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BIPHASIC CHANGES IN BODY TEMPERATURE PRODUCED BY INTRACEREBROVENTRICULAR INJECTIONS OF HISTAMINE IN THE CAT

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SUMMARY

1. Intracerebroventricular administration of histamine to cats caused hypothermia followed by a rise in body temperature. 2-Methylhistamine caused a similar biphasic response, while 3-methylhistamine had no effect on body temperature and 4-methylhistamine produced a delayed hyperthermia. Some tolerance to the hypothermic activity developed when a series of closely spaced injections of histamine was given.

2. Doses of histamine and 2-methylhistamine which altered body temperature when given centrally were ineffective when infused or injected I.V.

3. Pyrilamine, an H_1-receptor antagonist, prevented the hypothermic response to histamine.

4. Hypothermic responses to histamine at an environmental temperature of 22° C were comparable to responses in a cold room at 4° C in both resting animals and animals acting to depress a lever to escape an external heat load. A change in error signal from the thermostat could account for these results. However, lesser degrees of hypothermia developed when histamine was given to animals in a hot environment. In some, but not all animals, this smaller response could be attributed to inadequate heat loss in spite of maximal activation of heat-loss mechanisms.

5. The hyperthermic response to histamine was antagonized by central, but not peripheral, injection of metiamide, an H_2-receptor antagonist.

6. The results indicate that histamine and related agents can act centrally to cause both hypothermia, mediated by H_1-receptors, and hyperthermia, mediated by H_2-receptors.

INTRODUCTION

Although, in a number of species, histamine occurs in relatively high concentrations in the hypothalamus (Rönnberg & Schwartz, 1969; Green, 1970; Taylor, Gfeller & Snyder, 1972; Abou, Adam & Stephen, 1973; Lipinski, Schaumberg & Baldessarini, 1973), a brain region intimately involved in thermoregulation, the possible role of histamine as a transmitter within the thermoregulatory system has received little attention until recently (Lomax & Green, 1975). Central administration of histamine causes hypothermia in both the rat (Brezenoff & Lomax, 1970; Turnbull & Slater, 1970; Lomax & Green, 1975) and mouse (Shaw, 1971). To date, there have apparently been no positive findings of alterations of body temperature produced by central injection of histamine in animals which may react quite differently from the rat and mouse to administration of other amines (Myers, 1974; Hellon, 1974), pyrogens (Atkins, 1960; Borison & Clark, 1967) or antipyretics (Polk & Lipton, 1975; Cranston, Hellon & Mitchell, 1975). We have examined the effects on body temperature of centrally injected histamine in the cat, the species in which specific neurotransmitter involvement in thermoregulation was first studied and have determined the effects of pyrilamine, an H_1-receptor antagonist, and metiamide, a representative of a new class of histamine antagonists which block at H_2-receptors (Black, Duncan, Durant, Ganellin & Parsons, 1972) on the responses to histamine. Also studied were responses to the methylated congeners of histamine, 2-methylhistamine, which in some systems is relatively more active at H_1-receptors than at H_2-receptors (Black *et al.* 1972), 4-methylhistamine, which is active primarily at H_2-receptors (Black *et al.* 1972), and 3-methylhistamine, a major metabolite of histamine in the brain of the cat (White, 1960). The results demonstrate that histamine can cause both hypothermia and hyperthermia in the cat and indicate that these responses are mediated centrally via H_1- and H_2-receptors respectively.

A preliminary report of some of these experiments has appeared in abstract form (Clark & Cumby, 1975*b*).

METHODS

Forty-nine unanaesthetized cats weighing between 2·3 and 5·9 kg were used. Procedures for care and feeding of the animals, for recording body temperature (T_{rp}) automatically from the retroperitoneal space, for implanting I.V. catheters and lateral cerebral ventricular cannulae, for sterilization of glassware and for otherwise avoiding pyrogenic contamination have been described previously (McCarthy & Borison, 1966; Clark & Moyer, 1972). The animals were kept and most experiments were done in a chamber maintained at an ambient temperature (T_a) of $22 \pm 1°$ C. In specified experiments the temperature of the chamber was raised to 30° C or higher.

For studies at lower T_as, individual animals were temporarily transferred to another room maintained at $4 \pm 2°$ C. Some animals studied at $T_a = 4°$ C were trained to avoid the heat from infra-red lamps mounted above the cage by pressing a lever which turned them off and simultaneously turned a fan on. The training procedures, apparatus and experimental design were identical to those described previously (Clark & Lipton, 1974). In 'heat-escape' trials, the behavioural apparatus was operative. In 'resting' trials, the animals were placed in the same cage, but the lamp-fan assembly was not turned on.

Cats were exposed to the experimental T_a for at least 1 hr before drug injection to allow T_{rp} to stabilize. The average of T_{rp} readings at 0, 15 and 30 min before the initial injection on any given day was used as the base line from which changes were measured. Deviations from this base line were tabulated at 15 min intervals, and a change in temperature was quantified both by its maximum and by a 'thermal response index' (TRI), one unit of which is equivalent to a 1° C change lasting for 1 hr (Clark & Cumby, 1975*a*). Unless otherwise designated by a subscript, TRIs for hypothermic responses were determined from the time of histamine injection until T_{rp} had risen to base line, and TRIs for hyperthermic responses were determined from the beginning of hyperthermia until the temperature had fallen back to base line or until 20 hr after injection. Subscripts indicate a specific interval in hours after injection over which the TRIs were determined. TRIs after saline injections were determined for the same period as for the corresponding histamine test in the same animal. The Wilcoxon matched-pairs signed-ranks test (Siegel, 1956) was used for statistical analysis.

