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THERMOREGULATORY CHARACTERISTICS OF NEUROGENIC HYPERTHERMIA IN THE RAT

BY DEBORAH ACKERMAN AND T. A. RUDY
From the School of Pharmacy, University of Wisconsin, Madison, Wisconsin, U.S.A.

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SUMMARY

1. The thermoregulatory characteristics of the neurogenic hyperthermia produced in rats by unilateral mechanical destruction of the rostral hypothalamic/preoptic region were studied.

2. The investigational methods employed included (*a*) observing the thermoregulatory effector activities which were responsible for generation of hyperthermia, (*b*) observing the thermoregulatory reactions elicited by forcefully elevating or lowering core temperature during neurogenic hyperthermia and (*c*) observing the effect of ambient temperature on hyperthermia magnitude.

3. At 26 °C, hyperthermia was effected by a transient increase in shivering thermogenesis and a concomitant minimization of heat loss through the tail.

4. At 26 °C, perturbations of core temperature during the plateau phase of hyperthermia were induced by internal or external heating and cooling. The disturbances elicited compensatory changes in shivering activity and in tail vasomotor tonus, and core temperature was rapidly and precisely returned to its pre-perturbation level.

5. The magnitudes of hyperthermias experienced by rats lesioned at 10, 15, 26 and 32 °C, as measured by the change in colonic temperature and by the area under the fever curve, were not significantly different. At 36 °C, rats were hyperthermic prior to lesioning, and the magnitude of the lesion-induced hyperthermia was significantly attenuated.

6. The results indicate that the neurogenic hyperthermia produced by unilateral hypothalamic puncture in the rat is generated by a coordinated modulation of thermogenic and heat retentive effectors and that the plateau level of hyperthermia is well regulated. These characteristics are compatible with the hypothesis that neurogenic hyperthermia is mediated by prostaglandins released from injured tissue and acting on surviving rostral hypothalamic tissue.

INTRODUCTION

Acute injury to the rostral hypothalamic region of the brain can produce a rise in body temperature which has been termed 'neurogenic hyperthermia' (see Rudy, Williams & Yaksh, 1977, for references). How hypothalamic injury produces hyperthermia is not known. However, the prevailing view seems to be that the temperature elevation arises from an injury-induced derangement of thermoregulation, such as persistent thermogenesis and/or a crippling of heat dissipation (see Rudy *et al.*, 1977, for references).

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Injured brain tissue releases prostaglandins (Wolfe & Mamer, 1975; Wolfe, Pappius & Marion, 1976). Prostaglandins of the E series injected into the rostral hypothalamus or into the third cerebral ventricle are strongly pyrogenic (Hellon, 1975). The prostaglandins synthesis inhibitor, indomethacin, prevented and reversed the hyperthermia evoked in rats by unilateral destruction of the rostral hypothalamus (Rudy *et al.* 1977). We have therefore proposed that neurogenic hyperthermia associated with hypothalamic trauma is not mediated by mechanical disruption of the thermoregulatory pathways but, rather, by prostaglandins released by injured tissue and acting on surviving rostral hypothalamic tissue (Rudy *et al.* 1977).

Although either mechanical disruption of thermoregulatory pathways or prostaglandins release could produce a temperature elevation, the functional characteristics of the hyperthermias produced by the two mechanisms would differ appreciably. Fever produced by prostaglandins is generated and maintained by a coordinated modulation of thermogenic and heat dissipation effectors, the magnitude of the hyperthermia is not strongly affected by variations in ambient temperature, and the elevated core temperature is defended as precisely and as vigorously as is the normal core temperature (Stitt, 1973; Hori & Harada, 1974; Veale & Whishaw, 1976; Lin, 1978). Effector coordination during a hyperthermia caused by damage to the thermoregulatory pathways should be poor, the magnitude of the hyperthermia should be strongly affected by ambient temperature, and the elevated core temperature should not be well defended (Stitt, 1979). In the present paper, we describe the functional characteristics of hyperthermia evoked in the rat by unilateral puncture of the rostral hypothalamus. The results support the hypothesis that neurogenic hyperthermia so evoked is mediated by prostaglandins.

