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Evaluation of Hypothalamic Thermosensitivity by Feedback Signals

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Summary. In four conscious goats with chronically implanted hypothalamic thermodes, forty-three experiments were carried out at environmental conditions between +5°C and 30°C DB/18°C WB. The temperature of the hypothalamus was altered by perfusing the thermodes with water whose temperature, as measured at the inlet of the thermodes, varied between 30°C and 43°C. Heat production, respiratory evaporative heat loss, rectal and oesophageal temperatures were measured. Hypothalamic cooling resulted in an elevation of rectal temperature, while hypothalamic heating caused a fall in temperature. The relation between the intensity of hypothalamic thermal stimulation and the induced change in core temperature can be well described by linear regressions. No difference in sensitivity and no dead band between responses to cold and warm stimulation was found. The experiments show that hypothalamic and extra-hypothalamic sensors of core temperature continuously operate at high sensitivity even within the narrow range of physiologically occurring core temperatures. Qualitatively, this sensitivity is independent of air temperatures between +5°C and +30°C.

Key words: Temperature Regulation — Hypothalamic Thermal Stimulation — Core Temperature — Continuous Temperature Signals — Feedback Control.

There is general agreement in current theories about temperature regulation in homeothermic animals that the stable state of internal body temperature is achieved by interaction of temperature signals generated on the body surface and within the body core. Core sensors of temperature are found within the hypothalamus (Hammel, 1968), within the spinal cord (Thauer and Simon, 1972) and at other sites, e.g. the abdomen (Rawson and Quick, 1969; Riedel *et al.* 1973). The relevance of these thermosensitive structures to the temperature regulating system is usually inferred from the fact that local thermal stimulation of a single set of these structures is able to elicit appropriate responses of effector systems which modulate the rates of heat production and heat loss. It is the major advantage of such an approach that the open loop gain of a selectively stimulated set of thermosensitive structures can be evaluated in this way (Hammel, 1968).

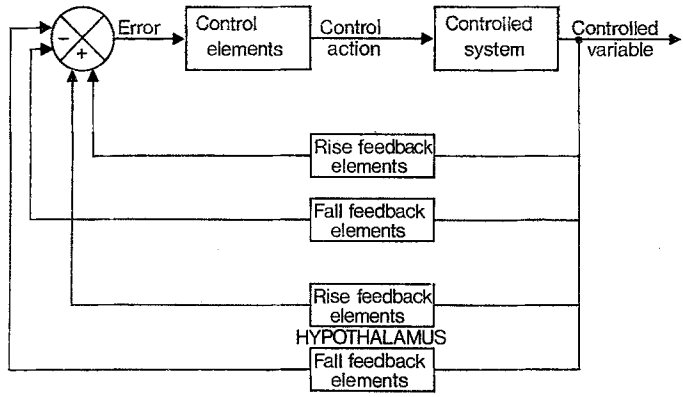

Fig. 1. Feedback control system of temperature regulation. The controller compares signal rates from different feedback loops. The controller action is to keep zero difference between rising and falling feedback elements. Adapted from Mitchell *et al.* (1970)

However, generating specific responses like shivering or panting by selective stimulation of thermosensitive structures within the body core in conscious animals requires intensities of thermal stimulation, which even in the best preparations, extend beyond the range of temperatures normally occuring in living animals. — Furthermore, inherent to present techniques of local thermal stimulation the intensity of the applied stimuli is usually underestimated, since for technical reasons, the thermode temperature cannot be measured correctly and is usually replaced by a tissue temperature taken at some distance from the thermodes and accordingly showing a level of stimulation below the maximum applied to the tissue (Jessen and Mayer, 1971). Therefore, if the relevance of core temperature sensors within the narrow range of physiologically occurring core temperatures is to be investigated, one has to face the fact that the approach mentioned above deduces this relevance from rather abnormal experimental conditions.

A second way of evaluating the function of thermosensitive structures of the body core within the normal range of core temperature can be based on the interaction of positive and negative feedback signals, which is generated by stimulating a single set of core temperature sensors. This can be expressed in terms of a model recently proposed by Mitchell *et al.* (1970) for temperature regulation in homeotherms (Fig. 1). According to this model, constancy of core temperature is achieved by means of a controller comparing signal rates from rising and falling feedback elements. Within the framework of this model, selectively stimulating a single set of core temperature sensors out of

the multiple sets generates an imbalance between signal rates from rising and falling feedback elements of the body core. Since the controller acts to restore the balance, the signal rate from feedback elements outside the stimulated area must change during sustained stimulation. With regard to the body core, this is achieved by changing the core temperature in a direction opposite to the primary thermal stimulus. That this is indeed the case, was already shown as early as 1912 by Barbour who reported that heating the corpus striatum in rabbits caused the rectal temperature to fall, whereas cooling the same area increased the rectal temperature.

Due to the multiple sets of temperature sensors and feedback loops within the body core, this approach is on principle not able to estimate the open loop gain of a single set of core temperature sensors (Brown and Brengelmann, 1970). However, the method has one basic advantage. The sustained change in core temperature in response to the sustained thermal stimulation at one location displays the combined effects of all induced modulations of heat production and heat loss and indicates the mean displacement of all other core temperature sensors needed to counter the experimentally induced change at the one location. It can therefore be expected to react as a sensitive indicator even at small intensities of thermal stimulation.

