A theoretical consideration of the means whereby the mammalian core temperature is defended at a null zone

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Bligh, John. A theoretical consideration of the means whereby the mammalian core temperature is defended at a null zone. J Appl Physiol 100: 1332–1337, 2006; doi:10.1152/japplphysiol.01068.2005.—The neural process by which it is generally supposed that the stability of the body temperature of mammals is achieved has long been sought, but it remains unresolved. One hypothesis is that, as with many engineered physical systems, there is a stable reference signal with which a signal representative of body temperature is compared. Another hypothesis is that the differing coefficients of two signals that vary with temperature changes provide the set-level determinant. These could be the activities of the “cold” and “warm” sensors in response to temperature changes. Reciprocal crossing inhibition between the cold sensor to heat production effector pathways and the warm sensor to heat loss effector pathways through the central nervous system is a likely occurrence, and it could create the null-point temperature at which neither heat production nor heat loss effectors are active. This null point would be, seemingly, the set point at which body temperature is regulated. Neither hypothesis has been validated unequivocally. Students should be aware of this uncertainty about the physiological basis of homeothermy and, indeed, of homeostasis more generally. Perhaps we should be looking for a general principle that underlies the many physical and chemical stabilities of the internal environment, rather than considering them as quite separate accomplishments.

homeothermy; thermoregulation; reference signal set point; reciprocal crossing inhibition

When considering the nature of mammalian thermoregulation at a set point, the very use of those terms needs first to be considered. Claude Bernard (1) wrote of the constancy of the internal environment, and body temperature is the most often observed example of that. It seems unlikely that Claude Bernard meant to imply the rigidity that regulation (derived from a Latin word meaning to rule or to make straight) might be taken to mean. To draw us away from Bernard’s word fixité, which might seem to imply an invariability, Walter Cannon (5) introduced the term homeostasis. The subtlety of his choice of word lies in the difference between the Greek prefixes hemo (similar) and homo (= same). This verbal distinction is crucial, for life depends on the sustained integration of myriad isolatable, but not isolated, functions; and their integration requires some degree of flexibility of them all. Thus there is both physiological and etymological correctness in preferring homeostasis to regulation, and homeothermy to temperature regulation. Like all else of homeostasis, body temperatures vary to a greater or less extent between species, between environmental and organismic circumstances, with the time course of each day, and seasonally. Any hypothetical account of how homeothermy is “managed” must incorporate tentative explanations for these variations.

To understand why there must be at least some degree of variability, consideration must first be given to the apparent fundamental raison d’etre of a central nervous system (CNS). If its function were to be simply that of connecting particular sensors to particular response effectors, the inherent danger of concentrating the many specific sensor-to-effector pathways through a single structure would surely have forbidden such an evolutionary development. Throughout the evolutionary development of a CNS, any advantage gained by the concentration of the many sensor-to-effector pathways through a central structure had to outweigh the disadvantage of its vulnerability to damage. That advantage was surely that it facilitated the communications between sensor-to-effector pathways. It is now evident that the integration of the responses to an infinitely variable pattern of external and internal occurrences depends on a massive assembly of interpathways connections. These interconnections between pathways through the CNS render it unlikely that any particular response is solely the consequence of one particular stimulus. Hence there is the inevitability of some
degree of variability in any stabilized quality or quantity of the internal environment.

Engineers will point out that, even in a singular regulatory process, to activate a corrective response, there must be some degree of divergence of the stabilized quality or quantity from the set level. Thus there is some variation in even the most precisely regulatory processes. This could apply equally to biological processes of homeostasis, but there is clearly more than that to the variability of the parameters of mammalian homeostasis, including homeothermy. Some of this is likely to be the consequence of the effects of activities in neural interconnections between sensor-to-effector pathways, which vary the magnitude of a particular response to a particular species of sensor.