METHODS

Female Sprague Dawley rats, individually caged at 22 ± 2 °C, and weighing between 250 and 350 g at the time of surgery were used in these studies. Employing a procedure described in detail elsewhere (Rudy *et al.* 1977), an 18-gauge stainless-steel guide tube, 9 mm in length, was implanted in the brain of each rat so that the guide tip rested approximately 2 mm above the dorsal surface of the anterior commissure and 0·5–1·0 mm lateral to the mid line. The tube was fixed to the skull with acrylic cement and stainless steel screws and occluded with a solid stainless-steel stylet which extended to the guide tip. After a seven day recovery period, some rats were subjected to an additional surgical procedure in which a polyethylene coil was inserted within the peritoneal cavity. The coil, formed from approximately 1 m of PE-50 tubing wound into a tight planar spiral, was loosely sutured into position over the liver. The free ends of the coil were brought subcutaneously to exit through a stab wound at the nape of the neck. All rats were permitted to recover from their various surgical procedures for a minimum of 14 days before experiments were begun.

The studies were carried out with the rats loosely restrained in hemi-cylindrical wire mesh cages. The restrained rats were placed in an environmental chamber within which ambient temperature would be controlled to within $\pm 0{\cdot}5$ °C. Core and tail skin temperatures were recorded continuously. Deep core temperature was measured using a thermistor probe inserted 5·0–6·0 cm beyond the anus. The probe was held in place by taping its lead wire to the base of the tail. To measure tail skin temperature, a small disk-shaped thermistor was affixed with tape to the dorsal surface of the tail. In some experiments, the electromyographic (e.m.g.) activity of the lateral thigh muscles of one hind leg was recorded. Two hook electrodes, insulated except for 1 mm at their tips, were inserted in the lateral thigh muscles just before placing the rat in restraint. A third electrode, placed in the skin of the back at mid line, served as a ground. E.m.g. potentials were amplified by a Grass 7P3B AC preamplifier, and the full-wave rectified signal was integrated using a Grass 7P10B long-term integrator.

Effect of forcefully disturbing core temperature during neurogenic hyperthermia

In these studies, four rats implanted with polyethylene coils and one rat without an implanted coil were subjected to forced deviations of core temperature during the plateau stage of neurogenic hyperthermia. In each experiment, the rat was placed in the environmental chamber at 26 °C, and base line measurements of core temperature (T_c), tail skin temperature (T_{ts}) and e.m.g. activity were recorded for 1–2 hr. The stylet was then removed from the guide tube and replaced with a sterile stylet 6 mm longer. This procedure produced an instantaneous destruction of the anterior hypothalamic and preoptic tissue below the guide tip (Rudy *et al.* 1977). When the ensuing hyperthermia reached a stable plateau, core temperature was forcefully elevated or lowered by either internal or external heating or cooling. In the four animals with implanted coils, the thermal loads were applied by perfusing the coil with warm (50–55 °C) or cold (12–15 °C) water. In one animal, core temperature was lowered by applying ice water to the fur of the back and elevated by transiently raising the chamber temperature to 50 °C. In three rats, the treatment sequence consisted of cooling followed by heating. The sequence was reversed in the other two rats.

Neurogenic hyperthermia elicited at different ambient temperatures

Forty rats without implanted coils were divided by random selection into three groups of ten and two groups of five animals. The three groups containing ten rats were lesioned at ambient temperatures of 15, 26 and 32 °C. The other two groups were lesioned at 10 and 36 °C respectively. In these studies, T_c and T_{ts} were recorded continuously, but e.m.g. activity was not measured. The restrained animals were placed in the environmental chamber at 26 °C, and the temperature of the chamber was then gradually raised or lowered to the desired level. An additional 1–2 hr was allowed for core temperature to stabilize, and then hypothalamic puncture was carried out as described above.

Data analysis

The magnitude of the hyperthermia induced by hypothalamic puncture was quantified on the basis of the maximum absolute core temperature reached within the 3 hr period following lesioning (T_{c-max}), the maximum increase in T_c above base line observed within the same time period (ΔT_c) and the 6 hr fever index ($F.I._6$). The latter was obtained by planimetric measurement of the area between the fever curve and the extrapolated base line temperature. Base line temperature (T_{c-o}) was defined as the colonic temperature existing just before lesioning. In the studies of the effect of ambient temperature on neurogenic hyperthermia, the T_{c-max}, ΔT_c, $F.I._6$ and T_{c-o} data were subjected to individual one-way analyses of variance and the individual means compared at the 0·05 level of significance using the least significance difference test (Steele & Torrie, 1960).

The tail skin temperature measurements were used to compute Tail Thermal Conductivity Indices (*TTCI*) using the following equation (modified from Stitt, 1973):

$$TTCI = \frac{T_{ts}-T_{ambient}}{T_c-T_{ts}} \times 10.$$

TTCI is an index of tail vasomotor tonus. Low values indicate vasoconstriction and high values, vasodilitation. *TTCI* is superior to skin temperature measurements as an index of vasomotor tonus in that *TTCI* compensates for the passive changes in skin temperature which accompany changes in ambient temperature and/or core temperature.