The experiments reported here were undertaken to test whether this change in core temperature, generated by artificially changing the balance between rising and falling feedback elements within the body core, can provide more information about the action of core sensors of temperature within the narrow range of physiologically occuring core temperatures. For this purpose, selective thermal stimulation of the hypothalamus was performed in conscious goats by a newly designed water perfused multithermode. The intensity of stimulation was judged from perfusion temperature, which excluded underestimation of stimulus intensity, and the response to the stimulation was evaluated in terms of the induced changes in core temperature.

Methods

1. Animals and Preparation. The experiments were performed on four female goats:

19	Saanen	30 kg	2 years
32	Toggenburg	28 kg	$1^1/_2$ years
39	Saanen	50 kg	4 years
52	Toggenburg	30 kg	$2^1/_2$ years

Several weeks before the experiments were started, the animals were prepared by implanting hypothalamic thermodes (Hammel, Jackson, Stolwijk, Hardy, and Strømme, 1963). Twenty-five stainless steel tubes (o. d. 1.0 mm) were implanted stereotaxically into the hypothalamus. The tubes were arranged to form a square

of side 12 mm. Accordingly the distance between the centres of adjacent tubes was 3 mm in both the frontal and the sagittal planes. The central tube served for the measurement of hypothalamic temperature, while the surrounding 24 tubes were perfused with water. The exact placement of the thermodes was performed under X-ray control after the 3rd ventricle had been filled with contrast medium (Hume and Ganong, 1956). The middle column of thermodes was positioned on the midline and the middle row of the thermodes was positioned in line with the posterior end of the recessus supraopticus. — The ovaries were removed in order to minimize variations in core temperature due to the ovarial cycle.

When the experiments were completed, the position of the hypothalamic thermodes in animals 32, 39 and 52 was verified histologically. The brains were perfused with saline and formalin. Serial paraffin sections (15 μ) were cut in frontal planes. One section in 10 was stained according to the method of Klüver and Barrera (1953). By comparing the sections with those published by Sajonski (1959/60) and by Tindal *et al.* (1968) it was verified that the position of the thermodes was in accordance with that shown by the contrast filling of the 3rd ventricle in the living animal.

2. Plan of Experiments. In the 4 goats 43 experiments were performed following a fixed schedule:

48 h before start of perfusion: last feeding

18 h before start of perfusion: animal brought into climatic chamber and exposed to air temperature chosen for the experiment.

Day of experiment:

8^{00}:	Attachment of perfusing system and measuring probes,
11^{30}:	Beginning of control period,
12^{00}:	Beginning of hypothalamic thermal stimulation,
15^{00}:	End of hypothalamic thermal stimulation,
17^{00}:	End of experiment.

In each experiment, one period of hypothalamic thermal stimulation lasting for 3 h was performed. The temperature of the water which perfused the thermodes varied between 30 °C and 43 °C throughout the course of the experimental series. However, during each single experiment the intensity of the thermal stimulation, as given by the temperature of the perfusing water, was kept constant. The relation between the temperature of the perfusing water and the hypothalamic tissue temperature 5 min after start of perfusion and 5 min before end of perfusion is given for all experiments by the following regressions:

$$T_{\text{hypo}}\,1205\text{ h} = 0.79\,T_{\text{perf}} + 7.47 \qquad r = 0.97$$

$$T_{\text{hypo}}\,1455\text{ h} = 0.74\,T_{\text{perf}} + 9.52 \qquad r = 0.96$$

From the regressions:

T_{perf}	°C	30.00	32.00	34.00	36.00	38.00	40.00	42.00
T_{hypo} 1205 h	°C	31.28	32.86	34.45	36.04	37.63	39.21	40.80
T_{hypo} 1455 h	°C	31.72	33.20	34.68	36.16	37.64	39.12	40.60

All experiments took place in a climatic chamber at constant external conditions. The trained animals were restrained within a frame, with their heads enclosed in a ventilated head cage. The thermodes were perfused with water whose temperature was kept contant within 0.1 °C by means of a thermostatically controlled water bath. The flow rate through the hypothalamic thermodes was in the order of 400 ml/min with minor variations between the different animals.

3. Recordings. The intensity of the thermal stimuli applied to the hypothalamus was determined from the temperature of the perfusing water, measured at the inlet of the thermodes. This temperature, the hypothalamic tissue temperature and the oesophageal temperature of the animal were measured with thermocouples and recorded continuously. The oesophageal thermocouple was inserted via the external nares and the temperature was measured at a depth of 55 cm. The accuracy of measurement was within $\pm$ 0.1 °C. The rectal temperature at a depth of 15 cm was measured by a quartz thermometer probe and recorded continuously. The probe was calibrated to within 0.02 °C absolute accuracy (Hewlett Packard).

An open circuit respiratory system was used to calculate heat production and respiratory evaporative heat loss (Jessen and Mayer, 1971). The air flow rate was measured by a dry gas meter ($\pm$ 1%) and corrected to STPD. The difference in oxygen content between inlet and outlet air was calculated from continuous recordings of the oxygen partial pressure (Beckman F3). A constant RQ of 0.85 was assumed. Oxygen consumption was converted to heat production by using 20.349 kJ/l as a caloric equivalent for oxygen. The difference in water content of inlet and outlet air was measured by continuous recordings from an infrared analyser (Uras, Hartmann, and Braun). The increase in water content was converted to respiratory evaporative heat loss by using 2.411 kJ/g as the latent heat of vaporisation of water.

