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TEMPERATURE REGULATION DURING FEVER: CHANGE OF SET POINT OR CHANGE OF GAIN? A TENTATIVE ANSWER FROM A BEHAVIOURAL STUDY IN MAN

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SUMMARY

1. Four subjects were immersed in a stirred water-bath maintained at either 30 or 40° C. The left hand was placed out of the bath in a glove receiving water at a temperature selected by the subject as most pleasurable. Experiments were conducted during the euthermic state and during either spontaneous or induced fever.

2. The results of control experiments confirm a previous observation using the same method, that preferred hand skin temperature was a linear function of internal temperature but also indicated an influence by mean skin temperature.

3. The general pattern of response during fever was identical to that when fever was absent except that the regulated steady state internal temperature was higher and the slopes of preferred temperature plotted against internal temperature were steeper.

4. The results seem to support the concept of a change in set point rather than that of a change in the gain of the thermoregulatory processes during fever.

INTRODUCTION

Fever is considered as a state where the body thermostat is set at a higher level and body temperature is being regulated at this higher level (see review of Cooper, 1972). This shift of the regulated variable during fever can be used to study the nature of the system which regulates body temperature. It is generally admitted that the physiological thermostat has the characteristics of a proportional regulator with a set point (Hardy, 1965; Hammel, 1965) but recently Mitchell, Snellen & Atkins (1970) have offered an alternative theory based on changes in the slope of the regressions which describe the relations between electrical activity and tem-

perature of hypothalamic temperature sensitive neurones. They have postulated that if warm sensors become less responsive and cold sensors more responsive to temperature changes during fever, this change in slope rather than change in the intercept is indicative of a change in gain of the thermoregulatory system during fever, rather than a change in set-point of the system.

Here we report the results of a behavioural study of thermal comfort in man during afebrile and febrile states, and relate the results to these opposing hypotheses of a change in set-point or a change in gain of the human thermoregulator during fever.

METHODS

The general method was described by Cabanac, Cunningham & Stolwijk (1971), Cabanac, Massonnet & Belaiche (1972) and is only given briefly here. It consists of letting the subjects choose the most pleasurable hand skin temperature and monitoring this together with that of the rest of the body and internal body temperature.

Subjects were adult male volunteers, naked except for small bathing trunks, and immersed to their chins in a bath of water, the temperature of which was maintained at 30 or 40° C and continuously stirred. The left arm of the immersed subject was outside the bath. The hand was held in a glove which was perfused with water supplied through a mixer valve controlled electrically by the subject from two tanks of water, one at 10° C and the other at 50° C. The perfusion was at a constant rate of 300 ml. min^{-1}. The control valve was operated by the subject with the other hand from inside the bath. The subject was instructed to select the most pleasurable glove temperature (T_{pref}). Bath temperature (T_{bath}), glove temperature (T_{pref}) and oesophageal temperature (T_{es}) were monitored with copper constantan thermocouples and recorded. Fever was spontaneous in four subjects and induced in two subjects (the authors) by a shallow I.M. injection of Propidon[R] (Specia) (attenuated *Streptococcus*, *Staphylococcus*, and *Bacillus pyocyaneus*). Injections followed a sequence of increasing daily doses, 0·25, 0·5 and 0·75 ml., producing on the third day a 1° C fever which was stable for several hours after the injection. Each fever experiment was matched by a control experiment, conducted at the same time of the day, but on another day, on a euthermic subject. The continuous analogue records of T_{pref} and T_{es} were converted to digital records at intervals of 2 min for analysis by averaging the continuous records. For each T_{bath}, T_{pref} was computed as a function of T_{es}. The regression lines for mean values collected during 2 min intervals were computed by the least-squares method. The parameters when fever was present and absent were then compared.

RESULTS

Mean rectal temperature of the subjects in the morning immediately before the experiments was: control $37 \pm 0{\cdot}4°$ C (S.D.), fever $38 \pm 0{\cdot}4°$ C (S.D.). Nine experiments were made on subjects with fever and nine on subjects without fever. The results of a representative pair of experiments are given in Fig. 1. On this example the opposite directions of the changes in preferred hand temperature and of deep body temperature are evident.