A volume of 0·10 ml. was used for all intraventricular injections. With the exception of the initial study of the histamine dose–response relation and the experiments on tolerance, cannulae were routinely flushed with 0·2 ml. 0·9% NaCl solution about 24 hr after drug injections to remove residual drug. Intravenous injections were immediately flushed from the catheters with 1·0 ml. NaCl solution.

Materials. Histamine dihydrochloride (Sigma), 2-methylhistamine dihydrochloride, 3-methylhistamine dihydrochloride (Calbiochem) and 4-methylhistamine dihydrochloride were injected intraventricularly at 10.00 a.m. ± 5 min with the exception of a few experiments in which the former two agents were given I.V., either by infusion with a Harvard model 944 infusion/withdrawal pump or by injection. Except in experiments on tolerance to histamine, injections of these agents were spaced at least 48 hr apart. Histamine receptor blockers were given at 9.30 a.m., 30 min before histamine unless otherwise specified. Pyrilamine maleate was given I.V. Doses of the above agents refer to their salts. Stock solutions in NaCl solution were stored at 4° C. Metiamide was prepared just before each injection by dissolving it in acidified NaCl solution which was then adjusted approximately to pH 7 with NaOH.

RESULTS

Dose–response relation. 'Novice' cats which had not previously received histamine were used. As each animal became available, it was randomly allocated a dose of histamine. The order of administration of histamine and the saline control injection was also random. We were expecting only a brief hypothermic response and, therefore, in this first study only (Fig. 1, Table 1*A*), the cannulae were flushed 6 hr after histamine injection. The lower two doses caused similar hypothermic responses but 100 μg also caused a secondary hyperthermia. The largest dose caused a considerably

greater hypothermia, likewise with subsequent hyperthermia. Moderate tachypnoea with respiratory rates seldom over 100/min accompanied the development of hypothermia. Other effects often noted were emesis, vocalization, defaecation and salivation. The 200 μg dose was tested in another set of five novice cats without the flush at 6 hr to determine the full response including the hyperthermic phase (Fig. 2, Table 1*B*). The

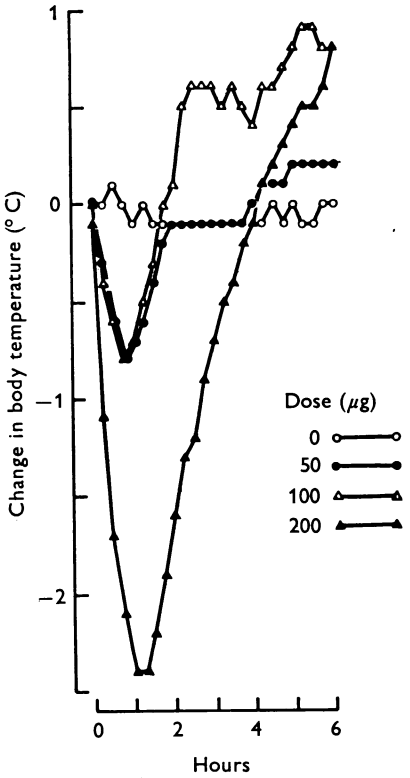

Fig. 1. Histamine-induced hypothermia in novice cats. Mean responses of five cats to each dose. The mean response of all fifteen animals to NaCl solution alone is also shown.

mean hypothermic response in these animals was less than in the initial group, but the hyperthermic phases were comparable whether the cannulae were flushed before the end of the response or not.

Development of tolerance to the hypothermic action of histamine. Series of from seven to fourteen injections of a given dose of histamine were given to seven cats, usually at intervals of 1–3 days. Fig. 3 shows a partial series of responses in an animal which developed complete tolerance. Four of the cats did not develop complete tolerance but instead exhibited fairly con-

sistent, but reduced, hypothermic responses after the third or fourth injection. Although the hyperthermic phase showed considerable variability to a series of injections, there was no consistent pattern indicative of tolerance.

TABLE 1. Hypothermic and hyperthermic responses of novice cats to intraventricular injection of histamine dihydrochloride. Results are expressed as mean values with the range in parentheses. T_a = 22° C

			Hypothermic phase		Hyperthermic phase	
	Dose (μg)	No. of cats	Maximum decrease (° C)	TRI (Δ° C × hr)	Maximum increase (° C)	TRI (Δ° C × hr)
A	0	15	0·2 (0·0–0·7)	−0·2 (0·6 to −2·7)	—	—
	50	5	0·8 (0·0–1·4)	−1·2 (0·0 to −2·0)	—	—
	100	5	0·8 (0·2–1·3)	−1·1 (−0·1 to −2·1)	—	—
	200	5	2·6 (1·3–3·8)	−5·4 (−2·4 to −9·3)	1·1 (0·5–1·5)	8·7 (1·9 to 13·5)
B	0	5	0·1 (0·0–0·3)	0·4 (1·1 to −0·1)	0·6 (0·3–1·0)	2·7 (−0·5 to 5·0)
	200	5	1·4 (0·4–2·9)	−2·6 (−0·4 to −5·7)	1·4 (1·0–1·7)	9·1 (4·4 to 15·6)

Injections of methyl derivatives of histamine (*Fig. 4*). Responses to 2-methylhistamine (200–400 μg, four cats) were similar to histamine-induced responses with a definite hyperthermic phase. Little or no initial hypothermia was caused by 4-methylhistamine (200–400 μg, five cats). Instead there was a small rise in T_{rp} (range 0·2–0·5° C) during the first 30 min after injection. The major hyperthermic response, beginning 2–3 hr later, was more prolonged than after a comparable dose of histamine. 3-Methylhistamine (430–860 μg, three cats) did not appreciably alter T_{rp}, even though subsequent injections of histamine doses equivalent to half the dose of 3-methylhistamine caused hypothermic responses averaging 1·5° C and hyperthermias averaging 1·7° C.