Results

Three experiments performed in animal 39 at an air temperature of + 5 °C are given in Fig. 2. The figure shows heat production and rectal temperature during hypothalamic heating (open circles) and hypothalamic cooling (filled circles). Additionally, the rectal temperature during an experiment with minimal thermal stimulation of the hypothalamus is shown as a control (open triangles). All parameters are plotted against time of day.

Hypothalamic heating, with a perfusion temperature of 38 °C, was started at 1200 h. This caused the rectal temperature to fall from 35.7 °C at 1200 h to its lowest value of 35.4 °C, which was reached at 1320 h. In spite of the continuing hypothalamic heating, the rectal temperature started then to rise again and it reached 35.8 °C by 1500 h, which was the end of the perfusion. Later on, rectal temperature rose further and reached 36.8 °C at 1700 h. The changes in core temperature were accompanied by appropriate changes in heat production, which showed a transient decrease during the first part of hypothalamic heating, but went up again while the stimulation continued. After the end of the perfusion, the heat production showed a further increase and reached a peak value of 3 watt/kg before levelling at its control value toward the end of the experiment.

The opposite effect was observed during hypothalamic cooling (filled circles). Perfusing the hypothalamic thermodes with an inlet water temperature of 35 °C caused the rectal temperature to rise from its control value of 36.2 °C at 1200 h to 37.6 °C at the end of the perfusion at 1500 h. The rise of rectal temperature consisted of a steeper part

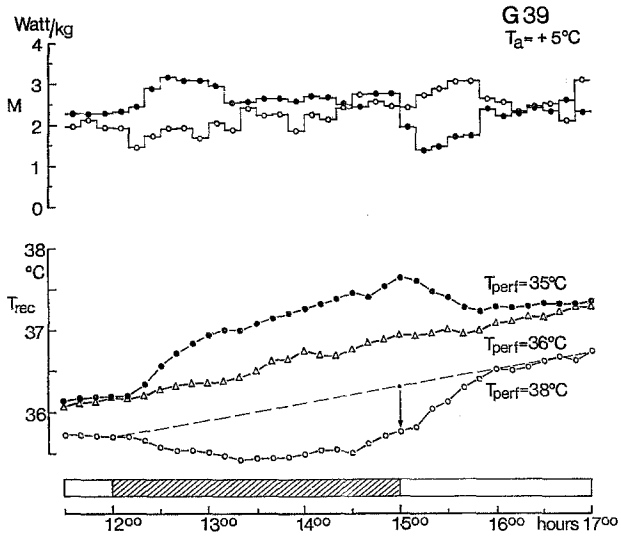

Fig. 2. Heat production and rectal temperature during hypothalamic thermal stimulation from 1200 to 1500 h. Animal 39, air temperature + 5 °C. Hypothalamic cooling with perfusion temperature of 35 °C (filled circles) induced a persistent increase of rectal temperature and a transient increase of heat production. Hypothalamic heating at a perfusion temperature of 38 °C (open circles) lowered the rectal temperature and caused a transient decrease of heat production. Perfusing the hypothalamic thermodes with water of 36 °C (open triangles) caused no change in rectal temperature

during the first hour of the perfusion, which is reflected in the parallel increase of heat production, and of a slower increase during the last two-thirds of the cooling period. After hypothalamic cooling was over, rectal temperature and heat production fell at first, until later on rectal temperature again increased and heat production levelled at its control value.

Both experiments show clearly that hypothalamic thermal stimulation generates opposite changes of rectal temperature, but illustrate at the same time that these induced changes of rectal temperature interfere with an independent trend of the rectal temperature. This independent trend can be clearly seen in the third experiment (open triangles). In this experiment, the perfusion of the hypothalamic thermodes was carried out with an inlet water temperature of 36 °C. Since the rectal temperature at 1200 h was 36.2 °C, the perfusion was performed virtually without thermal stimulation. Accordingly, the rectal temperature did not show any obvious deviation from a spontaneous linear drift between 1200 h and 1700 h.

To separate experimentally induced changes from independent trends of rectal temperature, the effects of hypothalamic thermal stimulation were evaluated as the difference between the actual temperature at 1500 h (end of stimulation) and a supposed temperature for the same time, which was calculated from linear interpolation between the rectal temperature at 1200 h and 1700 h. This procedure is illustrated for the heating experiment by the broken line and the vertical arrow. The difference, calculated in this way, amounts to an increase of 0.74 °C for hypothalamic cooling with a water temperature of 35 °C and a decrease of 0.50 °C for hypothalamic heating with a water temperature of 38 °C. The control experiment (water temperature 36 °C) resulted in an increase of 0.10 °C.

All changes in rectal temperature, reported later on and correlated to the intensity of hypothalamic thermal stimulation, are calculated in this way, i.e. by the difference between the actual rectal temperature at 1500 h and a supposed temperature for this time calculated from linear interpolation between rectal temperature at 1200 h and at 1700 h. In order to compare these changes in temperature and parameters of heat balance with absolute levels, Table 1 shows mean values and standard deviations for rectal temperature, oesophageal temperature, heat production and respiratory evaporative heat loss for selected periods of all experiments in all animals.