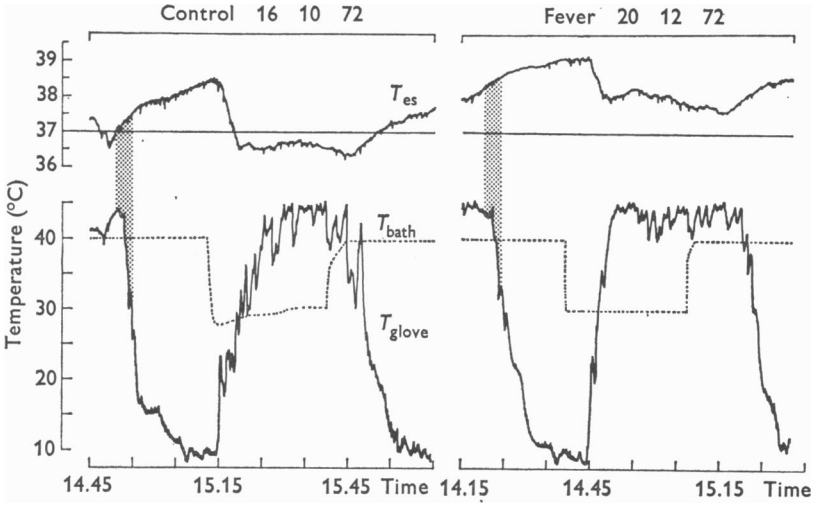

Fig. 1. Examples of one experiment during fever (right) and its control (left). In the upper part of the charts a horizontal line has been drawn to indicate normal body temperature. The abrupt changes in bath temperature (interrupted lines) were effected by the addition of ice or hot water to the bath. The pattern of response is identical in both experiments except for the level of oesophageal temperature. The stippled zone shows the time when the behavioural preference shifted from warm to cool water, i.e. presumably when core temperature of the subject had just exceeded his core temperature set point. Glove temperature chosen by the subject is the same as T_{pref}.

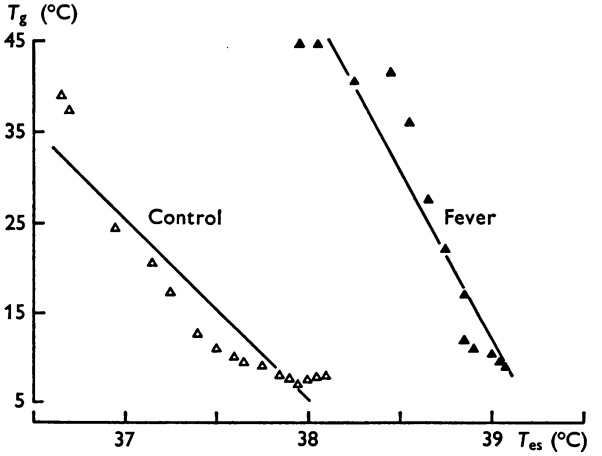

Fig. 2. One example of the way experimental results were analysed. For each bath temperature, here 40° C, time was divided into periods of 2 min and the regression lines were drawn. Each point represents therefore the average choice of glove temperature (T_g) during 2 min plotted against average oesophageal temperature during the same period.

The behavioural responses as well as the changes in core temperature are almost identical in the two experiments. When core temperature rose the subject chose a cooler glove temperature, when core temperature fell a higher glove temperature was chosen. The main difference between the two experiments is in the phase lag between changes in core temperature and the behavioural responses. The behavioural shift in the preferred glove temperature from warm to cold occurred at a higher oesophageal temperature during fever.

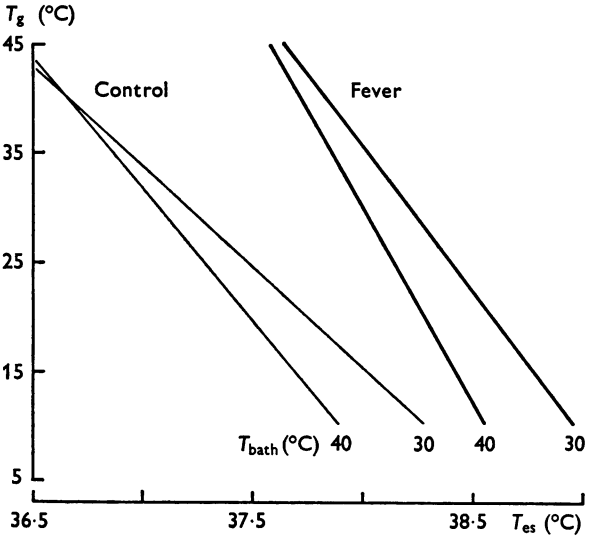

Fig. 3. Theoretical glove temperature choice obtained by averaging the parameters of individual regression lines obtained during control and fever experiments on the four subjects in eighteen experiments.