E.m.g. data were acquired as both raw e.m.g. tracings and as integrated e.m.g. activity as described previously. The raw tracings were used to monitor the qualitative aspects of the e.m.g activity. Integrated e.m.g. (averaged over 7 min periods) provided an estimate of the quantity of shivering activity per unit time. A combination of electronic attenuation and manual adjustment of the data were used to subtract out e.k.g. artifact and artifact arising from spontaneous movements of the animal. Integrated e.m.g. is reported in arbitrary units of mm of pen rise per minute.

Histology

Each rat was killed within 48 hr after hypothalamic puncture and its brain perfused with saline followed by 10% formalin. The fixed brains were embedded in celloidin, sectioned at 60 μm and stained by a modification of the Kluver–Barrera method (1953). The position and extent of the lesions were verified microscopically, and individual lesions were examined for evidence of haemorrhage into the ventricles.

RESULTS

In agreement with our previous experience (Rudy *et al.* 1977), neurogenic hyperthermia characteristically began within 5 min of hypothalamic puncture, reached its peak magnitude within 1–3 hr and lasted 8–16 hr. Occasionally, shorter or longer lasting responses were observed.

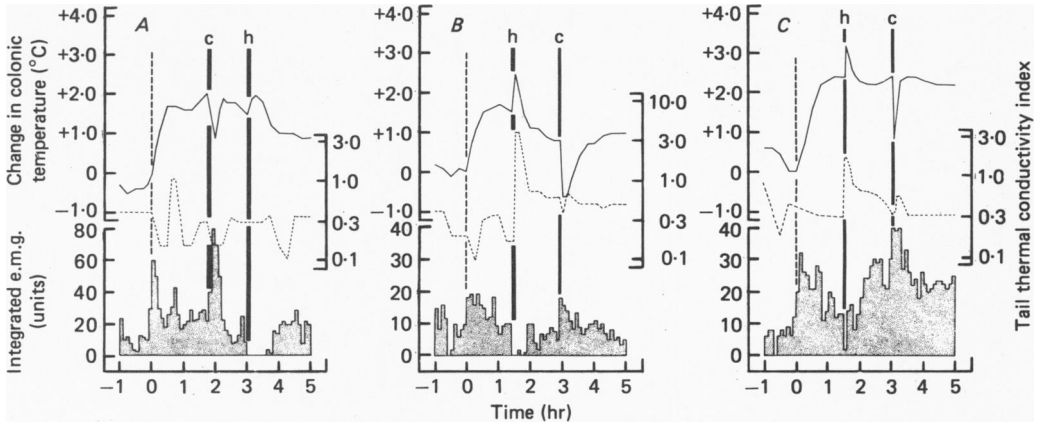

Fig. 1. Records of colonic temperature change, integrated e.m.g. activity and tail thermal conductivity of three rats (*A*, *B* and *C*) lesioned at 26 °C and subsequently subjected to brief periods of internal heating and cooling. Note the difference in ordinate scaling for e.m.g. activity for rat *A* *vs.* rats *B* and *C* and that the ordinate scaling for tail thermal conductivity index is logarithmic. The vertical dashed line at time zero indicates the time of hypothalamic puncture. Vertical filled bars labelled C and H indicate the periods of cooling and heating, respectively.

Effect of forcefully disturbing core temperature during neurogenic hyperthermia

Four rats were lesioned at an ambient temperature of 26 °C and, after hyperthermia had developed, were subjected to internal heating and cooling. The results from three of these rats are depicted in Fig. 1. The results from the fourth animal were similar, as were those from a fifth rat which was heated and cooled by external means. In Fig. 2 are shown segments of raw e.m.g. tracings from rat *C* taken at nine different periods during the experimental session shown in Fig. 1.

Figs. 1 and 2 illustrate that shivering activity and tail vasomotor tonus were modulated in an appropriate fashion during the rising and plateau stages of hyperthermia. During the rising phase of the response, e.m.g. activity increased dramatically in all animals, and *TTCI* decreased or remained at its already nearly minimal

level. As the plateau phase of hyperthermia was approached, shivering decreased considerably, and, in two of the rats, *TTCI* increased transiently.

Figs. 1 and 2 additionally illustrate that neurogenic hyperthermia during the plateau stage was actively defended; shivering and tail vasomotor tonus were modulated in a coordinated manner so as to minimize the effect on core temperature of the applied thermal loads and to return core temperature to the pre-loading level.