Fig. 3 represents all results obtained in 13 experiments in animal 39 at an air temperature of +5 °C. The bottom half of the figure shows the change in rectal temperature plotted against the temperature of the perfusing water. It is clear that all the points lie on a straight line. This line cuts the line of zero response, i.e. zero change in rectal temperature, at a perfusion temperature of approximately 37 °C. The open triangle presents the mean interpolated rectal temperature for 1500 h and is close to perfusion temperature for zero response. The upper part of the figure shows the difference in heat production between the control period (1130—1200 h) and the first half hour of stimulation (1200 to 1230 h). For perfusion temperatures between 34 °C and 39 °C, the change in heat production is characterized by considerable scattering of data around the zero line. Below perfusion temperature of 34 °C, hypothalamic cooling led to a clear increase in heat production as compared to the control period, whereas hypothalamic heating above 39 °C decreased heat production by about 1 watt/kg.

Fig. 4 shows the results of another series of experiments in the same animal 39 at a mild external heat stress (30 °C DB, 18 °C WB). At the bottom half of the figure, the change in rectal temperature is plotted against the temperature of the perfusing water. It is obvious that in these different environmental conditions, there is again a straight line

Table 1. Five series of hypothalamic thermal stimulations in four animals. Air temperature, number of experiments, mean values and standard deviations of rectal temperature and oesophageal temperature at the start and at the end of hypothalamic thermal stimulation and at the end of the post stimulation period. Mean values and standard deviations for heat production and respiratory evaporative heat loss during the last half hour before start of hypothalamic thermal stimulation

Animal	T_{air} (°C)	n	$T_{rec\ 12^{00}}$ (°C)	$T_{oeso\ 12^{00}}$ (°C)	$T_{rec\ 15^{00}\ interpol.}$ (°C)	$T_{oeso\ 15^{00}\ interpol.}$ (°C)	$T_{rec\ 17^{00}}$ (°C)	$T_{oeso\ 17^{00}}$ (°C)	Heat production $11^{30}-12^{00}$ (Watt/kg)	Resp. evap. heat loss $11^{30}-12^{00}$ (Watt/kg)
1	2	3	4	5	6	7	8	9	10	11
39	+ 5	13	36.20 ± 0.37	36.10 ± 0.39	36.91 ± 0.25	36.71 ± 0.22	37.39 ± 0.34	37.15 ± 0.23	2.231 ± 0.134	—
39	+ 30	14	38.90 ± 0.35	38.87 ± 0.35	39.26 ± 0.51	39.20 ± 0.50	39.58 ± 0.57	39.50 ± 0.58	1.518 ± 0.291	0.740[a] ± 0.116
52	+ 5	5	38.50 ± 0.17	38.22 ± 0.17	39.09 ± 0.33	38.72 ± 0.25	39.50 ± 0.43	39.05 ± 0.32	2.516 ± 0.397	—
32	+ 25	6	38.89 ± 0.10	38.71 ± 0.13	39.14 ± 0.18	38.95 ± 0.31	39.34 ± 0.29	39.11 ± 0.46	1.720 ± 0.146	0.743 ± 0.296
19	+ 30	5	39.12 ± 0.25	39.31 ± 0.27	39.24 ± 0.32	39.41 ± 0.32	39.32 ± 0.41	39.47 ± 0.42	—	0.570 ± 0.100

[a] $n = 10$.

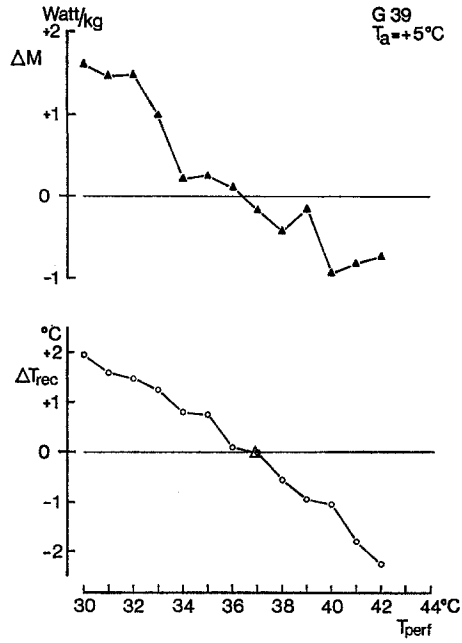

Fig. 3. Change in rectal temperature (ΔT_{rec}) after 3 h of hypothalamic thermal stimulation and change in heat production (ΔM) from the control period (1130 to 1200 h) to the first half hour of stimulation (1200—1230 h) plotted against perfusion temperature (T_{perf}). Thirteen experiments in animal 39 at an air temperature of +5°C

relation between the temperature of the perfusing water and the resulting change in rectal temperature. This line shows a zero response for perfusing temperatures between 38°C and 39°C. The mean interpolated rectal temperature for 1500 h (end of perfusion) in this series was 39.26°C. The upper part of the figure shows the differences in heat production and respiratory evaporative heat loss, which occurred between the last half hour of the control period and the first half hour of the stimulation period. Except two values for heat production, which showed a definite increase at water temperature of 31°C and 35°C, there is no clear relation between the intensity of hypothalamic heating or cooling and appropriate effector responses. This implies that even the major changes in rectal temperature at the higher levels of stimulation were achieved by the animal without substantial changes in heat production and respiratory evaporative heat loss.

