A Physiological Systems Approach to Human and Mammalian Thermoregulation

Contribution of thermal and nonthermal factors to the regulation of body temperature in humans

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Mekjavic, Igor B., and Ola Eiken. Contribution of thermal and nonthermal factors to the regulation of body temperature in humans. J Appl Physiol 100: 2065–2072, 2006; doi:10.1152/japplphysiol.01118.2005.—The set point has been used to define the regulated level of body temperature, suggesting that displacements of core temperature from the set point initiate heat production (HP) and heat loss (HL) responses. Human and animal experiments have demonstrated that the responses of sweating and shivering do not coincide at a set point but rather establish a thermoeffector threshold zone. Neurophysiological studies have demonstrated that the sensor-to-effector pathways for HP and HL overlap and, in fact, mutually inhibit each other. This reciprocal inhibition theory, presumably reflecting the manner in which thermal factors contribute to homeothermy in humans, does not incorporate the effect of nonthermal factors on temperature regulation. The present review examines the actions of these nonthermal factors within the context of neuronal models of temperature regulation, suggesting that examination of these factors may provide further insights into the nature of temperature regulation. It is concluded that, although there is no evidence to doubt the existence of the HP and HL pathways reciprocally inhibiting one another, it appears that such a mechanism is of little consequence when comparing the effects of nonthermal factors on the thermoregulatory system, since most of these factors seem to exert their influence in the region after the reciprocal cross-inhibition. At any given moment, both thermal and several nonthermal factors will be acting on the thermoregulatory system. It may, therefore, not be appropriate to dismiss the contribution of either when discussing the regulation of body temperature in humans.

temperature regulation; set point; interthreshold zone; neuronal models

OUR INCREASING KNOWLEDGE OF mechanisms governing thermal balance in the cells notwithstanding, at a systems level, several fundamental problems remain unresolved. One such issue is the manner in which body core temperature ($T_c$) is maintained at a set temperature. As recently summarized by Cooper (13): “The mechanism by which the set point is determined is still a mystery.” The present review will summarize some main concepts suggested to represent the manner in which temperature is regulated, specifically whether this regulation can be defined as set-point regulation, or whether $T_c$ is allowed to fluctuate within a range. This may appear as a fairly irrelevant issue at a systems level, but it is quite pertinent in terms of the manner in which didactic models of thermoregulation are developed. It is well documented that many nonthermal factors that humans are exposed to in their daily life interfere with the thermoregulatory system (cf. Ref. 31). The action of these nonthermal factors is often dismissed simply as an inhibitory or excitatory stimulus somewhere along the thermoregulatory neuraxis, which manages to displace the set point about which body temperature is regulated. The present review will conclude with an examination of the actions of several such nonthermal factors within the context of neuronal models of temperature regulation, suggesting that examination of these factors may provide further insights into the nature of temperature regulation.

AUTONOMIC TEMPERATURE REGULATION

Analysis of any regulatory system with a processing unit, for which the characteristics are unknown, requires that the output be evaluated with respect to different inputs to the system. In the thermoregulatory system, cold and warm sensory inputs provide autonomic and behavioral outputs. The present discussion will be limited to the autonomic thermoregulatory responses. The basic traits of the autonomic thermoregulatory system are often described by presenting a given autonomic response as a function of the sensory input. The initial defense of body temperature is achieved by vasomotor tone, responding to the prevailing ambient temperature, as shown in Fig. 1.
This range of ambient temperatures, void of any changes in metabolic heat production (HP) or evaporative heat loss (HL), is defined (32, 42) as the thermoneutral zone (TNZ). It is now well recognized that, within a given species, the TNZ will vary in width, as a consequence of the influence of nonthermal factors on the vasomotor response (cf. Ref. 38). The effect of nonthermal factors can be to attenuate or enhance the cold-induced vasoconstriction and/or heat-induced vasodilatation, in the manner indicated in Fig. 1.

