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Problems with Neuronal Models in Temperature Regulation

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Neuronal models in temperature regulation are primarily considered explicit statements of assumptions and premises used in design of experiments and development of descriptive equations concerning the relationships between thermal inputs and control actions. Some of the premises of current multiplicative models are discussed in relation to presently available experimental evidence. The results of these experiments suggest that there is no skin temperature compatible with life which completely suppresses a rise of heat production in response to low internal temperature. The slope of heat production versus internal temperature at a given skin temperature is not constant but depends on internal temperature and the level of heat production. Therefore, a concept involving additive interaction of central and peripheral temperature signals appears more flexible in accepting data obtained even under extreme conditions.

The nervous control mechanisms of body temperature in homeotherms have repeatedly been conceptualized in the form of models. It may have been partly for semantic reasons that the models have encountered some resistance: the older term "hypothesis" implied some tentativeness because of limited evidence in the face of an imperfectly comprehended phenomenon, while the term "model" can also refer to something that is eminently worthy of imitation. To the extent to which the word "model" is a synonym for working hypothesis, models are an indispensable part of science, and their formulation may in fact be considered its final goal.

A particular species of hypothesis is called the neuronal models. These models attempt to design neuronal networks capable of coupling thermal stimuli to effector responses. Despite the implication of the name neuronal, the models take neurophysiological results merely as supporting evidence and have been deduced essentially from input/output functions of the thermoregulatory system, i.e., relationships between temperatures at various sites of the body and autonomic and behavioral responses. Hence, a neuron in a neuronal model does not represent an anatomically or neurophysiologically defined entity, but rather the behavior and function of a class of neurons, which may be accomplished by an unknown number of neurons arranged in a cascade-like, serial structure [1].

According to Hardy's classification [2], these models are verbal-pictorial in the sense that the authors commit themselves to some arrangements between components and processes which are most useful for teaching purposes. The question is, however, whether these models have any research value. It may be argued that deducing neuronal models from input/output relationships and summarizing large numbers of components in a single function squeezes out the neurons, their large numbers, complex connections, and heterogeneous responses—in fact, all the problems. A model of a neuronal network should be guided by the relationships between thermosensory inputs and thermoeffector outputs but must be built primarily on neurophysiological results.

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However, even if present neuronal models cannot fulfill their claims, they might nevertheless serve an important purpose at a quite different stage of analysis, at which the functional relationships between particular inputs or body temperatures and control actions are experimentally determined, and the data are reduced to descriptive equations. The type of data reduction used by an experimenter implies certain assumptions about the function of the controlling system. A linear regression between a particular body temperature and heat production assumes, if not stated otherwise, a linear relationship between temperature and input signal; if an author chooses to complement descriptive equations by a so-called neuronal model, he may be doing no more than stating explicitly the assumptions and premises used in analyzing the data. In this sense, neuronal models could help to improve clarity and understanding between scientists.

As pointed out by Mitchell et al. [3], models of the controlling system are sometimes liable to criticism because of the model makers' tendencies to build models which present a tenable answer but then to forget about equally possible alternatives. Benzinger [4] based his concept on tympanic temperature and never discussed the possibility that a fast-responding core temperature such as esophageal would have almost certainly yielded the same perfect correlations. Hammel's model [5,6] relies on true thermoreceptors in the skin and on temperature-dependent sensory transmission as the exclusive source of hypothalamic thermosensitivity, but Simon et al.'s recent papers [7,8,9] show in detail that a model which in addition incorporates primary central thermoreceptors fits the data equally well.

If, then, a neuronal model is primarily an explicit statement of the apriorities which were adopted for the design of the experiments and analysis of data, further discussion can focus on the premises themselves: what are the rationales behind them, and how far do they carry?