Fig. 5 shows the same data for three animals in three different environmental conditions. Again the activity of effector systems and the change in rectal temperature is plotted against temperature of the perfusing

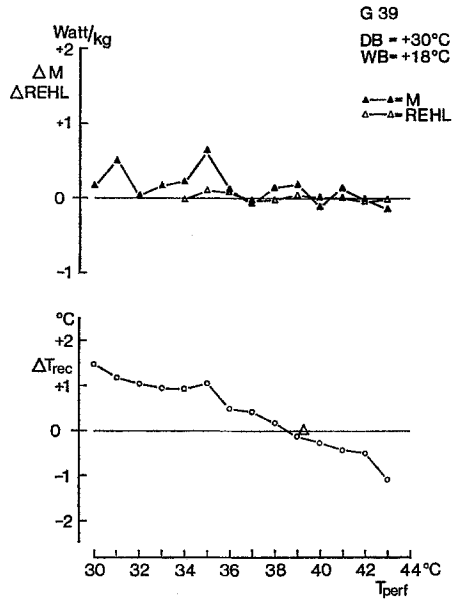

Fig. 4. Change in rectal temperature (ΔT_{rec}) after 3 h of hypothalamic thermal stimulation and changes in heat production (ΔM) and respiratory evaporative heat loss (Δ *REHL*) from the control period (1130—1200 h) to the first half hour of stimulation (1200—1230 h) plotted against perfusion temperature (T_{perf}). Fourteen experiments in animal 39 at +30°C DB and +18°C WB

water. Obviously, change in rectal temperature is a constant and regular effect of hypothalamic heating or cooling and, in a qualitative sense, is independent of air temperature. On the contrary, when the perfusing temperatures were around body core temperature, only at +5°C air temperature does the change in heat production bear a close relation to the intensity of hypothalamic thermal stimulation.

As shown above, the relation between intensity of hypothalamic thermal stimulation and subsequent changes in rectal temperature can be described by a straight line. Therefore, for all series linear regressions were calculated. The regression equations are presented in Table 2 together with the calculated values for perfusion temperature giving zero change in rectal temperature. Additionally, the correlation coefficients, which are highly significant ($P < 0.001$), are shown.

Discussion

1. The experiments presented above have shown that the rectal temperature of conscious goats altered during thermal stimulation of the hypothalamus. As can be concluded from simultaneous measure-

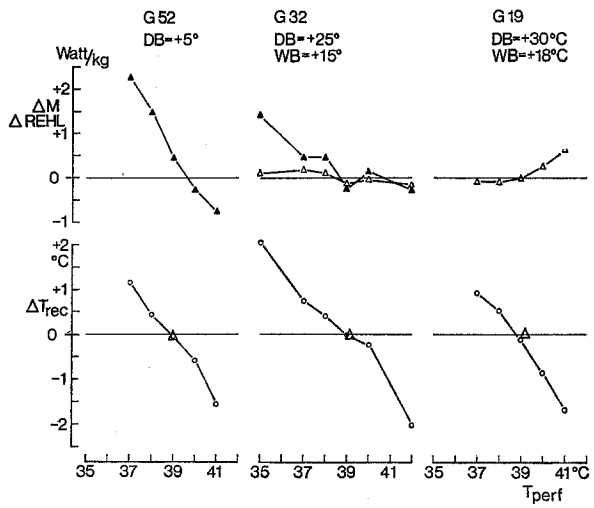

Fig. 5. Change in rectal temperature (ΔT_{rec}) after 3 h of hypothalamic thermal stimulation and changes in heat production (ΔM, filled triangles) and respiratory evaporative heat loss (Δ *REHL*, open triangles) from the control period (1130 to 1200 h) to the first half hour of stimulation period (1200—1230 h) plotted against perfusion temperature (T_{perf}). Five experiments in animal 52 at +5°C DB, six experiments in animal 32 at +25°C DB, +15°C WB, five experiments in animal 19 at +30°C DB, +18°C WB

Table 2. Five series of hypothalamic thermal stimulation in four animals. Air temperature, number of experiments, and linear regressions for change in rectal temperature (y) following hypothalamic thermal stimulation (x = perfusion temperature). Calculated perfusion temperatures for zero change in rectal temperature and correlation coefficients

Animal 1	T_{air} 2	n 3	Regression 4	$X_{(y=o)}$ 5	r 6
39	+ 5°C	13	$y = 12.457 - 0.343\,x$	36.28	−0.99
39	+30°C	14	$y = 6.908 - 0.179\,x$	38.65	−0.98
52	+ 5°C	5	$y = 25.006 - 0.644\,x$	38.93	−0.99
32	+25°C	6	$y = 20.939 - 0.539\,x$	38.81	−0.98
19	+30°C	5	$y = 25.006 - 0.662\,x$	38.67	−0.99

ments of oesophageal temperature, similar changes took place also in other parts of the body core. Whitin the scope of these experiments, rectal temperature can therefore be considered to be representative of the body core temperature.