Once the capacity of the vasomotor response to maintain a stable Tc is exceeded, the appropriate autonomic responses of sweating or shivering are activated. The Tc at which these effectors are initiated are defined as the thermoeffector threshold temperatures for sweating and shivering. As indicated in Fig. 2, the gain as well as the core threshold temperatures of these responses may be influenced by nonthermal factors. As a consequence, the magnitude of the interthreshold zone for Tc may also vary.

It should be noted that the concepts presented in Fig. 1 and particularly Fig. 2 do not support the likelihood of body temperature being regulated at a precise level, often termed a set point. By contrast, they suggest that the regulation is coarse, allowing Tc under normal physiological conditions to fluctuate within the interthreshold zone. However, before dismissing the set-point concept of temperature regulation, the evidence favoring the existence of the set-point and interthreshold zone should be reviewed.

**SET POINT**

Thermoregulatory models, predictive and didactic, have strived to appropriately include regulation of body temperature about a set point. As a consequence, the definition of the set point has evolved over the past decades, as have the models either simulating the manner in which body temperature is regulated, or simply predicting the heat balance during exposures to different environments.

The set-point theory of temperature regulation was introduced as a convenient analogy of how deep body temperature is regulated in mammals (18, 19). The thermoregulatory system was not the only physiological system subject to interpretation using control systems theory. Engineering models seemed in many instances to be a method of improving our understanding of the regulation of physiological variables (37). Models were continuously updated to include most recent findings. In contrast to models representing most other physiological systems, the simple engineering analog for temperature regulation soon became accepted, by some, as a true representation of the neurohumoral regulation of deep body temperature.

As summarized in Fig. 3, such engineering models assumed that deep body temperature is somehow compared with a reference temperature, resulting in a temperature error signal, which then evokes appropriate effector responses. This negative feedback control system may be considered to comprise controlling and controlled systems. The controlled system is temperatures for sweating and shivering. As indicated in Fig. 2, the gain as well as the core threshold temperatures of these responses may be influenced by nonthermal factors. As a consequence, the magnitude of the interthreshold zone for Tc may also vary.

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Evidence that appeared to support the existence of set-point regulation of $T_c$ in humans was presented by Cabanac and Massonnet (12), who developed an elegant experimental protocol in which subjects were initially rendered mildly hyperthermic, by immersion in a bath of water maintained at 38°C, and then slowly cooled by immersion in 28°C water. The immersion in 38°C water elevated $T_c$ and initiated the sweating response. During the subsequent immersion in 28°C, they observed, with progressive cooling of the core, a decrease in the sweating response and finally an elevation in the oxygen uptake, indicative of the onset of shivering thermogenesis. The striking feature of this study was that it clearly revealed that the cessation of sweating and onset of shivering occurred at a common $T_c$. In fact, the sweating and shivering responses overlapped, but this overlap was not deemed significant.

Using this protocol (12), Mekjavic and Bligh (25) wished to investigate the manner in which particular nontermal factors affected the $T_c$ set point. In the process, they discovered that the protocol needed to be modified so that the change in $T_c$ was not predominantly reflecting a change in peripheral temperature. Namely, the transition from a hot (40°C) to a warm (28°C) bath initiated a substantial change in $T_c$; in retrospect, this was also evident from the results of Cabanac and Massonnet (12). The observed coincidence of thresholds for sweating and shivering at a common $T_c$ was due to abrupt and large changes in peripheral temperature affecting the temperature of the blood perfusing the peripheral tissue, with this, in turn, being reflected in rather large changes in esophageal temperature. It would, therefore, be inappropriate to define esophageal temperature under the conditions of the experimental protocol of Cabanac and Massonnet as a mean temperature of the thermal core, especially in view of the fact that, during such a protocol, a rapid fall is not observed in the rectal temperature (49). For this reason, the protocol was modified in such a manner that skin temperature remained stable throughout the experiment and thus did not influence the thermal core (30). This was achieved by immersing the subjects in 28°C water and elevating their $T_c$ by exercise on an underwater cycle ergometer. The underwater cycle ergometry elevated $T_c$ and initiated sweating. Once a stable level of sweating was attained, the exercise was stopped, and subjects remained seated in the tank of water for an additional 100 min, which gradually rendered them hypothermic. Using this protocol, it became evident that the core threshold temperatures for sweating and shivering do not coincide, but they in fact establish a zone within which neither effectors are active. As a consequence of no activity of either of these effectors, it was termed the “null zone” (30), but a more appropriate term is the interthreshold zone or thermoeffector threshold zone (32). Such notion of an interthreshold zone rather than a set point in humans is in agreement with experiments in animals (17, 22) and is also in keeping with data obtained in humans (6) before the aforementioned experiments.