When the average values for periods of 2 min are plotted as in Fig. 2 the behavioural choice of glove temperature can be expressed as a function of oesophageal temperature. Typical results of all experiments at the two bath temperatures are indicated in Fig. 3. Since the level of fever was not exactly the same from day to day and from subject to subject it was not possible to average all the results and draw regression lines for all the fever experiments and all the control experiments. Averages can be obtained, however, from the parameters of individual regression equations. These parameters are given on Table 1. Fig. 3 indicates therefore, the typical average responses of a feverish subject and a euthermic subject obtained by using the average parameters of Table 1.

TABLE 1. Parameters of the equation $T_{pref} = aT_{es} + b$ which describes regression of the relation of the preferred glove temperature (T_{pref}) to oesophageal temperature (T_{es}), obtained by averaging individual results of control and fever experiments on four subjects, at the two bath temperatures: average fever was 38° C ± 0·4

Bath temperature	Mean parameter	Control	Fever
40° C	*a*	−25·2	−35·4*
	b	963·8	1375·4*
30° C	*a*	−19·4	−26†
	b	751·3	986·4†

* $P < 0{\cdot}1$ compared to control value, paired comparison *t* test.
† $P < 0{\cdot}05$ compared to control value, paired comparison *t* test.

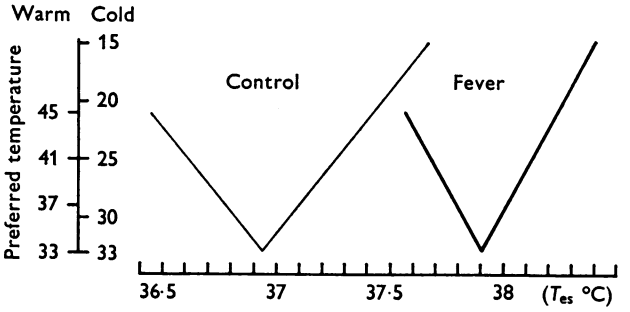

Fig. 4. A reconstruction of Fig. 3 in order to represent the behavioural reactions against cold and heat assuming 33° C constitutes a neutral stimulus. Only the choice in a 40° C bath is represented here.

DISCUSSION

The above results confirm the report by Cabanac *et al.* (1972) that the preferred hand temperature is inversely proportional to oesophageal temperature but the influence of mean skin temperature is somewhat different to that previously reported. In both studies the lower the mean skin temperature was, the higher was the preferred temperature, resulting in a higher curve for preferred temperatures when the subject was immersed in a 30° C bath than when immersed in a 40° C bath. The difference between the two sets of results lies in the precise values of the parameters and therefore in the point of convergence of regression lines for the two bath temperatures, 40 and 30° C. These differences between the two series of results are not important compared with the similarities: (i) proportionality of preferred temperature to oesophageal temperature and (ii) multiplicative rather than additive influence of bath temperature. As

already pointed out this multiplicative influence of $\bar{T}_s$ is probably itself without real significance when one looks at the physiological range of temperature. It is remarkable that these results obtained on a limited skin surface, the hand, can be extended to the whole body surface as shown by Bleichert, Behling, Scarperi & Scarperi (1973).

The above results confirm the great influence of fever on thermal preference in man. This response is analogous to the behavioural responses of feverish cats (Weiss, Laties & Weiss, 1967), dogs (Cabanac, Duclaux & Gillet, 1970) and baboons (Gale, Mathews & Young, 1970) and gives further evidence of a close relation between behavioural thermoregulation and autonomic thermoregulation. These results are more quantitative than those of a previous study on feverish man (Cabanac, 1969) and can be considered in relation to the hypothesis offered by Mitchell *et al.* (1970) who have proposed that fever is due to a rotation of the curves which relate the autonomic responses to core temperature, caused by a change in a gain of the thermostatic mechanism, in the same way as the changes in electrical activities of hypothalamic neurones in response to change in local temperature are altered during fever. The result would be an increased slope of heat production and a decreased slope of heat loss plotted against core temperature, in response to a pyrogen. The results reported above would support this theory if the curve describing the relation between glove and core temperatures at the low core temperature were steeper during fever and the curve at the high core temperature were less steep. During fever there was a shift of these response curves to the right (Fig. 3) indicating that the major effect of a pyrogen was to change the set point of the thermostat. As the slopes of the curves during fever were statistically significantly greater than those when fever was absent, there was also evidence of a change in gain. However, the change in the behavioural response, which remained approximately linear, was the same for preferences towards cold and warm glove temperatures: both were steeper than in the afebrile state. This means that although the gain is modified this change is an increase affecting the responses to both heat and cold. There is, therefore, an increased gain of response to cold but also an increased gain of response to heat. This appears on Fig. 4 which is a simple redrawing of Fig. 3, separating cold defence from heat defence as is usually done with shivering and evaporative heat loss. This increase of the gain of both warm and cold responses does not support the hypothesis of fever as a result of change of gain. There is, on the other hand, a striking analogous similarity between these results and those obtained by Sharp & Hammel (1972) when they recorded the dog's salivary secretion during fever. Above a threshold hypothalamic temperature, salivary secretion increased linearly with hypothalamic temperature in normal as well as