Comparison of changes in T_{rp} produced by intraventricular and I.V. administration of histamine. Four cats, including two novices (Fig. 5), were given infusions of 200 or 400 μg histamine or 2-methylhistamine at the rate of 2 μg/min (equivalent to 1·2–1·3 μg/min base). No appreciable changes in T_{rp} resulted. The next day at the same time as the start of the infusion, the same total dose of drug was injected intraventricularly. Hypothermic responses of at least 1·3° C resulted. Even when 200 μg

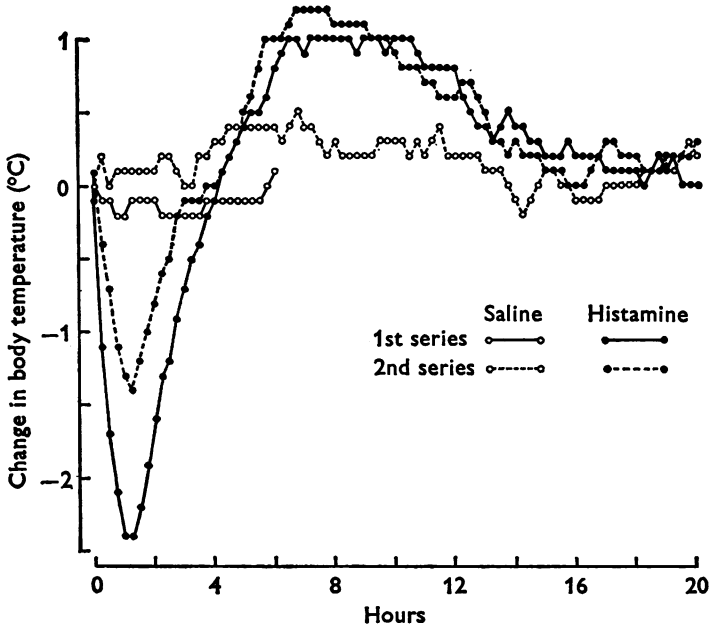

Fig. 2. Complete response of novice cats to 200 μg histamine. In the first series, also shown partially in Fig. 1, the ventricular cannulae were flushed at 6 hr. No flush was given during the second series. Mean responses in five cats.

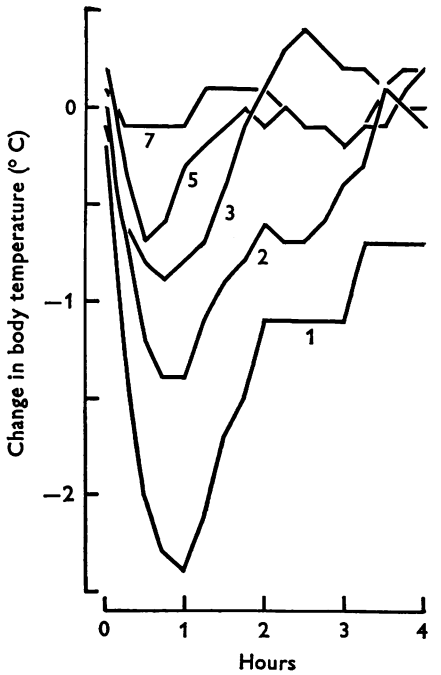

Fig. 3. Diminishing responses to seven injections of 100 μg histamine given to one cat over a period of 10 days. The number under each line indicates the position of that response in the sequence.

histamine was given I.V. as a bolus to the same cats used for Fig. 5, no mean change in T_{rp} occurred. One animal responded with immediate salivation, transient mydriasis and ataxia, while the other vocalized and developed mydriasis. When this dose of histamine was given intraventricularly 2 or 3 hr later, the T_{rp} of both cats fell 1·4° C within 60–75 min and later arose to produce the usual hyperthermia.

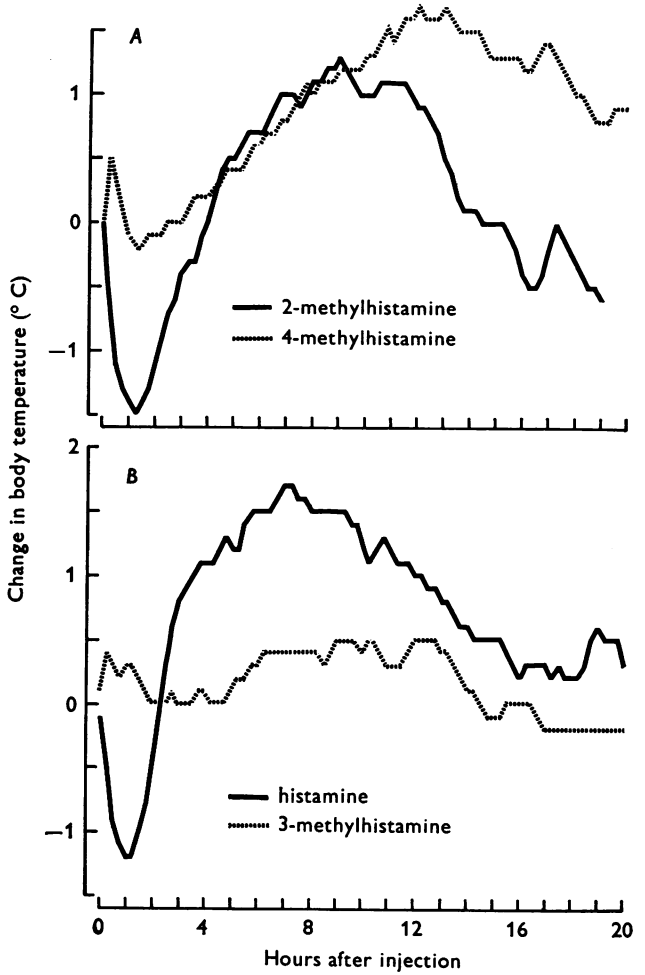

Fig. 4. Responses of one cat to histamine and some of its methyl derivatives. *A*, illustrates the response to an initial injection of 200 μg 2-methylhistamine and the response to the same dose of 4-methylhistamine given 15 days later with no intervening histamine injections. *B*, after a number of subsequent histamine injections, the cat was tested with 860 μg 3-methyl histamine and 400 μg histamine the next day.