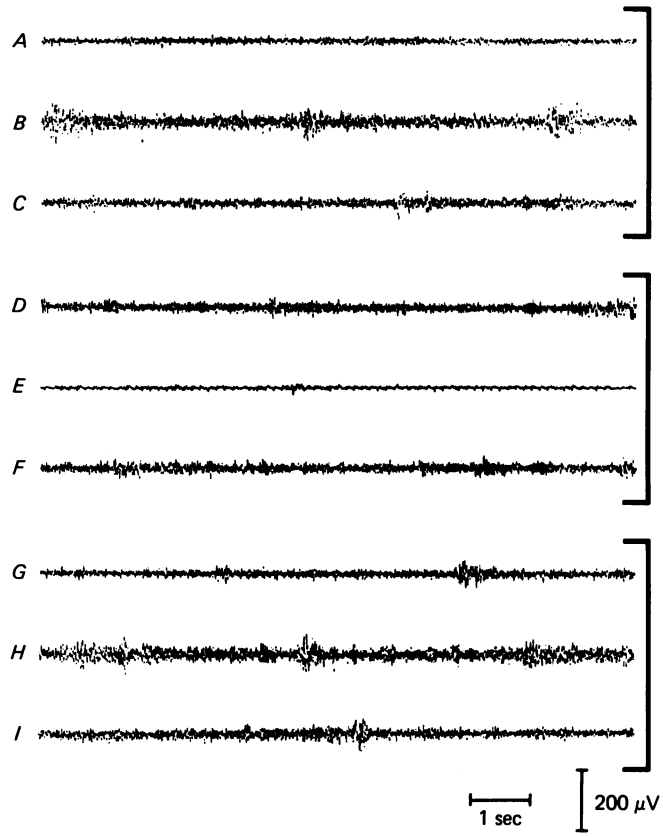

Fig. 2. Samples of raw e.m.g. activity from rat *C* taken at nine different times during the session illustrated in Fig. 1. Time and voltage calibrations appear at lower right. Shivering activity is indicated by an increase in background tonus and by the appearance in the records of distinct bursts of high amplitude potentials. Sampling times were as follows: *A*, 1 min prior to hypothalamic puncture. *B*, 4 min following hypothalamic puncture. *C*, 60 min following hypothalamic puncture. *D*, 1 min prior to internal heating. *E*, 4 min following the termination of heating. *F*, 30 min following the termination of heating. *G*, 1 min prior to internal cooling. *H*, 4 min following the termination of cooling. *I*, 30 min following the termination of cooling.

Internal cooling elicited vigorous shivering in all four animals tested, as did external cooling in the fifth. Accentuated shivering continued throughout the period of depressed core temperature but decreased in intensity as core temperature rose to near the level existing before forced cooling. In animals *A* and *B* in Fig. 1 and in the two rats for which data are not shown, *TTCI* decreased slightly during the period of

lowered core temperature. Forced elevation of core temperature suppressed shivering in all five rats. Shivering increased again as core temperature fell to near the pre-loading level. Internal heating elicited a clear increase in *TTCI* in three of the four rats tested by this method. The vasodilitation subsided as core temperature fell to its former level. Thermal conductance could not be accurately determined in the one rat which was heated by external means.