Most neuronal models treat hypothalamic temperature as a separate entity. This has been done for two reasons. First, the supraspinal central nervous system has been assumed to contain all central thermosensitive structures, and, second, the temperatures of these structures have been assumed to be manipulable in their entirety by hypothalamic thermodes. The first premise is difficult to maintain in view of the numerous studies proving the importance of core sensors of temperature outside the brain (e.g., [10,11]). The second, more technical point is equally open to argument: present experiments in the goat show that even a large and efficient hypothalamic thermode cannot clamp the thermosensitive structures of the supraspinal CNS (Fig. 1). In these experiments, two methods are used to separate hypothalamic from extrahypothalamic sources of brain thermosensitivity. A large multithermode consisting of 25 single probes is employed to alter hypothalamic temperature [13]. The correct position of the thermode has been ascertained by stimulating single rows and columns of probes [13]. Heat exchangers inserted in carotid loops are used to influence brain temperature as a whole. Before the first experiment was done, all cutaneous branches of the trigeminal nerves had been cut to ensure that the responses to changing carotid blood temperature were not spuriously affected by cutaneous thermoreceptors of the face. The experiment shows that even an efficient hypothalamic thermode cannot provide a reasonably accurate estimate of the specific thermosensitivity of the supraspinal CNS.

However, there can be other reasons to treat hypothalamic temperature separately than to manipulate a larger or smaller share of the total core temperature signal:

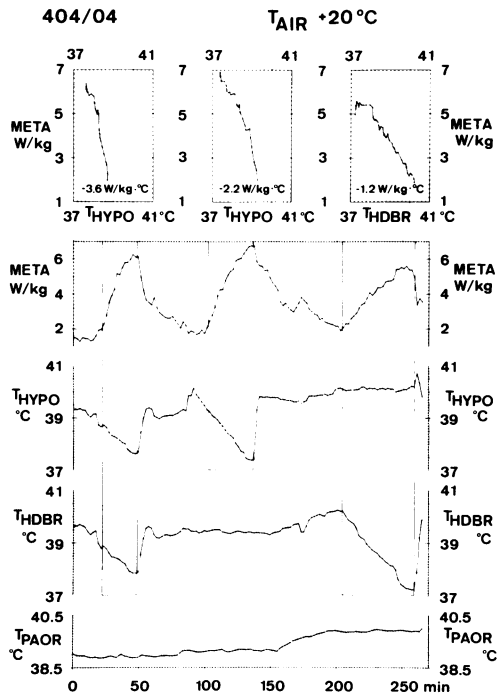

FIG. 1. Single experiment in a conscious goat. The animal had intravascular heat exchangers and carotid loops to alter the temperatures of head and trunk independently of each other [12] and hypothalamic thermodes [13]. All cutaneous branches of the trigeminal nerves were surgically interrupted. Minutes 22–48: Cooling the head via carotid heat exchangers lowered hypothalamic temperature (T_{HYPO}) and hindbrain temperature (T_{HDBR}), while trunk temperature (T_{PAOR}) was maintained at control level. Heat production (**META**) rose at a slope of −3.6 W/Kg · °C. Minutes 102–136: Cooling the hypothalamus via local thermodes, with extrahypothalamic brain temperature and trunk temperature maintained constant, increased heat production at a slope of −2.2 W/Kg · °C. Minutes 204–259: Cooling the head via carotid heat exchangers, with hypothalamic temperature and trunk temperature maintained constant, increased heat production at a slope of −1.2 W/Kg · °C [Heath and Jessen].

hypothalamic thermosensitivity may be considered qualitatively different from that of the rest of the body. According to Simon [7], the hypothalamus does not just contain true temperature sensors but is also a site of nonsensory thermosensitivity of integrative neurons. This quality is discernable from specific thermosensitivity by means of the effects of cooling. Specific sensors respond to local cooling by initiating shivering and cutaneous vasoconstriction, while integrative neurons respond to local cooling by inhibiting shivering and inducing cutaneous vasodilation [14]. However, even this property is not unique to the hypothalamus.