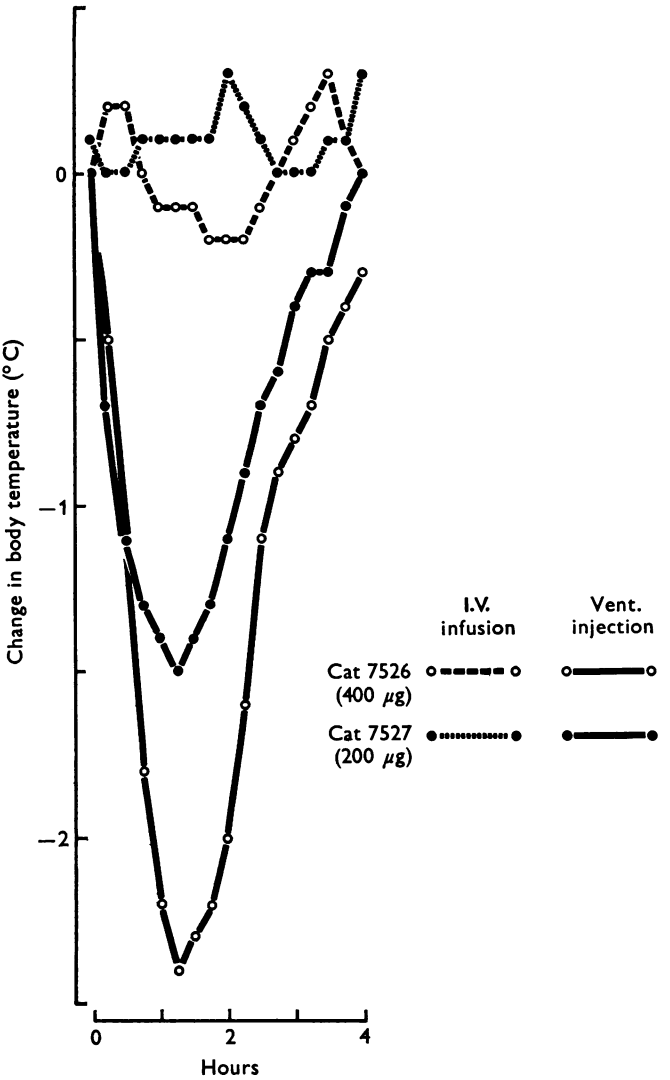

Fig. 5. Responses of two novice cats to 2-methylhistamine. The infusions were performed the day before the ventricular injections.

Blockade of histamine-induced hypothermia by pyrilamine. Cats were pretreated with saline or 2·0 mg/kg pyrilamine in a cross-over study, randomized so that half of the animals first received saline solution before histamine and half first received pyrilamine before histamine. The dose of histamine was the same for any pair of experiments but was increased to 400 or 800 μg if necessary to obtain good responses in partially tolerant

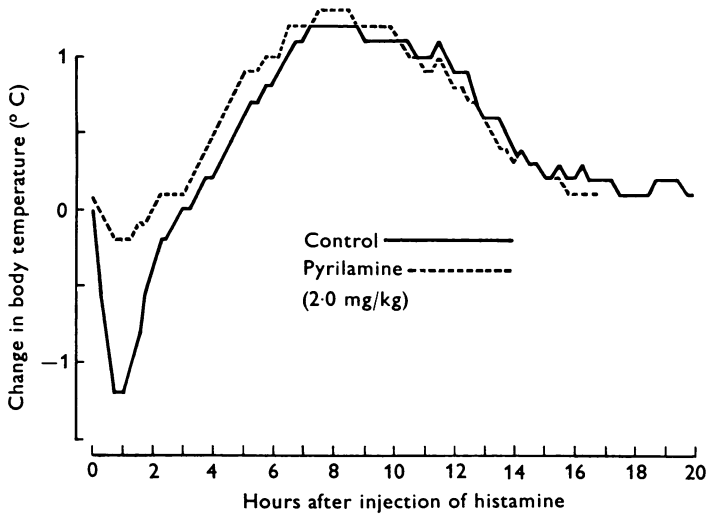

Fig. 6. Inhibition of histamine-induced hypothermia. Pyrilamine or NaCl solution was given I.V. 30 min before histamine (200–800 μg). Mean responses in eight cats.