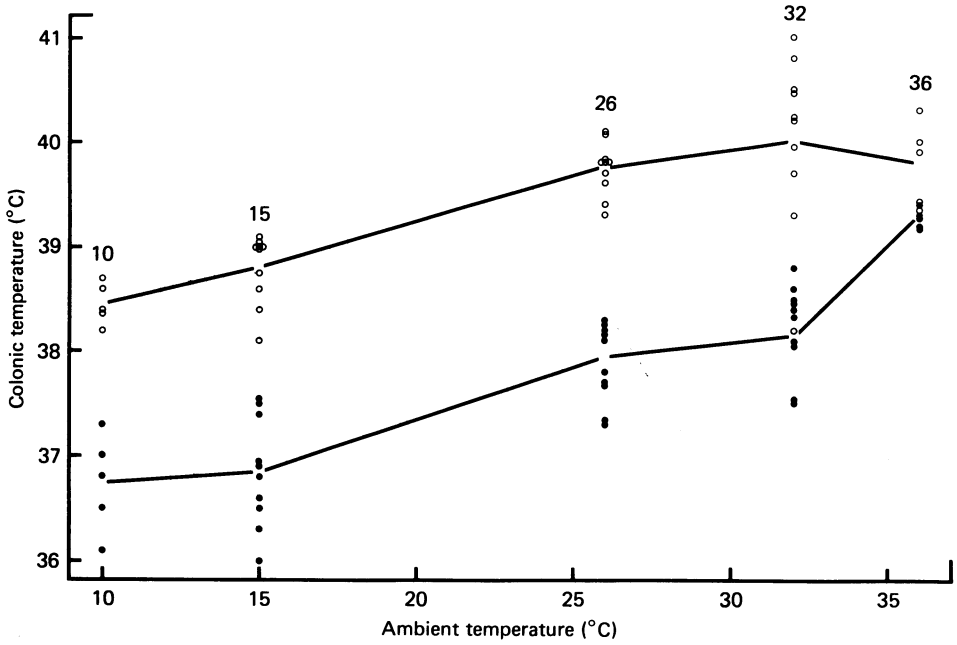

Fig. 3. Relationship between T_a, T_{c-o}, T_{c-max} and ΔT_c. Filled circles denote the pre-lesioning colonic temperature (T_{c-o}) of individual rats tested at the ambient temperature (T_a) indicated in small numerals above each column. Open circles denote the maximum post-lesioning colonic temperature (T_{c-max}) of the same rats. Continuous lines connect group means. Mean ΔT_c at each T_a is indicated by the distance between the upper and lower within-column means.

Information regarding the effect of internal heating and cooling during *normo*-thermia was not obtained in any of the five rats discussed above. However, such information was obtained in two additional rats following a sham puncture of the hypothalamus (removal and reinsertion of the occluding stylet) which did not elicit fever. The thermoregulatory defence mechanisms elicited by heating and cooling in these animals were qualitatively and quantitatively similar to those elicited in the rats with neurogenic hyperthermia.

Neurogenic hyperthermia elicited at various ambient temperatures

Ambient temperature affected pre-lesioning core temperature and, thus, the effect of ambient temperature on hyperthermia magnitude depended upon how magnitude was expressed (Table 1 and Fig. 3). ΔT_c and $F.I._{\cdot 6}$ values did not differ significantly

among the groups of rats lesioned at 10, 15, 26 and 32 °C. However, at 36 °C, hyperthermia magnitude, as measured by these indices, was significantly diminished. The influence of T_a on the other index of magnitude, T_{c-max}, followed a different pattern. T_{c-max} values were not significantly different among the groups of rats lesioned at 26, 32 and 36 °C, but T_{c-max} values in the rats lesioned at 10 and 15 °C were significantly lower. It should be noted, however, that regardless of how the magnitude of hyperthermia was measured, the neurogenic hyperthermia was not enhanced in the rats which were lesioned in the hot (36 °C) environment and that cold exposure had no profound effect on the ability of hypothalamic puncture to elicit hyperthermia.

TABLE 1. The effect of ambient temperature on basal colonic temperature and on the magnitude of neurogenic hyperthermia as measured by three indices. T_a = ambient temperature. n = number of animals tested at each ambient temperature. T_{c-i} = colonic temperature 10 min after placing rats in restraint and before ambient temperature had been changed from 26 °C to its final level (see text for explanation). T_{c-o} = base line colonic temperature. T_{c-max} = maximum change in colonic temperature occurring within 3 hr after lesioning. $F.I._6$ = area between the colonic temperature curve and the extrapolated base line temperature for the first 6 hr after lesioning. Tabulated values are means ± S.E. of mean. In each column, each mean differs significantly ($P < 0.05$) from every other mean in the column not enclosed within the same bracket; means enclosed within a given bracket do not differ significantly ($P > 0.05$) from each other

T_a (°C)	n	T_{c-i} (°C)	T_{c-o} (°C)	T_{c-max} (°C)	ΔT_c (°C)	$F.I._6$ (°C.hr)
10	5	37·78 ± 0·09	36·74 ± 0·21	38·46 ± 0·09	1·72 ± 0·12	6·43 ± 0·80
15	10	38·10 ± 0·13	36·84 ± 0·16	38·80 ± 0·10	1·96 ± 0·16	8·73 ± 0·78
26	10	38·25 ± 0·20	37·97 ± 0·10	39·74 ± 0·08	1·77 ± 0·11	7·85 ± 0·61
32	10	37·84 ± 0·10	38·15 ± 0·16	40·04 ± 0·26	1·89 ± 0·24	9·18 ± 1·42
36	5	38·13 ± 0·08	39·26 ± 0·05	39·78 ± 0·19	0·52 ± 0·15	1·79 ± 0·63

The involvement of changes in tail vasomotor tone in the generation and maintenance of neurogenic hyperthermia at various ambient temperatures can be estimated from the *TTCI* recordings made in each of the lesioned rats. In all fifteen rats lesioned at 10 or 15 °C, tail skin vasoconstriction was intense before hypothalamic puncture, and *TTCI* remained very low after lesioning. The twenty rats lesioned at 26 and 32 °C all exhibited slight to marked *TTCI* decreases during the rising phase of the hyperthermic response. During the plateau stage. *TTCI* increased transiently and then returned to a level near to or lower than that existing before hypothalamic puncture.