**THERMOREGULATION IN HUMANS AS INFLUENCED BY THERMAL FACTORS**

Following the discovery of neural foci in the preoptic posterior hypothalamus responsible for HP (21) and in the preoptic anterior hypothalamus responsible for heat dissipation (1), Meyer (33) suggested that regulation of body temperature may be achieved by coordinated activity of these two centers; namely, that the activity of the posterior center preventing...
cooling is somehow balanced with the activity of the anterior center preventing heating. Bazett (4) considered that these two centers are mutually inhibiting one another. He suggested that the nerve fibers carrying thermoafferent information to one center might have collaterals innervating the other. Thus an excitatory stimulus in one branch might lead to an inhibitory one in the other. A balance would, therefore, be maintained between the sensations of warmth and cold, resulting in thermal comfort. Bazett suggested that this manner of regulation would allow rapid adjustments to any change in the environmental conditions and that such rapid adjustments in the balance of activity of the two neural foci responsible for HP and HL would prevent alterations in $T_c$ in response to changes in the environmental temperature. Evidence of additional thermosensitivity of the regions in the hypothalamus involved in temperature regulation demonstrated that thermoeffectors were initiated as a consequence of changes in hypothalamic temperature. This type of two-tier regulation, namely peripheral and central, seemed to Bazett to be indicative of the fact that shivering was initiated somewhat below the normal body temperature and sweating above this level.

Based on the results of physiological studies investigating the contribution of thermal factors in human temperature regulation and the emerging knowledge of the manner in which neural structures involved in temperature regulation interact (cf. Ref. 7), it became apparent that both behavioral and autonomic thermoregulation in humans were achieved primarily by peripheral cold reception and central warm reception and that central cold reception and peripheral warm reception played secondary roles. Thus, in addition to the mutually inhibiting central structures for HP and HL, this theory proposed that sweating initiated by increased $T_c$ is also inhibited by the activity of the skin cold sensors and that the increased HP as a result of peripheral cold sensor excitation may be inhibited by the central structures for HL.

At the time, it was reasoned that central to this theory of regulation of body temperature is the establishment of a regulated temperature (i.e., set point). Vendrik (45) suggested that the region of overlap of the bell-shaped static firing characteristics of the warm and cold sensors (cf. Ref. 51) could provide the function of a set point. This approach, together with the concept of mutually inhibiting neural structures regulating HP and HL, were included in several subsequent modeling approaches of human temperature regulation (3, 26, 50). The concept of such reciprocal cross-inhibition (RCI) of sensor-to-effector pathways constituting a salient neural control mechanism was initially introduced by Sherrington (40) to represent the innervation of agonist and antagonist muscle. RCI was subsequently incorporated by Wyndham and Atkins (50) in their model of human thermoregulation and later translated by Bligh (8, 9) into a neuronal model of temperature regulation, components that also prevail in the model of Boulant (11). The common feature of these models is the absence of a reference signal (Fig. 3). The set point is established simply by the reciprocal inhibition of the HP and HL pathways. It has been emphasized that RCI is a crucial feature of the thermoregulatory controller, as independent sensor-to-effector pathways could allow the concurrent action of the HP and HL pathways (8, 9). Evidence of functional characteristics of the postsynaptic preoptic sensors in the HP and HL pathways (11) would appear to reduce the significance of the presynaptic RCI to the thermoeffector responses. Neuroanatomical and physiological evidence certainly supports the existence of neural communication between the HP and HL pathways (for references see Ref. 9); the significance of this interaction at the systems level is, however, not as obvious.