The expectation must be that the stability of body temperature depends on the existence of some definable neuronal properties of thermosensors, of thermoresponsive effectors, and of the interconnections between them through the CNS. It can be further surmised that the determination of the relationships between thermal disturbances and the thermocorrective responses will be influenced by other concurrent nonthermal disturbance and response activities via the CNS. It was the patterned change in the level at which body temperature is seemingly being maintained during infection that led Liebermeister (16) to describe the occurrence of fever as the resetting of a biological thermostat.

The essential difference between the so-called cold and warm sensors is that they have differing activity-temperature profiles. Within a limited and seemingly physiological range of temperature variation, the activities of “warm” sensors increase as temperature increases, whereas those of the “cold” sensors decrease as temperature increases. The effector responses to thermal change are separable into those that vary heat production within the body and those that vary the exchange of heat with the external environment. A likely basic sensor-to-effector relationship is expressible as in Fig. 1. The assumption in this neuronal model is that the warm sensor inputs and the cold sensor inputs are each separately summed to provide the two activating drives, the one to heat loss effectors, and the other to heat production effectors. With the universality of interpathway influences within the CNS, there could well be reciprocally crossing influences between these two sensor-to-effector pathways, as well as excitatory and inhibitory influences derived from other nonthermal pathways through the CNS. These are also indicated in Fig. 1A. A noteworthy point is that, whereas generally the diametric changes in the activities of the warm and cold sensors as local temperature is changed are overlapping, those of the heat production effectors (HP) and the evaporative heat loss effectors (HL) occur on either side of a null point or null range. The cause of this distinction between the input from thermosensors and the output to thermoregulatory correction effectors lies, presumably, within the CNS.

This allows some speculation of what seems to happen within the CNS. What ever actually happens, it must ultimately be attributable to particular properties of nerve cells, and/or of the particular ways nerve cells interconnect to exert excitatory or inhibitory influences on the relationships between thermosensors and thermocorrection effectors. Without some definite knowledge about the central nervous interface, however, theoretical considerations of the nature of the set-level determinant remain no more than speculations based on the readily observed relationships between thermal disturbances and thermocorrective responses.

In the absence of any clear physiological evidence of the nature of the set-level determinant, James Hardy (11), who was probably influenced by the interest at the John B. Pierce Foundation Laboratory at New Haven, Connecticut, in the engineering of air-conditioned buildings, considered mammalian thermoregulation in terms of the regulatory principles employed in engineered physical systems. The most widely understood principle of the ways the temperature of a physical mass can be regulated is for a representation of the actual temperature to be compared with a fixed value representative of the required level of thermal stability. Any difference between the two values, referred to as the error, is used to determine the quality and/or the quantity of the corrective

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**Fig. 1. Set-level determination: theoretical considerations**

A: the idealized expression of the activity (A)-temperature (T) profiles of the “warm” (W) and “cold” (C) thermosensors and of heat loss (HL) and heat production (HP) correction effectors. The W-to-HL and the C-to-HP pathways are via the central nervous system (CNS). There are sure to be nonthermal excitatory (+) and inhibitory (−) convergences, derived from other concurrent CNS activities, onto each thermosensor to thermocorrection pathway through the CNS while the thermosensor to thermocorrector pathways could exert influences on each other by lateral excitation and/or inhibition.

B and C: the simplest possible neuronal format that could account both for the homeothermic set level, and for the conversion of overlapping input from W and C thermosensors, into the nonoverlapping activities of HL by sweating or panting and HP by shivering when these activities are plotted against temperature. Each pathway could receive a separate inhibitory influence (B), or there could be one such influence, acting on both pathways (C).
that many naturally occurring substances, which could be synaptic transmitters or modulators, also cause changes in body temperature when similarly applied to the brain. Many of these have been pain-takingly catalogued in a series of publications in Neuroscience and Behavioral Reviews by Clark and coworkers between 1979 and 1986 (see Ref. 6 as a representative paper). Although the effects on body temperature may be consistent in a particular set of circumstances, the effects of these substances can vary between species, between sites of application, between the applied dosages, and between the prevailing external environments. Thus much of the synaptic involvement in homeostasis has still to be clarified. Sadly, so much diligent research has added little to the understanding of the homeothermic set-point determinant. As is mentioned below, however, some possible indication did emerge from these neurochemical studies.