feverish dogs at several ambient temperatures. The effect of fever was to push the threshold for salivary secretion towards higher values of hypothalamic temperature as if the set point had been reset in an upward direction. This is comparable to the behavioural response obtained here in man and is contrary to what would be expected on the basis of the change of gain theory.

The increased slopes of the curves describing the glove temperature selected in response to both heat and cold is difficult to explain. One possibility is that suggested by Sharp & Hammel (1972): in accordance with the Vant'Hoff–Arrhenius law the neurones concerned in temperature regulation are more active when body temperature is elevated during fever. But if this were true, a 1° C fever should have the same effect on these neurones as a 1° C hyperthermia, and this is not the case. Furthermore, the Q_{10} for the thermostat, computed from the parameters of Table 1, does not fit with this explanation. Another possibility is that, as suggested by Bligh (1966), there is an upper limit to the range within which normal thermoregulatory responses occur and when the regulated temperature is pushed by a change in set-point towards this upper limit the response curve is steepened by some influence related to this limit. According to this view the increased gain of the thermostat would be a result rather than a cause of fever.

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REFERENCES

BLEICHERT, A., BEHLING, K., SCARPERI, M., SCARPERI, S. (1973). Thermoregulatory behaviour of man during rest and exercise. *Pflügers Arch. ges. Physiol.* **338**, 303–312.

BLIGH, J. (1966). The thermosensitivity of the hypothalamus and thermoregulation in mammals. *Biol. Rev.* **41**, 317–367.

CABANAC, M. (1969). Plaisir ou déplaisir de la sensation thermique et homéothermie. *Physiol. & Behav.* **4**, 359–364.

CABANAC, M., CUNNINGHAM, D. J. C. & STOLWIJK, J. A. J. (1971). Thermoregulatory set point during exercise: a behavioral approach. *J. comp. physiol. Psychol.* **76**, 94–102.

CABANAC, M., DUCLAUX, R. & GILLET, A. (1970). Thermorégulation comportementale chez le chien: effets de la fièvre et de la thyroxine. *Physiol. & Behav.* **5**, 697–704.

CABANAC, M., MASSONNET, B. & BELAICHE, R. (1972). Preferred skin temperature as a function of internal and mean skin temperature. *J. appl. Physiol.* **33**, 699–703.

COOPER, K. E. (1972). The body temperature 'set-point' in fever. In *Essays on Temperature Regulation*, ed. BLIGH, J. & MOORE, R., pp. 149–162. Amsterdam London: North Holland Publ. Co.

GALE, C. C., MATHEWS, M. & YOUNG, J. (1970). Behavioral thermoregulatory responses to hypothalamic cooling and warming in baboons. *Physiol. & Behav.* **5**, 1–7.

HAMMEL, H. T. (1965). Neurons and temperature regulation. *Physiological Controls and Regulations*, ed. YAMAMOTO, W. S. & BROBECK, J. R., chap. 5, pp. 71–97. Philadelphia: Saunders.

HARDY, J. D. (1965). The set point concept. *Physiological Controls and Regulations*, ed. YAMAMOTO, W. S. & BROBECK, J. R., chap. 6, pp. 98–116. Philadelphia: Saunders.

MITCHELL, D., SNELLEN, J. W. & ATKINS, A. R. (1970). Thermoregulation during fever: change of set point or change of gain. *Pflügers Arch. ges. Physiol.* **321**, 293–302.

SHARP, F. R. & HAMMEL, H. T. (1972). Effects of fever on salivation response in the resting and exercising dog. *Am. J. Physiol.* **223**, 77–82.

WEISS, B., LATIES, V. G. & WEISS, A. B. (1967). Behavioral thermoregulation by cats with pyrogen induced fever. *Archs int. Pharmacodyn. Ther.* **165**, 467–475.