TABLE 2. Antagonism of histamine-induced changes in body temperature. Results are expressed as mean values in eight cats with the range in parentheses. T_a = 22° C

Antagonist	Maximum change (° C)		TRI_x (Δ° C × hr)		
	Control	Antagonist	x	Control	Antagonist
A, pyrilamine maleate (2 mg/kg)	↓ 1·4 (0·6–2·3)	↓ 0·5* (0·0–1·4)	0–3	−1·9 (−0·7 to −3·1)	−0·2* (1·7 to −2·8)
	↑ 1·4 (0·4–3·0)	↑ 1·5 (0·6–3·7)	3–9	4·5 (8·5 to 0·5)	5·6 (14·3 to 0·2)
B, metiamide (1 mg)	↓ 1·3 (0·9–2·7)	↓ 1·7 (0·7–3·8)	1–4	−1·3 (0·9 to −4·6)	−2·6 (−0·4 to −7·9)
	↑ 1·4 (0·5–2·1)	↑ 0·4* (0·0–1·1)	4–20	8·3 (19·7 to −3·4)	−0·7* (10·5 to −11·4)

* $P \leqslant 0{\cdot}01$ *vs.* control.

animals. Pyrilamine reduced or abolished the hypothermic phase of the response (Fig. 6, Table 2*A*) and may have hastened slightly the appearance of the hyperthermic phase. Pyrilamine (2·0 mg/kg) alone did not alter T_{rp}, but 10 mg/kg given to two cats caused hypothermia which was preceded by a severe tonic-clonic seizure within 1 min of injection in one of the animals.

Response to histamine at varied T_as. When novice cats were given histamine at T_a = 4° C (Fig. 7*C*), the mean decrease in T_{rp} was similar to the response of the first group of cats to the same dose at T_a = 22° C, and the total hypothermic response as indicated by the TRIs was intermediate between the two groups at T_a = 22° C (Table 3). These animals were removed from the cold room 5 hr after histamine injection, and therefore no determination of the hyperthermic phase was obtained. The mean

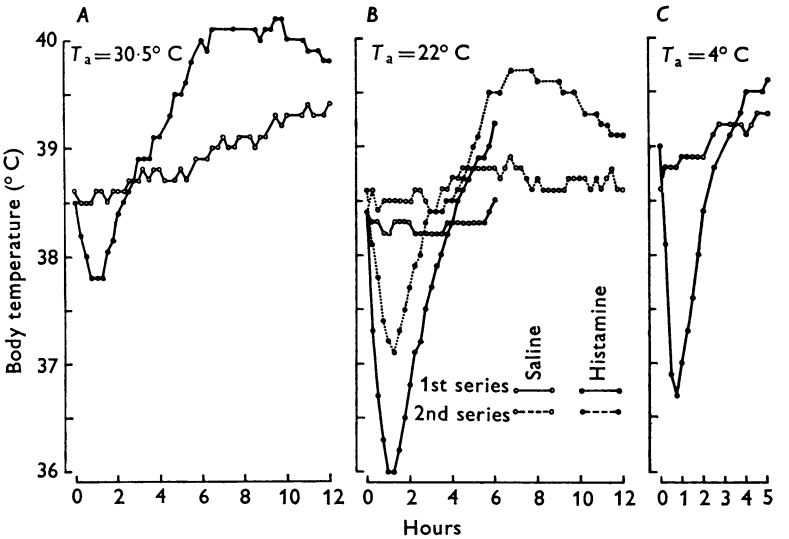

Fig. 7. Mean responses to 200 μg histamine at different environmental temperatures. Five novice cats were tested in each group. The order of administration of histamine and saline solution was random.

TABLE 3. Hypothermic effect of 200 μg histamine dihydrochloride at varied environmental temperatures. Results are expressed as mean values from five novice cats with the range in parentheses

T_a (° C)	Maximum decrease (° C)		TRI (Δ° C × hr)	
	Saline	Histamine	Saline	Histamine
30·5	0·1 (0·0–0·4)	0·8 (0·3–2·1)	0·2 (1·5 to −0·5)	−1·2 (−0·2 to −4·1)
22	0·3 (0·0–0·7)	2·6 (1·3–3·8)	−0·7 (0·6 to −2·7)	−5·4 (−2·4 to −9·3)
22	0·1 (0·0–0·3)	1·4 (0·4–2·9)	0·4 (1·1 to −0·1)	−2·6 (−0·4 to −5·7)
4	0·1 (0·0–0·6)	2·5 (1·8–3·5)	0·6 (1·8 to −1·0)	−3·7 (−2·0 to −6·6)

hypothermic response of cats given histamine at T_a = 30·5° C (Fig. 7*A*, Table 3) was less than that of the other groups. This lesser response was apparently not due to selection of a group of animals weakly sensitive to histamine since another set of five animals in which the mean maximum fall in T_{rp} after histamine injection at T_a = 32° C was only 0·4° C developed

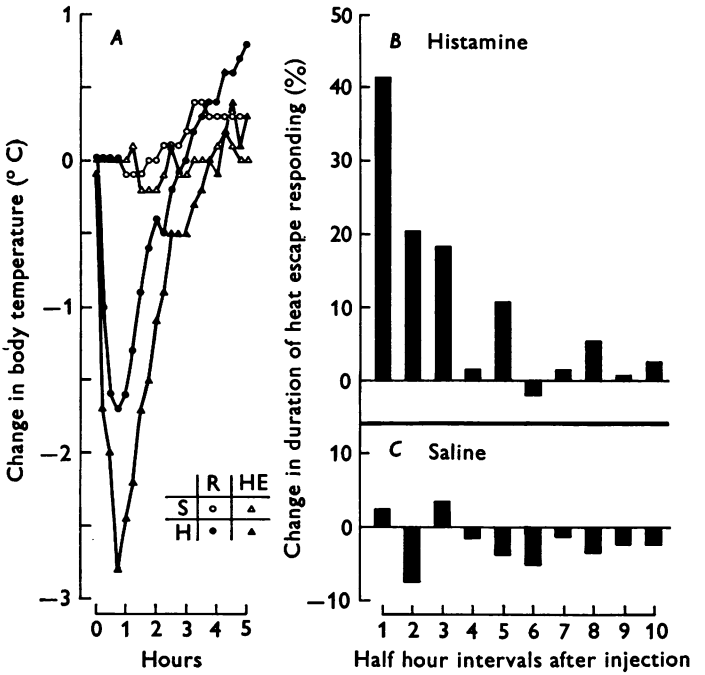

Fig. 8. Behavioural study of histamine-induced hypothermia. Panel *A*: mean changes in T_{rp} after intraventricular injection of saline (S) or histamine (H) in five cats which were resting (R) or lever pressing to escape heat (HE). T_a = 4° C. Panels *B* and *C*: mean changes in heat escape responding after histamine and saline respectively, expressed as % change from the time spent lever pressing during the half hour period immediately preceding injection.