Records from two rats representative of those lesioned at 32 °C are presented in Fig. 4. Similar effects were seen in two of the five rats lesioned at 36 °C (Fig. 5). The other three rats experienced neurogenic temperature increases which were smaller and much shorter than those depicted in Fig. 5. In these three animals, tail vasomotor tone changed little during the rising phase of hyperthermia. It is noteworthy that in none of the forty rats studied did persistent compensatory vasodilitation appear during the plateau stage of neurogenic hyperthermia.

Post-mortem examination of the brains of rats lesioned at each ambient temperature and comparisons between experimental groups revealed no major differences in lesion size or position, although there was considerable variation within each group.

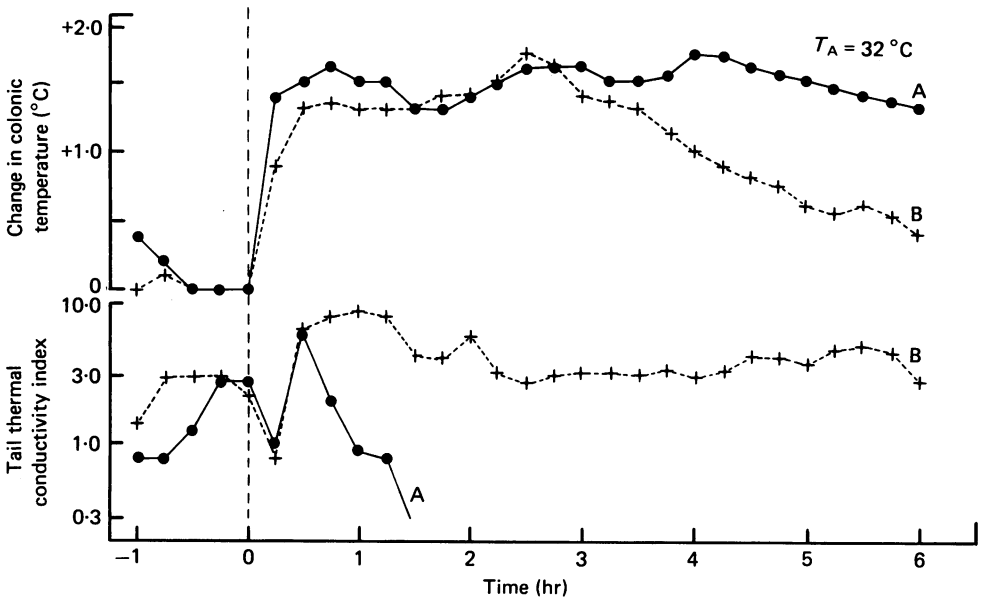

Fig. 4. Records of colonic temperature change and tail thermal conductivity of two rats lesioned at 32 °C. Vertical dashed line at time zero denotes the time of hypothalamic puncture. Note the logarithmic ordinate scaling for tail thermal conductivity index. The tail thermal conductivity index for rat *A* remained below 0·3 from time 1·5 hr to time 6 hr.