Figure 2 is taken from a series of experiments in goats in which the brain stem was straddled by thermodes from the preoptic region to the rostral medulla [15]. Cooling the three most caudal rows of probes, which were located in the lower pontine and medullary area, consistently caused a rise in ear skin temperature, indicating vasodilation. The same sites could also be used to stimulate panting by cooling. Thus, nonsensory thermosensitivity is not unique to the hypothalamus but is likely to occur at all synapses of the afferent and efferent thermoregulatory pathways.

Analyzing complex input/output relationships with preconceived models sometimes tends to neglect the effects of uncontrolled variables on these relationships. Simon et al.'s models [7,8,9] describe heat production and heat loss as functions of two inputs: hypothalamic temperature on the one hand, and extrahypothalamic temperature, measured in the esophagus, on the other. If both equations are solved for a hypothalamic temperature of 38°C and an extrahypothalamic temperature of 39°C, however, the simultaneous occurrence of shivering (heat production ≈4.5 W/kg) and panting (respiratory evaporative heat loss ≈0.85 W/kg) are predicted. This apparent inconsistency is caused by the fact that the equations were calculated from results obtained at different air temperatures: +10°C for shivering and +39°C for panting. The compari-

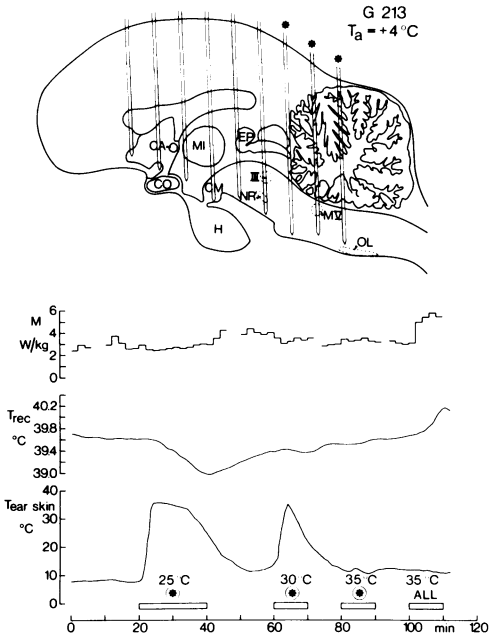

FIG. 2. Single experiment in a conscious goat, the brain stem of which was straddled by nine rows of thermodes. Perfusing the three most caudal rows, designated by stars, with water at 25°C increased ear skin temperature by cutaneous vasodilation and induced a fall in rectal temperature. Milder cold stimuli (30 and 35°C) gave weaker responses. Cooling all nine rows generated strong shivering. Compiled from data in [15].

son shows that, particularly in a cold environment, not all extrahypothalamic inputs can be computed in a single number, and that an equation describing cold defense as a function of hypothalamic and esophageal temperatures neglects an important variable: skin temperature.

Another example of the effect of an uncontrolled variable may have been illustrated by Stitt's models, which describe heat production and heat loss as functions of multiplicative interactions between linear signals generated by hypothalamic temperature and skin temperature [16,17,18]. The models include a reference skin temperature of 39.7°C, above which the skin temperature signal is zero. Consequently, no shivering can occur, but panting remains at its maximum regardless of how far hypothalamic temperature, as the only source of core temperature signals, is lowered. It appears conceivable that the good fit of data points to the models was primarily attributable to the experimenter's decision to select hypothalamic temperature as the only core temperature input and to neglect all extrahypothalamic core input signals. This is suggested by results of a present series of experiments in goats in which the relationships between skin and total core temperatures in control of heat production and heat loss are investigated. Skin temperature is clamped by means of a water bath, and core temperature is altered in a ramp-like fashion by means of a heat exchanger acting on blood temperature in an arterio-venous shunt. Figure 3 shows data from four experiments at a bath temperature of 44°C. Obviously, even a skin temperature that high does not prevent a goat from shivering and increasing its heat production to four times the resting level, provided that core temperature is sufficiently low. Similar results have been obtained before [19]. They certainly argue against the general acceptability of Stitt's models, although it must be mentioned that the design of our experiments excluded two possibly important factors from control: first, face skin temperature was unclamped and might have provided an uncontrolled input, and