In the course of this search for the “Holy Grail” of mammalian homeothermy, there was an emerging awareness of the fact that the set-level does not necessarily require a stable reference signal. Hammel, as I remember it, was clearly concerned about the growing acceptance of the stable reference signal generator as an all but proven requisite of homeostasis; and Hensel (13) commented that what is essential for the maintenance of body temperature at a set level is the provision of at least two input signals with different temperature coefficients. The comparison of a signal that varies with temperature and one that does not fits with this criterion, but is no more than a particular version of the principle. The differing activity-temperature-profiles of signals derived from cold and warm sensors are also in compliance. Werner (20) concluded that there is no substantial evidence supportive of the notion that mammalian homeothermy depends on a stable signal generator.

The activity-temperature coefficient of the warm sensors and cold sensors can only be described loosely as being reciprocal. The technical difficulties of obtaining sustained activity recordings from single fibers while the local temperature is being varied means that results are relatively sparse. The recorded slopes of the activity responses to temperature changes differ between individual recordings. Furthermore, the immediate activity responses to temperature changes differ markedly from the sustained responses to sustained temperature (15). Thus there is more than an element of license in the suggestion that the mean activity-temperature profiles of cold sensors and of warm sensors are reciprocal over a physiologically meaningful range of temperature variation. There are, however, clear indications that some such relationship exists. This generalization allows the theoretical possibility that body temperature stabilization within a narrow range of variability is not dependent on the central involvement of temperature-insensitive “reference neurons,” but on the different response coefficients of the cold and warm sensors to temperature changes, and on the influences these have on the heat production and heat loss effectors.

If that were to be so, there would be no need to hypothesize any additional central set determinant of the set level. Yet if there is no central modulation of signals passing from the thermosensor to the thermoregulatory effector pathways, it could be expected that heat production and heat loss effector activities would overlap much as do the sensor activities. In that case, thermal stability could still be achieved, but uneco-
nomically, with thermoregulatory HP and HL activities in continuous concurrent competition. It is well established, however, that in humans and other mammals, HP by shivering, and HL by panting or sweating, are not concurrent events, but occur one side and the other of a null point or null zone. This separation of the thermoregulatory HP and HL activities could be provided by the convergence on the cold sensor to HP, and the warm sensor to HL, pathways through the CNS of a reference-signal-like inhibitory influence (Fig. 1, B and C). Another possibility is that of reciprocal crossing inhibitory (RCI) influences of both sensor-to-effector pathways on each other. The weaker of the two activities would thus be nullified. This notion was discernible in the diagrammatic expression of the relationships between variations in environmental and deep body temperature on the thermoregulatory responses of humans by Wyndham and Atkins (21). The underlying principle of signal separation by reciprocal crossing inhibition was not stated explicitly, but this became evident when the diagram was redrawn in a neuronal format by Bligh (2). This is reproduced in Fig. 2A.

Ted Hammel (9, 10), who was aware of the alternative possible basis of set-level determination, interpreted the results of hypothalamic single-neuron activity studies and the known relationship between sensor activities and response-effector activities as in Fig. 2B. Here, again, there is the clear suggestion of RCI between the two sensor-to-effector pathways. At about the same time, Bligh (2) iterated the reasoning behind the interpretation of the consistently repeatable thermoregulatory effects in sheep when synaptically active substances (putative neurotransmitters) were introduced into a lateral cerebral ventricle of the sheep (4) (Fig. 2C). This neuronal representation, which was uninfluenced by those of either Wyndham and Atkins (21) or Hammel (9, 10), is remarkably similar in format and implication to those of both Wyndham and Atkins and Hammel. None was first presented as an attempt to provide an alternative theoretical explanation for mammalian set-level determination.