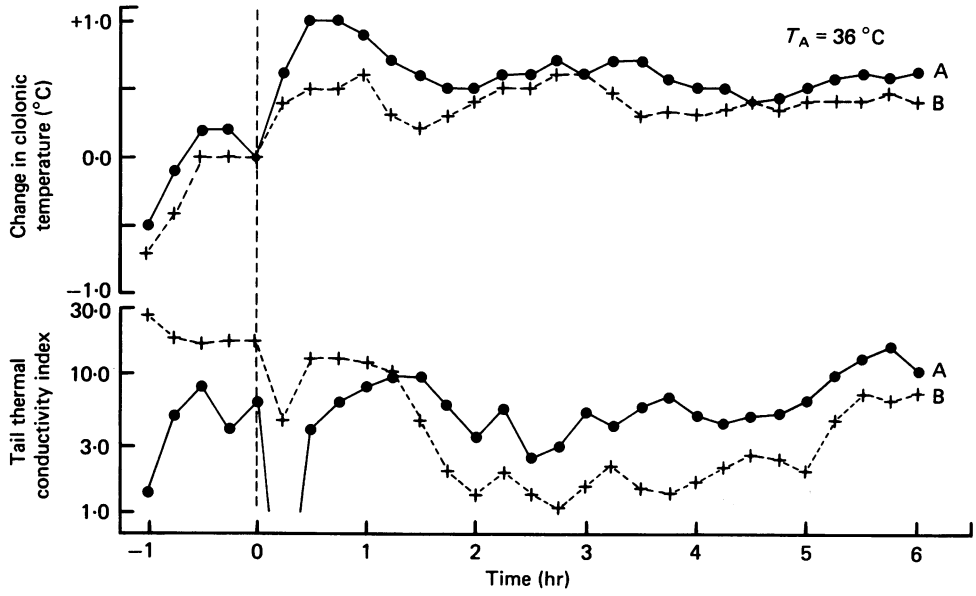

Fig. 5. Records of colonic temperature change and tail thermal conductivity of two rats lesioned at 36 °C. Vertical dashed line at time zero denotes the time of hypothalamic puncture. Note the logarithmic ordinate scaling for tail thermal conductivity index and that the range of this scaling differs from that in Fig. 4.

In general, the lesions resembled those described in detail in a previous study (Rudy *et al.* 1977). In about half of the lesions there was extravasated blood in the rostral hypothalamic-preoptic region, and in about one third there was evidence of haemorrhage into the cerebral ventricles.

DISCUSSION

Acute injury to the rostral hypothalamic region of the brain produces hyperthermia, but the cause and functional characteristics of temperature elevations thus induced have not been investigated. However, as discussed in the Introduction, the traditional view has been that the injury damages the hypothalamic thermoregulatory apparatus, thus causing a dysfunction of thermoregulation characterized by persistent heat production and impaired heat dissipation.

The results of the present study do not support the traditional view regarding the nature of neurogenic hyperthermia. For example, in our rats made hyperthermic by unilateral hypothalamic lesioning, neither persistent thermogenesis nor a crippling of heat dissipation was observed. That the lesioned, hyperthermic rats retained the ability to increase heat dissipation through the tail and thus were not in a state of tonic vasoconstriction is indicated by the transient vasodilitation observed during the early plateau stage of hyperthermia in rats lesioned at 26, 32 and 36 °C and also by the increase in tail conductance which appeared in three of four rats when core temperature was forcefully elevated by internal heating. A persistently high level of shivering thermogenesis could not have been responsible for the neurogenic hyperthermia because e.m.g. recordings in rats lesioned at 26 °C showed a return of shivering activity to near the pre-lesioning level as core temperature approached the plateau level of hyperthermia. That the rats were capable of inhibiting shivering is also indicated by the decrease in e.m.g. activity produced by forced elevation of core temperature above the plateau level and by the decrease of shivering as core temperature returned to the plateau level after application of a cold load. Although no measurements of non-shivering thermogenesis were made, it seems unlikely that persistent hyperactivity of non-shivering heat production effectors was the cause of hyperthermia. Core temperature ceased rising and entered the plateau stage at the same time as e.m.g. activity decreased, suggesting that the levelling off of core temperature was due primarily to the decline in shivering. Moreover, during the plateau stage, persistent vasodilitation of the tail was not present, although the rats were capable of increasing heat dissipation through the tail. If a persistently high level of non-shivering thermogenesis had been present, a continuous increase in core temperature could have been avoided only by a concomitant compensatory increase in heat dissipation.

Our findings regarding the effect of ambient temperature on the magnitude of the temperature increase evoked by hypothalamic puncture are also not supportive of a mechanism of pyrogenesis which depends on tonic thermogenesis and impaired heat dissipation. Because of the defect in effector control presumed to be present during a hyperthermia so mediated, the magnitude of the hyperthermia should be significantly increased in hot environments and attenuated in cold environments. In the present study, hyperthermia magnitude was not enhanced at 36 °C and, depending on the

particular index of hyperthermia magnitude used (*vide infra*), was either unaffected or only moderately decreased at cold ambient temperatures.