One prominent characteristic of temperature regulation, which should be considered by any theory of the control system, is the capability of body temperature being regulated at different levels, as in the situations of fever, hibernation, and exercise, to name but a few. According to the RCI model, any changes in the cold sensor-to-effector pathway will also be reflected in the HL pathway. Thus, functionally, the responses of HL and HP are linked. Excitation of one pathway causes inhibition in the other. According to this model, downward and upward shifts in $T_c$, as in fever, hibernation, exercise, etc., could be explained as inhibitory or excitatory drives acting on the sensor-to-effector neuraxis (9). In situations in which the entire thermoeffector threshold zone is shifted, the agent inducing the shift is most likely acting on the sensor-to-effector pathway before the point of crossing inhibitory influences. Alternatively, it might be acting after this point, in which case the agent must act on both HP and HL pathways but in opposite ways (excitatory vs. inhibitory). Conversely, should such an agent only induce a change in one effector, but not the other, then it is most likely acting on the pathway after the region of crossing inhibition. Presumably, widening of the thermoeffector threshold zone would then imply that the agent was acting on both sensor-to-effector pathways, but after the point of crossing inhibition.

The problem arises when trying to explain the responses observed at the systems level with models developed at the neuronal level. The interactions predicted by these models do not always appear to be significant, which is not to say they do not exist. One of the issues, which was addressed by the reciprocal inhibition theory, was how the overlapping bell-shaped static firing characteristics of the cold and warm receptors was transformed into the responses of shivering and sweating, particularly the fact that these responses did not overlap in the same manner as the activity of the temperature sensors. RCI (9) will result in such a transformation. Moreover, it will establish a regulated temperature on the effector side. However, the same algebraic proof cannot be used to demonstrate how a thermoeffector threshold zone could be established. Perhaps a more suitable neuronal model demonstrating the manner in which such a zone could be established is that of Boulant (11). It also includes converging signals from peripheral warm and cold sensors synapsing onto preoptic sensors with different firing characteristics. The firing characteristics of these central sensors provides the translation of thermoafferent information into a neural drive for shivering, vasomotor tone, and sweating.

According to Boulant (11), there are preoptic sensors receiving input from peripheral cold and warm sensors, which exhibit a similar activity temperature profile as that of shivering and sweating, respectively. Thus thermoafferent information from the cold sensors provides an excitatory drive to the preoptic neurons, with a similar profile as the shivering response. The question is, how significant is the inhibitory drive provided by thermoafferent information from the peripheral warm sensors, also synapsing on this pathway. The same would apply for the sweating response. The thermoeffector threshold zone, as re-
flected by the responses at the systems level, would be established without these inhibitory pathways. Thus, although the models of Bligh (9) and Boulant (11) predict converging inhibitory and excitatory pathways, this arrangement is not necessary to explain the existence of a thermoeffector threshold zone. The same could be established with two independent sensor-to-effector pathways. Future work will no doubt quantify the relevance of the converging pathways observed at the neuronal level from the perspective of the responses observed at the systems level.