a mean hypothermia of 2·6° C when subsequently tested with the same dose at T_a = 22° C. Even though marked tachypnoea and panting were evoked in five of the ten animals tested at the high T_as, the hyperventilation was not very effective in lowering T_{rp}. The other five cats did not develop respiratory rates greater than 100/min. After a delay of 1·5–3 hr, the animals developed hyperthermia which was roughly comparable to that seen at T_a = 22° C.

Lack of effect of heat-escape behaviour on the hypothermic response to histamine at T_a = 4° C. When trained cats were given histamine for the first time, they initially increased the amount of time spent pressing the lever, thereby promoting development of hypothermia (Fig. 8, Table 4) comparable to or greater than without heat-escape behaviour at the same

TABLE 4. Hypothermic effect of 200 μg histamine dihydrochloride with (HE) and without (R) heat-escape behaviour. Results are expressed as mean values in five cats with the range in parentheses. T_a = 4° C

	Maximum decrease (° C)		TRI (Δ° C × hr)	
	R	HE	R	HE
Saline	0·2 (0·0–0·6)	0·3 (0·0–0·5)	0·2 (1·0 to −1·0)	0·0 (0·7 to −0·9)
Histamine	1·9 (0·7–3·0)	3·1 (1·7–4·2)	−2·9 (−0·5 to −6·9)	−5·3 (−1·4 to −8·6)

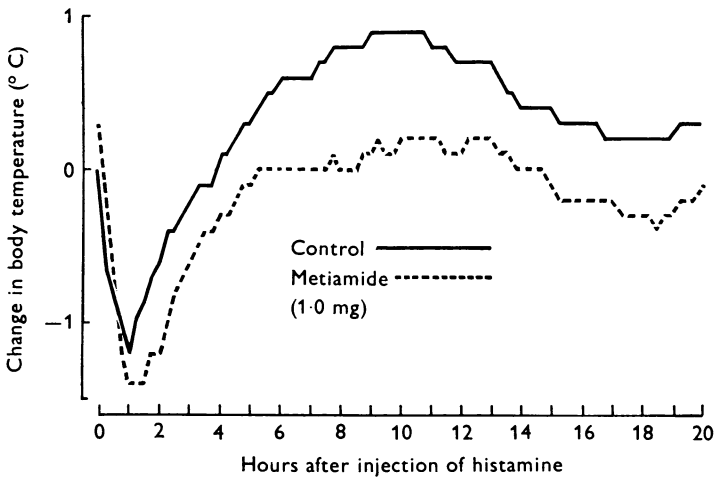

Fig. 9. Inhibition of histamine-induced hyperthermia. Metiamide or NaCl solution was given intraventricularly 30 min before histamine (200–800 μg). Mean responses in eight cats.

T_a or at T_a = 22° C (see Fig. 7, Table 3). The order of presentation of histamine and saline during heat-escape trials and of saline during the resting trial was randomly determined for each cat. After completing this series of three experiments, a subsequent injection of histamine during a resting trial caused a smaller hypothermia, most likely indicative of partial tolerance.

Blockade of histamine-induced hyperthermia by centrally administered metiamide. In a study designed similarly to that above with pyrilamine,

intraventricular injection of metiamide reduced the hyperthermic response to histamine (Fig. 9, Table 2*B*). Metiamide also enhanced or prolonged the hypothermic response in six of the animals. A small rise in T_{rp}, accompanied by shivering, often followed metiamide injection and can be seen in the Figure as a slightly higher temperature at the time of histamine injection. Intravenous injections of metiamide (10 mg/kg) before administration of histamine or during responses to histamine did not reduce the

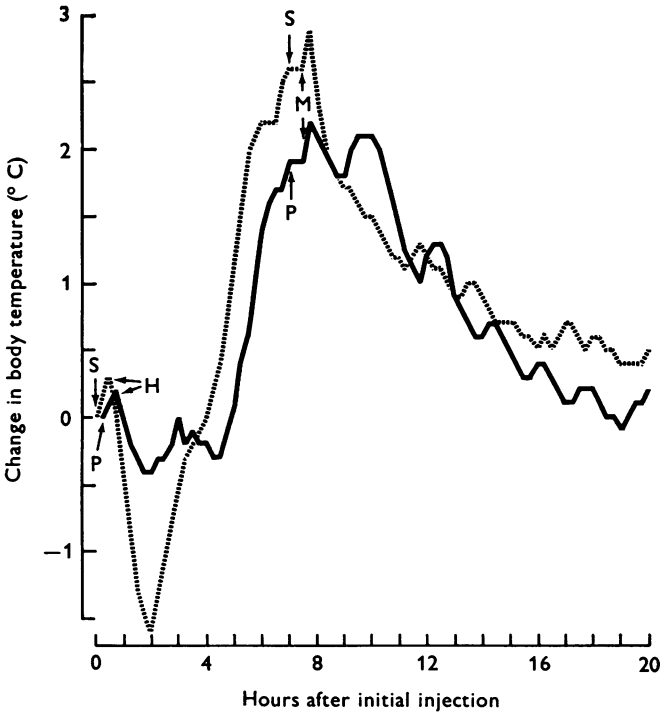

Fig. 10. Influence of pyrilamine (2 mg/kg I.V.) on the interaction between histamine (H, 200 μg) and metiamide (M, 1 mg). Responses of one cat given pyrilamine (P, ——) or saline (S, ----) 30 min before histamine and metiamide. Note that pyrilamine inhibited both the initial hypothermic response to histamine and the abrupt fall in T_{rp} shortly after metiamide.