The experiments in which core temperature was forcefully elevated or depressed during the plateau stage of hyperthermia also yielded results at variance with the hypothesis that neurogenic hyperthermia represents an unregulated consequence of defective effector control. During heating and cooling, the changes in core temperature were vigorously opposed by appropriate changes in the level of shivering thermogenesis and of heat dissipation through the tail. Core temperature was actively returned to a level near that existing before application of the disturbing stimulus. Furthermore, the correction of the displaced core temperature was rapidly effected. A hyperthermia mediated by tonic thermogenesis with or without concomitant inhibition of heat dissipation would not be well defended. Forceful elevation or depression of core temperature during the plateau stage might respectively augment and inhibit compensatory effector actions but would not alter the level of activity in the dysfunctional thermogenic or heat dissipation pathways. Thus, the perturbations would not be vigorously resisted, and core temperatures would only slowly return to the preperturbation level.

Although the functional characteristics of the neurogenic hyperthermia elicited by unilateral puncture of the hypothalamus are not consistent with the notion that these pyrexias are representative of a defective effector control system, they *are* consistent with the hypothesis that the lesions somehow caused a sudden elevation of the reference or setpoint temperature. According to an abundant literature on the subject (see reviews by Borison & Clark, 1967; Cooper, 1972; Bligh, 1973; Stitt, 1979), at all ambient temperatures not beyond the thermoregulatory capabilities of the species, hyperthermia arising from a setpoint elevation will be generated by a coordinated modulation of the activities of heat gain and heat dissipation effectors. At thermoneutral temperatures, once the plateau level of hyperthermia has been reached, thermogenesis will decrease and the new core temperature will be maintained primarily by minor adjustments in peripheral vasomotor tone; compensatory hyperactivity in heat dissipation effectors will not be present. Attempts to disturb the elevated temperature will be vigorously resisted by the activation and/or inhibition of the appropriate thermoregulatory effectors. If transient thermal stresses produce a displacement of core temperature from the regulated level, following termination of the stress, core temperature will be actively and precisely returned to the level existing prior to application of the stress. Our findings with regard to effector coordination during the generation and maintenance of hyperthermia at various ambient temperatures are consistent with these criteria as are the results of the studies in which thermal stresses were applied during the plateau phase.

Another characteristic of a temperature rise engendered by a setpoint increase is that the magnitude of the hyperthermia will be similar at all ambient temperatures which do not overtax the thermoregulatory capabilities of the species (Borison & Clark, 1967; Cooper, 1972; Stitt, 1979). This criterion is useful, but as pointed out by Cooper (1972), when basal core temperature varies with ambient temperature, as was the case in the present study, interpretation of the data becomes complex. These difficulties of interpretation centre about the questions of why basal core temperature varied at extreme ambient temperatures and whether a pyrogenic stimulus elevates

the setpoint *by* a certain amount or *to* a certain level. Unfortunately, space does not permit a resolution of these issues *vis-a-vis* the present data. Suffice it to say that our findings are clearly more consistent with a mechanism of pyrogenesis based on a setpoint shift than with a mechanism involving a defect in the control of heat production and heat loss effectors. Furthermore, empirical confirmation that our findings are consistent with the notion of a setpoint increase is provided by the work of Kerpel–Fronius, Kiss & Than (1966). These workers injected bacterial endotoxin intravenously into rats kept at ambient temperatures of 10, 20, 30 and 35 °C. It is generally accepted that the temperature increase produced by endotoxin is functionally equivalent to an elevation of the setpoint. With respect to the effect of ambient temperature on base line core temperature and on hyperthermia magnitude as measured by ΔT_c and T_{c-max}, the results of Kerpel–Fronius *et al.* differ from our own only in that they found that both ΔT_c and T_{c-max} were reduced in the 10 °C environment.

The results of the present study show that the functional attributes of neurogenic hyperthermia caused by unilateral puncture of the rostral hypothalamus in the rat are not those of a hyperthermia arising from a derangement of thermoregulation characterized by loss of control over heat production and heat dissipation. Rather, the temperature increases experienced by the lesioned rats had characteristics similar to those of fevers evoked by pyrogens or by prostaglandins. In a previous report (Rudy *et al.* 1977), it was shown that hyperthermia caused by hypothalamic trauma could be reversed or prevented by the antipyretic and prostaglandins synthesis inhibitor, indomethacin. It is difficult to understand how an antipyretic could prevent a hyperthermia arising from the physical destruction and concomitant loss of function of portions of the hypothalamic thermoregulatory apparatus. It was suggested that the results could be explained if the hyperthermia was a consequence, not of the lesion itself, but of prostaglandins released from the injured tissue and acting on surviving portions of the anterior hypothalamic-preoptic tissue. The findings of the present study provide additional evidence in favour of the hypothesis that at least some forms of neurogenic hyperthermia are mediated by such a mechanism.

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