THERMOREGULATION IN HUMANS AS INFLUENCED BY NONTHERMAL FACTORS

Regulation of body temperature would appear to be achieved primarily by thermal factors: initiation of thermoeffector mechanisms by the thermoafferent drive from peripheral temperature, \( T_c \), and central temperature sensors. However, many nonthermal factors that humans are exposed to, either in their daily activities or more rarely, impinge on the thermoregulatory system. Studies investigating the effect of various nonthermal factors on temperature regulation may improve our knowledge of the thermoregulatory system and, more specifically, enable us to evaluate the relevance of proposed theories of the manner in which homeothermy is established in humans.

Assuming that the effect of a nonthermal factor is reflected in the response of the thermoeffectors, it should be possible to determine whether it is acting in the region before the RCI (pre-RCI) or in the region after RCI (post-RCI), as shown in Fig. 4. In the hypothetical case of a nonthermal factor inhibiting HP by acting pre-RCI, this would be reflected in a reduced HP response and an augmented HL response, the latter as a consequence of the withdrawal of inhibition. Similarly, a nonthermal factor augmenting HL by acting pre-RCI would presumably cause a greater inhibition of the HP response. In contrast, the effect of nonthermal factors acting on a specific sensor-to-effector pathway post-RCI would only influence the thermoeffectors in this pathway. Finally, the effect of any nonthermal factor acting on all components of the thermoregulatory neuraxis would, according to this model, be reflected in the responses of all thermoeffectors.

For the purpose of discussion, the manner in which selected nonthermal factors influence thermoeffectors is presented in Table 1. Based on the observed effects on the thermoeffectors, the hypothesized regions of action of these nonthermal factors, nonthermal factors can affect components in the sensor-to-effector pathway before the region of RCI (pre-RCI) or after (post-RCI).

![Diagram of thermoregulatory pathways](image)

**Table 1. Influence of selected nonthermal factors, ranging from physiological and pathological to iatrogenic, on heat loss and heat production responses**

<table>
<thead>
<tr>
<th>Nonthermal Factor</th>
<th>Thermoeffectors Influenced</th>
<th>Region of Action: Pre- or Post-RCI</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise/postexercise</td>
<td>Heat loss</td>
<td>Post</td>
<td>24, 43</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>Heat production</td>
<td>Post</td>
<td>36</td>
</tr>
<tr>
<td>State of hydration/plasma osmolality</td>
<td>Heat loss</td>
<td>Post</td>
<td>15, 44</td>
</tr>
<tr>
<td>Sleep</td>
<td>Heat loss</td>
<td>Post</td>
<td>2</td>
</tr>
<tr>
<td>Motion sickness</td>
<td>Heat loss</td>
<td>Pre</td>
<td>28, 34</td>
</tr>
<tr>
<td>Fever</td>
<td>Heat production</td>
<td>Pre</td>
<td>9</td>
</tr>
<tr>
<td>Inert-gas narcosis</td>
<td>Heat production</td>
<td>Pre and/or Post (see text)</td>
<td>27, 29, 35, 46</td>
</tr>
</tbody>
</table>

Also listed are whether these factors are likely to exert their influence before (Pre) or after (Post) the region of reciprocal cross inhibition (RCI) in the thermoregulatory neuraxis.
either pre- or post-RCI, are also listed. Thus, for example, inert-gas narcosis, which presumably affects all neural structures involved in temperature regulation in the same manner (5), should affect all of the thermoeffectors. Nitrous oxide (N₂O), for example, inhibits synaptic transmission throughout the nervous system. As a consequence, it should affect both the sweating and shivering responses. The inhibitory effect of inert-gas narcosis on the shivering (27, 29, 35) and sweating (46) responses has been confirmed by several studies. This implies that inert gases do not exert their action on HP and HL mechanisms by means of RCI, regardless of whether their predominant actions are in the pre- or in the post-RCI region.

A nonthermal factor such as sleep, which affects both HL and HP responses (Table 1), would be judged to act pre-RCI (Fig. 4). However, it has been demonstrated that the actions on the HP and HL effectors are not in concert (2). If nonthermal factors associated with sleep acted on the HP and HL pathways simultaneously and pre-RCI, the temporal responses of the thermoeffectors should be similar. However, since the responses are temporally quite distinct, as indicated in Table 1, the region of action is most likely post-RCI.

