the rats exposed at an ambient temperature (12.5°—22°C) below the thermoneutral zone. Such dose-related hypothermic response of histamine in rats has been reported earlier, following its injection into the lateral ventricle (1, 21), or into the anterior hypothalamus (5).

The earlier report (25) that the ambient temperature is an important determinant in modifying or altering the physiological or pharmacological actions of a drug, has also emerged in the present investigation. Thus the hypothermic response occuring foliowing infusion of 18 mM histamine into the the lateral ventricle either at moderately low (11°C and 21°—22°C), or at thermoneutral ambient temperature (26°—27.5°C), was no longer observed when the ambient temperature remained at 31°C. Similar observation was made by another group of workers (8) who had shown that infusion of 200 μg histamine into lateral ventricle in cat produced hypothermia at an ambient temperature of 4°C and 22°C, and at 30 5°C the hypothermic response was very much diminished.

The ability of histamine to induce alteration of rectal temperature following its infusion into fourth ventricle demonstrates that the neural pathways of thermoregulation traversing through the periventricular region of medulla oblongata are interposed with histamine sensitive neurons (6, 7, 20). And it has further been observed that the ambient temperature besides modifying the hypothalamic thermoregulatory response, can also modify the histamine sensitive thermoregulatory mechanisms located at the lower brain stem level. Thus the thermoregulatory response of histamine following its administration into IVth ventricle becomes either hupothermic or hyperthermic depending on the ambient temperature to which the animals are chronically exposed.

At spinal cord level the presence of histamine sensitive thermoregulatory pathways has also been indicated in the present investigation. Thus a very slow hyperthermic

response has been observed following histamine infusion in the subarachnoid space of the spinal cord at C_3-T_1 level. On the other hand, the absence of change in rectal temperature following infusion of even higher doses of histamine into cisterna magna brings forth the idea that the histamine sensitive neurons involved in thermoregulatory pathways are atleast not located on the ventral surface of the brain stem region.

These thermal effects of centrally administered histamine are not dependent on the peripheral affect of the drug resulting from its escape into the blood from the brain. This is based on an observation made by Bhawe (2) who had estimated that i.c.v. administration of 500 μg histamine (base) led to its maximum uptake by blood of about 1.2 μg per min. Since in the present investigation, the dose of histamine used for further experiments was very small (20 μg), very little, if at all, of histamine would be expected to escape into the blood from c.s.f. compartments.

The general ways by which the body temperature may be modified by a centrally acting drug are atleast two : (i) the setting of the central thermostat may be changed with consequent activation of heat loss or heat gain mechanisms or (ii) the efferent thermoregulatory pathways may be directly activated. Behavioral methods have been devised to distinguish between these two possibilities (9). In using such techniques, it appears that activation of H_1 receptors in the preoptic/anterior hypothalamus causes a fall in body temperature in the rat that is accompanied by heat avoidance behavior, indicating a lowering of the thermoregulatory set-point (15) and similar observation has been made in cat (8). Histamine induced fall in rectal temperature may also be due to an alteration in the feedback signals from the thermosensors. This mechanism would be valid in model suggested by Bligh, Cottle & Maskrey (4) which does not require a thermostat, but instead, postulates coordination of heat loss and heat gain activities by means of crossed inhibitory pathways. When the ambient temperature was 30°C, the hypothermic response to histamine was however significantly diminished. This result is not appropriate for a consistent change in the error signal in the thermostat, which should cause equal changes in body temperature at ambient temperatures both above and below the thermoneurtral zone, as reported for agents which are thought to raise the set-point such be bacterial pyrogens (18) and prostaglandins (10, 11). One possible explanation for the diminished hypothermic response at high ambient temperature may be that although the same error signal was caused by histamine (as at the lower ambient temperature) the stress imposed by the high ambient temperature was severe enough so that heat loss could not be further increased sufficiently to minimize the error signal.

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