The question then arises to what extent can the observed changes in core temperature be causally attributed to the thermal stimulation of the hypothalamus? It is generally known that the core temperature

of conscious animals under experimental conditions undergoes some erratic fluctuations, which are not correlated to any controlled stimulation. In order to minimise these spontaneous fluctuations, all experiments were carried out according to a rigid time table. The scattering of single values around the calculated regression lines represents these spontaneous fluctuations of rectal temperature. The magnitude of the scattering can be evaluated from the correlation coefficients, which vary between 0.98 and 0.99.

Apart from the erratic fluctuations of core temperature, it has to be checked what bias is introduced by calculating the change in rectal temperature from the difference between real rectal temperature at the end of the stimulation period and a supposed, interpolated rectal temperature for the same time. This procedure was undertaken in order to separate experimentally induced changes of rectal temperature from independent trends, which may have been caused by the diurnal rhythm of core temperature. The magnitude of the involved error can be estimated by comparing the mean interpolated rectal temperature at the end of the hypothalamic stimulation (column 6 of Table 1) to the perfusion temperature giving zero change in rectal temperature as calculated from the regressions (column 5 of Table 2). The averaged difference is 0.46 °C, the maximum being 0.63 °C. This deduction from the regression lines is supported by the results of those single experiments of each series, in which the perfusion temperature was closest to the rectal temperature. In these experiments, the perfusion of the hypothalamic thermodes was performed virtually without thermal stimulation and the mean deviation of the real rectal temperature from the interpolated rectal temperature at the end of the perfusion was 0.06 °C, the maximum being 0.14 °C.

Assessment of hypothalamic and extra-hypothalamic thermosensitivity by feedback signals requires stable balance between hypothalamic and extra-hypothalamic core signals of temperature. To what extent this was achieved, can be deduced from the stability of rectal temperature during the last half hour of the stimulation period. Fig. 6 shows for all experiments in animal 39 the change in rectal temperature during the last half hour of hypothalamic thermal stimulation. Except for the highest levels of hypothalamic heating, there was a constant upward trend of rectal temperature for this period of time. This is in agreement with the general upward trend of core temperature during the course of the experiments, as can be seen in Table 1. Thus, for the majority of experiments the change in core temperature at the end of the hypothalamic stimulation period balanced the artificially altered hypothalamic temperature. The persistent change in core temperature with high levels of hypothalamic heating shows that for these experi-

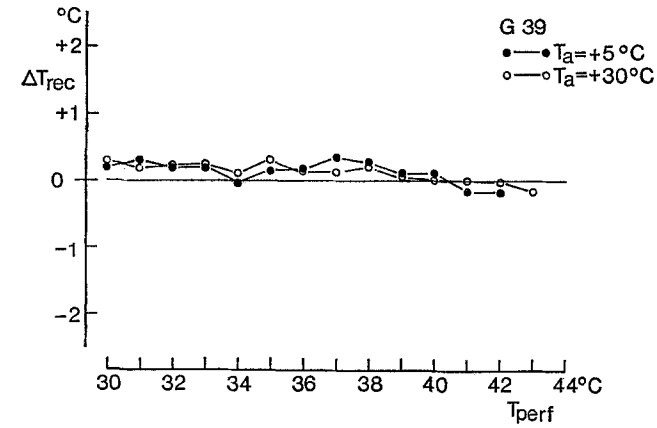

Fig. 6. Change in rectal temperature (ΔT_{rec}) during the last half hour of hypothalamic thermal stimulation plotted against perfusion temperature (T_{perf}). Twenty-seven experiments in animal 39 at an air temperature of +5 °C (filled symbols) and at +30 °C air temperature (open symbols)

ments the stimulation period of 3 h was not sufficient to achieve stable balance between hypothalamic and extra-hypothalamic core signals of temperature.

According to the model presented in the introduction, the stability of core temperature near the end of the stimulation period was achieved by a restored balance of core temperature signals from inside and outside the hypothalamus. However, two other possibilities may have to be considered. Firstly, the arterial blood, the temperature of which can be assumed to undergo similar changes as rectal temperature, may have locally acted upon the hypothalamus to cancel the effect of the thermodes. This possibility can be excluded on the evidence of measurements of hypothalamic temperature (see Methods), which indicates a negligible reduction of stimulus intensity during the experiment. Secondly, the stability of core temperature during continuous stimulation may be thought to occur not by balance of signals but by balance of heat loss and heat production at a new and higher level: e.g. hypothalamic cooling stimulates heat production and so core temperature rises. By the greater thermal gradient to the environment, heat loss then increases to balance heat production. Apart from the fact that this would require excessively high core temperatures, this possibility can be discarded on the fact that the primarily activated effector (e.g. heat production in the case of cooling, panting in the case of warming) regularly returned towards its control level in spite of the continuing stimulation (see Fig. 2). This is in accordance with an abundant number

of reports dealing with the effects of hypothalamic thermal stimulation (v. Euler, 1964; Hammel, 1968; Brown and Brengelmann, 1970).