It is now accepted that some type of communication between the HP and HL pathways exists, as described in Fig. 4 (RCI), and that the preoptic sensors in these pathways have distinct functional characteristics, which contribute to the nature of the effector response in terms of the thermoeffector core threshold temperature and gain of the response (Fig. 5). Silva and Boulant (41) have demonstrated that some of these preoptic sensors also respond to modalities other than temperature. They reported that a fraction of the population of cold-sensitive preoptic neurons is also glucosensitive and that similarly a fraction of the warm-sensitive preoptic neurons is also sensitive to plasma osmolality. This bimodal characteristic of the preoptic sensors affords modulation of HP and HL responses, respectively. Since these sensors are located after the region of RCI (Fig. 5), it is obvious that the level of blood glucose and plasma osmolality (Table 1) should affect the HP and HL effectors, respectively. This has been confirmed by studies conducted with human subjects. Passias et al. (36) have confirmed that hypoglycemia shifts the core threshold temperature for onset of shivering to lower temperatures and also reduces the gain of the shivering response. Similarly, dehydration suppresses the sweating response (15, 44). In these situations, the thermoeffector interthreshold zone, as shown in Fig. 2, is altered by the action of plasma glucose and osmolality directly on the preoptic sensors.

As alluded to by Bligh (9), the changes in the level of body temperature during fever and hibernation, as examples, can be explained simply by changes in the balance between HP and HL. There is no need for set-point regulation to explain these shifts. However, in contrast to the aforementioned nonthermal characteristics, fever would appear to exert its action in the pre-RCI region (9). A similar example is motion sickness, which has been shown to affect both HP and HL effectors (28, 34), suggesting a pre-RCI action.

Exercise is often used as an example of a shift in the set point. However, the exercise-induced increment in Tc does not need to be explained on the basis of a shifting set point, but of an altered balance between HP and HL. For any given level of HL, the increment in Tc during exercise should be proportional to absolute work being performed. However, since many exercise-related nonthermal factors may influence the HL response, the magnitude of the exercise-induced increment in Tc may vary at a given external work load and appears to be affected by the fitness level of the subject. This could be interpreted as evidence of nonthermal factors affecting the level of the regulated temperature during exercise and that the exercise-induced increase in Tc is related to the relative, rather

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**Fig. 5.** Neuronal model illustrating the mechanism by which PW and PC sensors integrate thermoafferent information and elicit the thermoregulatory responses of shivering, sweating, and vasomotor tone. The generalized activity/temperature characteristics of the peripheral sensors are presented in the left panels, whereas the characteristics of preoptic sensors in the three thermoeffector pathways are presented in the graphs above each of the sensors. [Modified from Ref. 11.]
than the absolute, work. Evidence points to the fact that the differences in the level of \( T_c \) during exercise at a given work load are primarily due to changes in the HL response (cf. Refs. 14, 23). The postexercise thermoeffect responses seem to suggest that exercise induces attenuation of HL responses, but does not affect regulation of HP responses (24, 43). This also suggests that nonthermal factors induced by exercise act on the thermoregulatory neuraxis post-RCI.

**CONCLUSIONS**

The precise regulation of \( T_c \) about a set point is energetically costly, and perhaps physiologically unnecessary, since sweating and shivering need not be initiated as soon as a displacement of \( T_c \) is sensed. This would be the case in set-point control of \( T_c \) and shivering need not be initiated as soon as a displacement occurs, particularly after the region of RCI. Therefore, it appears that RCI is of little consequence when comparing the effects of nonthermal factors on the thermoregulatory system. Because both thermal and several nonthermal factors will be present at all times, it may not be appropriate to dismiss the contribution of either when discussing the regulation of body temperature in humans.

**REFERENCES**