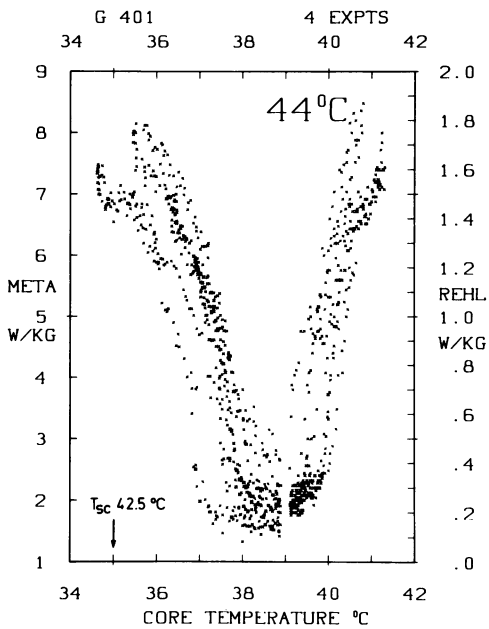

FIG. 3. Heat production (**META**) and respiratory evaporative heat loss (**REHL**) plotted against core temperature: four experiments in a goat immersed in a water bath of 44°C. Subcutaneous temperature, as measured at a single cell site on the thorax, was 42.5°C at a core temperature of 35°C.

second, the large arterio-venous shunt required a higher-than-normal level of sympathetic activity, which might have substituted skin temperature signals.

Another premise of the models presented by Stitt et al. [16,17,18] and earlier by others [20,21,22] is the rectilinear relationship between core temperature and heat production or heat loss at constant levels of skin temperature. The question is whether "a simple linear proportionality between internal receptors and most thermoregulatory effector output exists" (Stitt [18]), or whether it is conveniently presumed by linear regressions, not excluding a linear correlation between two variables. The experiments shown in Fig. 3 were part of a larger series in which the relationships between internal temperature and heat production/heat loss were tested at skin temperatures between 32°C and 44°C in 3°C steps. Internal temperature was changed in a ramp-like fashion at a speed of 0.05°C/minute, and data were collected at one-minute intervals. This procedure introduced the possibility of calculating the slopes of heat production or heat loss versus internal temperature step to step; i.e., from one data point to the next, after the data were smoothed by moving averaging over eight points.

Figure 4 shows, for bath temperatures of 32°C and 44°C, the relationships between internal temperature and heat production, and the instantaneous slopes $\Delta M/\Delta T$ for these data. In spite of the averaging procedure, the slopes show considerable scattering. However, a systematic pattern is apparent. First, the slopes at 44°C bath temperature were smaller than those at 32°C. This result is in good agreement with Stitt et al.'s previous findings and their model [16]. Second, at any given bath and therefore skin temperature, the slopes were far from constant. The slopes rose from the 2 W/kg range to the 3 W/kg range and decreased with higher levels of heat production. Consequently, reconstruction of the relationship between internal temperature and heat production results in a sigmoid curve, with the turning point at a level of heat production of approximately 4 W/Kg. This low turning point appears to exclude effector saturation as a ready explanation for the sigmoid curve.