2. If it then seems justified to assume that the change in core temperature shown above can be causally attributed to the hypothalamic thermal stimulation, it has to be asked, by what means is the change achieved? In terms of the model shown in Fig. 1, hypothalamic thermal stimulation initially causes an imbalance between rising and falling feedback elements within the body core.

For sake of clarity, hypothalamic and extra-hypothalamic sensors of temperature in Fig. 1 are shown as independent and parallel loops (Bligh, 1972). This is not meant to exclude serial or other organisation of extra-hypothalamic and hypothalamic feedback elements, which cannot be inferred from these experiments. Likewise, the role of skin feedback elements in this context remains open, since due to effector activity, skin sensors of temperature may have to be regarded as generating positive feedback signals.

This imbalance can exist on its own, or it can be superimposed on any imbalance already existing before start of hypothalamic thermal stimulation. The imbalance constitutes a load error proportional to the overall magnitude of the difference between rising and falling feedback elements. The load error proportionally drives appropriate effector systems, which, in the case of goats, are shivering, panting, sweating and variations in skin blood flow. Only two of these effector systems, i.e. shivering and panting, were quantitatively evaluated in these experiments by measuring heat production and respiratory evaporative heat loss. Apart from the experiments performed on animal 52 at an air temperature of $+5\,^{\circ}C$, these effector systems showed changes in activity only at higher levels of stimulation. It has therefore to be assumed that the lower levels of stimulation, which caused definite changes in core temperature, primarily influenced cutaneous blood flow, thereby adjusting the total heat loss in an appropriate manner. Consequently, direct calorimetric measurements of total heat loss would presumably show better agreement between change in core temperature and activity of effector systems. However, results reported by Calvert *et al.* (1972) and concerned with changes in total heat loss and meatal temperature during hypothalamic thermal stimulation in conscious oxen might suggest that even in such a comparison change in core temperature is the most sensitive indicator for effects of hypothalamic thermal stimulation, since the threshold for change in meatal temperature was lower than for change in heat loss.

The relation between intensity of hypothalamic thermal stimulation and induced change in core temperature can be well described by a linear regression. The regression line cuts the line of zero response at a perfusion temperature which is considerably less than one degree

different from the core temperature. There appears to be no difference in sensitivity and no dead band between responses to cold and warm stimulation. Apparently, the hypothalamic sensor of temperature provides a continuous temperature signal within the temperature range given by perfusion temperatures between 30 °C and 43 °C. This extends earlier findings by Andersson *et al.* (1963) concerned with effects of highly intensive hypothalamic thermal stimulation, to the narrow range of physiologically occuring core temperatures. Recently, similar experiments were performed by Lipton (1973) in conscious rats. Hypothalamic thermal stimulation led to opposite changes of rectal temperature, which were linearly correlated to the intensity of the thermal stimulation. Furthermore, the results presented above agree well with neurophysiological findings reported by Nakayama and Hardy (1969), Eisenman (1972), Guieu and Hardy (1970), Cabanac *et al.* (1968) and Hellon (1972) showing continuous function thermal response curves of hypothalamic neurons between 32 °C and 42 °C hypothalamic temperature.

However, a linear relationship between the intensity of hypothalamic thermal stimulation and the change in core temperature which balances it also implies that the extra-hypothalamic core sensors of temperature provide continuously operating temperature signals within ± 2 °C around the level of core temperature. Thus, both hypothalamic and extra-hypothalamic core sensors of temperature appear to operate continuously and at full sensitivity around the level of core temperature kept by the animal. Furthermore, if one regards hypothalamic and extra-hypothalamic sensors of temperature as providing parallel inputs to the controller, then linearity of interaction between both sets of sensors requires an identical type of continuous temperature response function for the entirety of hypothalamic sensors on one hand and of extra-hypothalamic sensors on the other hand. Within these limits, all types of response functions appear possible, the only condition being complete reciprocity of temperature response functions between hypothalamic and extra-hypothalamic sensors of temperature.

The slope of linear regression between intensity of hypothalamic thermal stimulation and subsequent change in core temperature describes the relative sensitivity of the hypothalamic sensor of temperature compared to the extra-hypothalamic temperature sensors. However, it has to be taken into account that specifying the intensity of the stimulation by the perfusion temperature describes the most unfavourable limit for the intensity of the stimulation. The true deviation of hypothalamic temperature must have been less than the difference between perfusion temperature and hypothalamic temperature before stimulation. The unknown relation between perfusion temperature and induced change of hypothalamic temperature may also account for the fact that the

slope of the regression lines for different animals at identical external conditions varied between 0.2 and 0.7. This is not regarded as indicative of between animal variation, but rather as a consequence of differences between thermode positions.

Even in the same animal different slopes were found for two series and this difference is highly significant ($P < 0.001$). At an air temperature of $+5\,^{\circ}C$, animal 39 displayed much greater change of core temperature per unit of hypothalamic stimulation as compared to the series performed at an air temperature of $+30\,^{\circ}C$. However, it has to be taken into account that at $+5\,^{\circ}C$, the temperature around which the body core was regulated was about $2^1/_2\,^{\circ}C$ below that at $+30\,^{\circ}C$ air temperature. If this does not indicate impairment of hypothalamic function by the thermodes, then different slopes at different air temperatures suggest that the sensitivity of hypothalamic temperature sensors relative to extra-hypothalamic sensors is not fixed but subject to change in changing conditions.