hyperthermic effect in four cats. When metiamide was given centrally during histamine-induced hyperthermia, it did not appear clearly to hasten recovery. However, in some cases, an apparent recovery was initiated about 15 min after metiamide (Fig. 10) or a transient reduction in temperature occurred (Fig. 11). The decrease in T_{rp} was delayed by administration of pyrilamine 30 min before metiamide (Fig. 10) and could be mimicked by re-injection of histamine during the hyperthermic phase

(Fig. 11). A fall in T_{rp} did not always occur after metiamide but was most pronounced in cats which responded with good initial hypothermic responses to the dose of histamine. These results suggest that metiamide can release histamine from binding sites, allowing re-stimulation of H_1-receptors. This interpretation is supported by other experiments in which administration of metiamide during the hyperthermic response to 4-methylhistamine did not cause any appreciable reduction in T_{rp}.

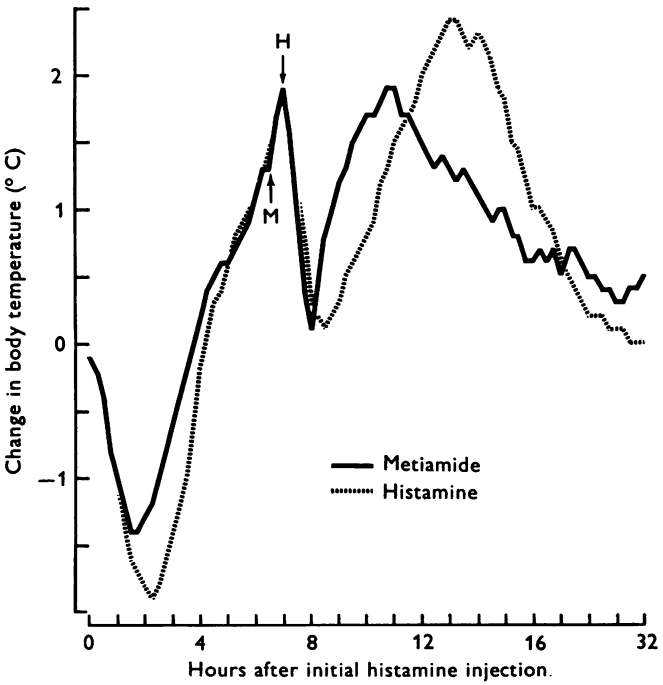

Fig. 11. Responses of one cat to lateral ventricular administration of metiamide (M, 1 mg) or histamine (H, 800 μg) during the hyperthermic phase of the response to 800 μg histamine.

DISCUSSION

In the cat, as in the rat and mouse, central administration of histamine initially caused a dose-related hypothermia. A number of the other effects noted, such as tachypnoea, panting and emesis, have been reported previously in the cat (Feldberg & Sherwood, 1954; White, 1961). Repeated histamine injections produced at least partial tolerance to the hypothermic action, necessitating the use of novice cats for many of the experiments.

Several studies have demonstrated that peripheral administration of

histamine at ordinary room temperatures will also cause hypothermia in rodents (Borison & Clark, 1967; Lomax & Green, 1975). This response is thought to be due primarily to peripheral vasodilatation and resulting heat loss. At T_as of 30–35° C, hyperthermia was produced by peripheral histamine injections (Borison & Clark, 1967). It has been shown that perfusion of histamine through the lateral and third ventricles of unanaesthetized cats can increase gastric acid secretion, attributed to uptake of histamine by blood leading to the peripheral effect (Draškoci, Feldberg, Fleischauer & Haranath, 1960). On the basis of comparisons of gastric acid secretion caused by central injection and I.V. infusion of histamine, Bhawe (1958) estimated that intraventricular administration of 500 μg histamine base led to a maximum uptake by blood of about 1·2 μg base/min. Such injections caused only transient changes in blood pressure. In our experiments in which intraventricular injections of 200–400 μg histamine or 2-methylhistamine, as the dihydrochlorides (121–253 μg base), caused hypothermia, considerably less than 1 μg base/min would be estimated to have escaped into blood. Yet infusions at the rate of approximately 1·2 μg base/min still caused little or no hypothermia. Furthermore, not even bolus I.V. injections of 200 μg histamine salt caused hypothermia. The hypothermic response to histamine has also been produced in rats by injecting very small amounts directly into the rostral hypothalamus (Brezenoff & Lomax, 1970; Lomax & Green, 1975) and by peripheral administration of histidine plus a decarboxylase inhibitor to prevent peripheral formation of histamine (Green, Simon & Lomax, 1975). As mentioned above, peripheral administration of histamine at high T_as results in hyperthermia in the rat and mouse. Yet central injection of histamine at high T_as did not cause hyperthermia initially in our cats although the hypothermic response was diminished. The association of tachypnoea with the development of hypothermia, especially when T_a was elevated, also favours a central action of histamine. From these considerations we conclude that there was probably no contribution of a peripheral histamine action to the initial response when histamine was given centrally.