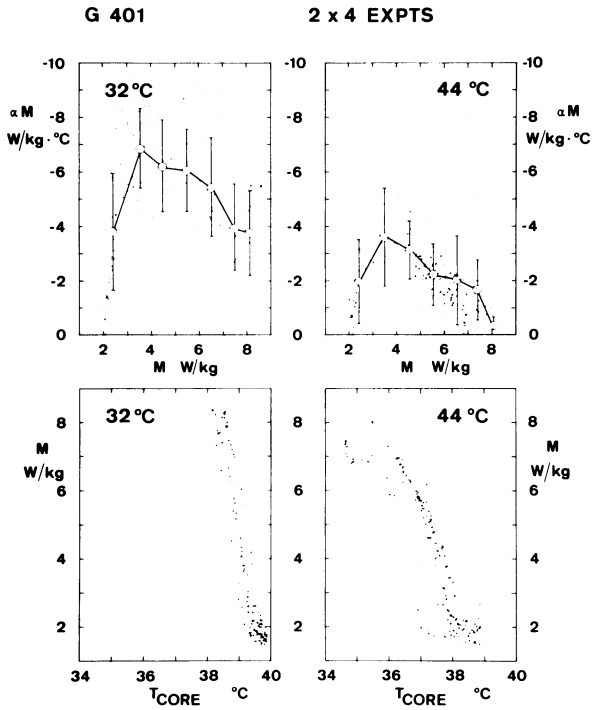

FIG. 4. *Bottom:* Heat production (**M**) plotted against internal temperature (T_{CORE}). *Top:* $\Delta M/\Delta T$ (αM) plotted versus **M**: Four experiments at 32°C and four experiments at 44°C water bath temperature in a single goat. Open circles and bars give mean values ± SD for ranges of **M** in steps of 1 **W/Kg.**

From Hammel's model [5,6] it is conceivable that the slope of thermoregulatory effector responses over internal temperature is not just related to skin temperature and level of effector activity, but might further depend on internal temperature. The various dependencies were tested using the results of the complete series of 20 experiments. Calculations were restricted to 1,339 single data points exhibiting a heat production larger than 2.99 W/Kg and a negative $\Delta M/\Delta T$ which was smaller than -10 W/Kg · °C. For these data the relationships between the slope $\Delta M/\Delta T$ and internal temperature (T_{CORE}), surface temperature (T_{BATH}), and heat production (META) were statistically evaluated (Table 1).

The second-order partial correlation coefficients revealed that the pure correlations between the slope and each of these variables, with the effects of the others excluded, were highly significant, with a probability of error or less than 0.001. The multiple linear regression showed that the slope of the relationship between heat production and internal temperature was steeper the higher the internal temperature, the lower the skin temperature, and the lower the magnitude of heat production.

On the basis of these data the premise of a rectilinear relationship between internal temperature and effector response, which the multiplicative models have in common, appears at least questionable. A more tenable alternative might be shaped along Hammel's configuration of the relationships between thermal inputs to the controller and effector responses. The hypothesis of an additive interaction between skin temperature signals and core temperature signals, which rise exponentially with internal temperature, avoids the constraints exerted by fixed reference values and is more flexible with regard to fitting data which were collected under extreme conditions. It gives better guidance for data reduction and development of descriptive

TABLE 1

Slope of Heat Production versus Internal Body Temperature as a Function of Internal Temperature (T_{CORE}), Surface Temperature (T_{BATH}), and Heat Production (META) (Calculations based on 1,339 single measurements in 20 experiments on a single goat; multiple linear regression and second-order partial correlation coefficients)

$ALPHA_{META} = F(T_{CORE}, T_{BATH}, META)$

FOR META > 2.99 W/kg and ALPHA > -10, < 0 W/kg META · °C T_{CORE}

G 401, 20 EXPTS, n = 1339

$ALPHA_{META} = (-.79\ T_{CORE}) \cdot (.10\ T_{BATH}) \cdot (.46\ META) \cdot 19.53$

p < .001 < .001 < .001 < .001

$R_{ALPHA \cdot T_{CORE}, T_{BATH}, META} = .673$ $p < .001$

2nd ORDER PARTIAL CORRELATION COEFFICIENTS:

$r_{ALPHA, T_{CORE} \cdot T_{BATH}, META} = -.211$ $p < .001$

$r_{ALPHA, T_{BATH} \cdot T_{CORE}, META} = .128$ $p < .001$

$r_{ALPHA, META \cdot T_{CORE}, T_{BATH}} = .263$ $p < .001$

equations of the input/output functions of the thermoregulatory system—and that appears to be the most valuable service a model can perform.