On the other hand, while the relative importance of hypothalamic and extra-hypothalamic sensors may vary, temperature sensitivity was shown to be, in a qualitative sense, independent of air temperature. At any condition between $+5\,^{\circ}C$ and $+30\,^{\circ}C$ air temperature, core sensors of temperature inside and outside the hypothalamus are capable of providing continuous signals of core temperature above and below its regulated level.

References

Andersson, B., Ekman, L., Gale, C. C., Sundsten, J. W.: Control of thyreotrophic hormone (TSH) secretion by the heat loss centre. Acta physiol. scand. **59**, 12—33 (1963)

Barbour, H. G.: Die Wirkung unmittelbarer Erwärmung und Abkühlung der Wärmezentra auf die Körpertemperatur. Naunyn-Schmiedebergs Arch. exp. Path. Pharmak. **70**, 1—15 (1912)

Bligh, J.: Neuronal models of mammalian temperature regulation. In: Essays on temperature regulation, pp. 105—120. Eds. J. Bligh and R. Moore. Amsterdam: North Holland Publ. Comp. 1972

Brown, A. C., Brengelmann, G. L.: The interaction of peripheral and central inputs in the temperature regulation system. In: Physiological and behavioral temperature regulation, pp. 684—702. Eds. J. D. Hardy, A. Ph. Gagge, and J. A. J. Stolwijk. Springfield, Ill.: Ch. C. Thomas 1970

Cabanac, M., Stolwijk, J. A. J., Hardy, J. D.: Effect of temperature and pyrogens on single-unit activity in the rabbit's brain stem. J. appl. Physiol. **24**, 645—652 (1968)

Calvert, D. T., Findlay, J. D., McLean, J. A.: Quantitative thermoregulatory responses of the ox to anterior hypothalamic warming. Int. J. Biomet. **16**, Suppl., 40—41 (1972)

Eisenman, J. E.: Unit activity studies of thermoresponsive neurons. In: Essays on temperature regulation, pp. 55—70. Eds. J. Bligh and R. Moore. Amsterdam: North Holland Publ. Comp. 1972

Euler, C. von: The gain of the hypothalamic temperature regulating mechanisms. In: Progress in brain research. Vol. 5: Lectures on the diencephalon, pp. 127—131. Eds. W. Bargmann and J. P. Schadé. Amsterdam: Elsevier 1964

Guieu, J. D., Hardy, J. D.: Integrative activity of preoptic units. 1. Response to local and peripheral temperature changes. J. Physiol. (Paris) **63**, 253—256 (1970)

Hammel, H. T.: Regulation of internal body temperature. Ann. Rev. Physiol. **30**, 641—710 (1968)

Hammel, H. T., Jackson, D. C., Stolwijk, J. A. J., Hardy, J. D., Strømme, S. B.: Temperature regulation by hypothalamic proportional control with an adjustable set point. J. appl. Physiol. **18**, 1146—1154 (1963)

Hellon, R. F.: Temperature sensitive neurons in the brain stem: their responses to brain temperature at different ambient temperatures. Pflügers Arch. **335**, 323—334 (1972)

Hume, D. M., Ganong, W. F.: A method for accurate placement of electrodes in the hypothalamus of the dog. Electroenceph. clin. Neurophysiol. **8**, 136—140 (1956)

Jessen, C., Mayer, E. Th.: Spinal cord and hypothalamus as core sensors of temperature in the conscious dog. I. Equivalence of responses. Pflügers Arch. **324**, 189—204 (1971)

Klüver, H., Barrera, E.: A method for the combined staining of cells and fibers in the nervous system. J. Neuropath. exp. Neurol. **12**, 400—403 (1953)

Lipton, J. M.: Thermosensitivity of medulla oblongata in control of body temperature. Amer. J. Physiol. **224**, 890—897 (1973)

Mitchell, D., Snellen, J. W., Atkins, A. R.: Thermoregulation during fever: change of set-point or change of gain. Pflügers Arch. **321**, 293—302 (1970)

Nakayama, T., Hardy, J. D.: Unit responses in the rabbit's brain stem to changes in brain and cutaneous temperature. J. appl. Physiol. **27**, 848—857 (1969)

Rawson, R. O., Quick, K. P., Coughlin, R. F.: Thermoregulatory responses to intraabdominal heating of sheep. Science **165**, 919 (1969)

Riedel, W., Siaplauras, G., Simon, E.: Intra-abdominal thermosensitivity in the rabbit as compared with spinal thermosensitivity. Pflügers Arch. **340**, 59—70 (1973)

Sajonski, H.: Zur makroskopischen und mikroskopischen Anatomie der Hypophyse und des Hypothalamus von Schaf und Ziege. Teil 1. Wiss. Z. Humboldt-Univ. Berlin, Math.-Nat. R. IX, 233—258 (1959/60)

Thauer, R., Simon, E.: Spinal cord and temperature regulation. In: Advances in climatic physiology. Eds. S. Itoh, K. Ogata, and H. Yoshimura. Tokyo: Igaku Shoin Ltd. 1972

Tindal, J. S., Knaggs, G. S., Turvey, A.: The forebrain of the goat in stereotaxic coordinates. J. Anat. (Lond.) **103**, 457—469 (1968)

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