Pyrilamine antagonized the hypothermic action of histamine. Chlorcyclizine, another H_1-receptor blocking agent, has also been reported to prevent induction of hypothermia by central injection of histamine in the rat (Brezenoff & Lomax, 1970) but not in the mouse (Shaw, 1971). Hence centrally mediated hypothermia in the cat and rat, but perhaps not in all species, apparently involves H_1-type receptors. This conclusion is supported by the inability of 4-methylhistamine, which has very little activity on H_1-receptors (Black *et al.* 1972), and of 3-methylhistamine, which is inactive at both H_1- and H_2-receptors (Black *et al.* 1972), to produce

hypothermia. Centrally injected 3-methylhistamine has also been shown not to alter body temperature in the rat (Lomax & Green, 1975).

Increased lever pressing to escape heat and comparable reductions of T_{rp} after histamine at two levels of T_a below the thermoneutral temperature of the cat are consistent with H_1-receptor stimulation causing an error signal in the thermostat (Borison & Clark, 1967; Clark & Lipton, 1974), either by lowering the thermoregulatory set-point or by altering feed-back signals from thermosensors. The latter mechanism would also be valid in models such as that of Bligh, Cottle & Maskrey (1971) 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 T_a was over 30° C, however, the hypothermic response to histamine was considerably reduced. This result is not appropriate for a consistent change in error signal which should cause equal changes in body temperature at T_as both above and below thermoneutrality, as reported for agents which are thought to raise the set-point such as bacterial pyrogens (Palmes & Park, 1965) and prostaglandins (Hales, Bennett, Baird & Fawcett, 1973; Stitt, 1973). One possible explanation for the reduced hypothermia is that, although the same error signal was caused by histamine as at the lower T_as, the stress imposed by the high T_a was severe enough that heat loss could not be further increased sufficiently to minimize the error signal. This may account for the failure of the five cats which panted to develop appreciable hypothermia. It is not, however, possible to attribute the small hypothermic responses of the cats which did not pant to maximal, but insufficient, activation of heat-loss mechanisms. Alternatively, there is *a priori* no reason to assume that a given neurotransmitter is involved in only one component of the many systems involved in thermoregulation. It is quite possible that this deviation at high T_as from the response expected to an agent which alters the error signal indicates a secondary action of histamine which, at least in some animals, limits the activity of the effectors required to cause hypothermia. Detailed quantitation of effector activities will be required to characterize this response to histamine more completely.

The hypothermic response to centrally administered histamine was succeeded by a more prolonged hyperthermia. Rats given intraventricular injections of 100 μg histamine have been reported to develop a 1° C increase in rectal temperature after a latent period of about 1 hr (Turnbull & Slater, 1970). The hyperthermic response in the cat was clearly not a non-specific effect of the injection since control saline injections were inactive. Likewise the hyperthermia was not due to contamination by bacterial pyrogens since it was blocked by metiamide, which does not alter responses to endotoxin or leucocytic pyrogen (Clark, W. G. & Cumby, H. R.,

unpublished). Its antagonism by metiamide indicates that the hyperthermia is mediated specifically by stimulation of H_2-receptors. These receptors must be located within the C.N.S. because histamine was not antagonized by peripherally injected metiamide, which does not readily cross the blood–brain barrier (Cross, 1973), in a dose at least thirty times the ID_{50} required in the anaesthetized cat for inhibition of gastric acid secretion (Black & Spencer, 1973). The hyperthermic action was not simply masked by a more powerful hypothermic action initially, since hyperthermia was still delayed when hypothermia was prevented by pyrilamine. Also 4-methylhistamine caused primarily a delayed hyperthermia. This delay may indicate that the H_2-receptors are located relatively far from the ventricular walls, requiring a longer time for diffusion to them. Alternatively, histamine could act early to trigger a series of events which ultimately leads to hyperthermia. 2-Methylhistamine also caused hyperthermia, so that it is perhaps less specific for H_1-receptors in the brain than in the periphery.

Although more data are necessary to determine a mechanism for the hyperthermia, the similarity of the hyperthermias after histamine at T_a = 22° C and over 30° C is most consistent with a rise in set-point or an altered signal from thermosensors. Numerous recent reports (Nahorski, Rogers & Smith, 1974; Rogers, Dismukes & Daly, 1975; Baudry, Martres & Schwartz, 1975; Sebens & Korf, 1975) have shown that histamine can increase brain and c.s.f. levels of cyclic AMP. Interestingly, the pattern of temperature changes after intraventricular injection of histamine in the cat is similar to that after dibutyryl cyclic AMP in which there is also a delayed hyperthermia which is preceded in some instances by hypothermia (Varagić & Beleslin, 1973; Clark, Cumby & Davis, 1974). Hyperthermia following both dibutyryl cyclic AMP (Clark *et al.* 1974) and histamine (Clark, W. G. & Cumby, H. R., unpublished) can be antagonized by the same doses of indomethacin and paracetamol. Hence the hyperthermic response to stimulation of central H_2-receptors may be mediated through stimulation of adenylate cyclase.

Perhaps note should also be taken of the brief, small increase in T_{rp} often recorded within 30 min after intraventricular injection of 4-methylhistamine and metiamide. That shivering was often noted to accompany such responses suggests that the rise was a thermoregulatory phenomenon rather than the result of excitement, etc. Although probably not of great thermoregulatory significance, it may be that 4-methylhistamine acts on two receptor pools; one which causes the delayed hyperthermia and another in closer proximity to the ventricles which causes the initial rise. The transient increase seen after metiamide might be due to some agonistic activity on this latter receptor pool.

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