In none of the representations was there any clear statement of the possibility that the set-level determination could be vested in the activity-temperature profiles of the thermosensors. Nor was the postulated RCI between the sensor-to-effector pathways explicitly suggested as the means by which the HP and HL activities are caused to occur on the one side and the other of a null point or null range. Only later (3) was an attempt made to marry evidence and theory to provide an integrative consideration of how mammalian homeothermy could be effected. It was proposed that the response coefficients of the thermosensors, together with central RCI, is all that is strictly necessary to provide a basis for the stabilization of body temperature within a small range of variation. The convergence onto the thermosensor-thermocorrecting pathways, of excitatory and inhibitory influences derived from other central nervous events, could account for variations in the set-level, or in the extent of a null range.

A difference between the models of Hammel (10) and Bligh (2) lies in the depiction of the central thermosensitivity. Whereas in Hammel’s model the central thermosensors are interneurons on the pathways through the CNS from extracranial thermosensors, in Bligh’s model they are depicted as primary thermosensors uninfluenced by any synaptic signal input. There is no a priori reason to favor the one possibility or the other, and no significance need be attached to this distinction. In both representations, there is RCI between the two principal thermosensor to thermoregulatory pathways, and there is no representation of a stable reference signal generator.

To validate the theoretical soundness of this assertion, Smullin (19) constructed a physical model in which two temperature sensors with overlapping reciprocal responses to temperature connected directly to HP and HL correction effectors with reciprocally crossing negative electrical influences of each sensor to effector pathway on the other (Fig. 3A). This construction effected the thermoregulation of a physical mass with a relationship between thermosensors and HP and HL response effectors that was essentially the same as that now being suggested as the means of achieving mammalian homeothermy. There was no set-point determinant other than the differing properties of the two sensors, and RCI between the two sensor-to-effector connections caused the HP and HL responses to occur on one side and the other of a temperature null point or null range. Additional convergent positive and negative inputs onto the sensor to effector pathways (Fig. 3B) were analogous to convergent influences on pathways through the CNS. Variations in these resulted in thermoregulatory variations that closely mimicked those of different species of mammals, or of one species in different circumstances, including those of fever and hibernation. Figure 3C is a neuronal translation of Fig. 3B. Although this physical model constituted a crucial verification of the theoretical validity of the alternative theory of mammalian homeothermy, it was apparently considered by referees to be outside the legitimate scope of thermal physiology, and it has remained unpublished except briefly.

Such is the specialization of physiological research that much of the consideration of the thermal stability has been
conducted as if this one evolutionary achievement can be considered as something apart from all else of the evolution of central nervous processes and apart from all the other components of homeostasis. This could be why the search for an explanation has been conditioned more by concepts derived from thermoregulatory engineering principles and practices than by an appreciation of the basic and often-occurring principles of neuronal organization. The attempt to introduce such considerations (3) was, it seems, not well received, for it provoked neither positive nor negative comment. Nevertheless, a brief iteration of that consideration is necessary to evaluate the full extent of its role in the central modulation of relationships between disturbances and responses, there is just sufficient evidence to allow the suggestion that this particular usage of the massive interactions between pathways through the CNS is probably far more general than is currently supposed. It is worthy of recall that with the embryological kinship between retinal and central nervous tissues, the prominence of RCI in the mammalian retina could have come with the evolution of the retina. If so, that would suggest most strongly that RCI has been a functionally crucial feature of neuronal organization through cons of evolutionary progression.
Considerations of the nature of the mechanism that underlies mammalian homeothermy might well have been somewhat different had it been recognized 1) that the abiding feature of systems of regulation is not the comparison of a variable with a constant but is the interplay of two variables with different response coefficients; 2) that RCI is an almost inevitable feature of the connections between pathways through the central nervous systems by which functional integration is effected; and 3) that those two, together, could provide the basis of separating opposing effector functions on one side and the other of a null point. This trinity of circumstances on which mammalian homeothermy could depend, remains more hypothetical than proven. Its possibility, however, raises the further possibility that similar neuronal features could underlie the management of other stabilized conditions of the internal environment.

REFERENCES