REFERENCES

1. Hammel HT: Neurons and temperature regulation. In Physiological Controls and Regulations. Edited by S Yamamoto, SR Brobeck. Philadelphia, Saunders, 1965, pp 71–79
2. Hardy JD: Models of temperature regulation. In Essays on Temperature Regulation. Edited by J Bligh, R Moore. Amsterdam, North Holland, 1972, pp 163–186
3. Mitchell D, Atkins AR, Wyndham CH: Mathematical and physical models of thermoregulation. In Essays on Temperature Regulation. Edited by J Bligh, R Moore. Amsterdam, North Holland, 1972, pp 37–54
4. Benzinger TH: Heat regulation: homeostasis of central temperature in man. Physiol Rev 49:671–759, 1969
5. Hammel HT: Regulation of internal body temperature. Ann Rev Physiol 30:641–710, 1968
6. Hammel HT: Phylogeny of regulatory mechanisms in temperature regulation. J Therm Biol 8:37–42, 1983
7. Simon E: Effects of CNS temperature on generation and transmission of temperature signals in homeotherms. A common concept for mammalian and avian thermoregulation. Pfluegers Arch 392:79–88, 1981
8. Inomoto T, Mercer JB, Simon E: Opposing effects of hypothalamic cooling on threshold and sensitivity of metabolic response to body cooling in rabbits. J Physiol 322:139–150, 1982
9. Inomoto T, Mercer JB, Simon E: Interaction between hypothalamic and extrahypothalamic body temperatures in the control of panting in the rabbits. Pfluegers Arch 398:142–146, 1983
10. Simon E: Temperature regulation: The spinal cord as a site of extrahypothalamic thermoregulatory functions. Rev Physiol Biochem Pharmacol 71:1–76, 1974
11. Mercer JB, Jessen C: Central thermosensitivity in conscious goat: Hypothalamus and spinal cord versus residual inner body. Pfluegers Arch 374:179–186, 1978
12. Jessen C, Feistkorn G: Some characteristics of core temperature signals in the conscious goat. Am J Physiol 247:R456–R464, 1984
13. Jessen C: Two-dimensional determination of thermosensitive sites within the goat's hypothalamus. J Appl Physiol 40:514–520, 1976

14. Simon-Oppermann C, Simon E, Jessen C, Hammel HT: Hypothalamic thermosensitivity in conscious pekin ducks. Am J Physiol 235:R130–R140, 1978
15. Schmieg G, Mercer JB, Jessen C: Thermosensitivity of the extrahypothalamic brain stem in conscious goats. Brain Res 188:383–397, 1980
16. Stitt JT, Hardy JD, Stolwijk JAJ: PGE_1 fever: Its effect on thermoregulation at different low ambient temperatures. Am J Physiol 227:622–629, 1975
17. Stitt JT: The regulation of respiratory evaporative heat loss in rabbit. J Physiol 258:157–171, 1976
18. Stitt JT: Variable open-loop gain in the control of thermogenesis in cold-exposed rabbits. J Appl Physiol 48:495–499, 1980
19. Jessen C: Independent clamps of peripheral and central temperatures and their effects on heat production in the goat. J Physiol 311:11–22, 1981
20. Brueck K, Wuennenberg W: "Meshed" control of two effector systems: Non-shivering and shivering thermogenesis. In Physiological and Behavioral Temperature Regulation. Edited by JD Hardy, AP Gagge, JAJ Stolwijk. Springfield, IL, CC Thomas, 1970, pp 562–580
21. Brueck K, Schwennicke HP: Interaction of superficial and hypothalamic thermosensitive structures in the control of non-shivering thermogenesis. Int J Biometeor 15:156–161, 1971
22. Jacobson FH, Squires RD: Thermoregulatory responses of the cat to preoptic and environmental temperatures. Am J Physiol 218:1575–1582, 1970