Thermoregulation: some concepts have changed.

Functional architecture of the thermoregulatory system

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Romanovsky AA. Thermoregulation: some concepts have changed. Functional architecture of the thermoregulatory system. Am J Physiol Regul Integr Comp Physiol 292: R37–R46, 2007. First published September 28, 2006; doi:10.1152/ajpregu.00668.2006.—While summarizing the current understanding of how body temperature (Tb) is regulated, this review discusses the recent progress in the following areas: central and peripheral thermosensitivity and temperature-activated transient receptor potential (TRP) channels; afferent neuronal pathways from peripheral thermosensors; and efferent thermoeffectort pathways. It is proposed that activation of temperature-sensitive TRP channels is a mechanism of peripheral thermosensitivity. Special attention is paid to the functional architecture of the thermoregulatory system. The notion that deep Tb is regulated by a unified system with a single controller is rejected. It is proposed that Tb is regulated by independent thermoeffectort loops, each having its own afferent and efferent branches. The activity of each thermoeffectort is triggered by a unique combination of shell and core Tbs. Temperature-dependent phase transitions in thermosensory neurons cause sequential activation of all neurons of the corresponding thermoeffectort loop and eventually a thermoeffectort response. No computation of an integrated Tb or its comparison with an obvious or hidden set point of a unified system is necessary. Coordination between thermoeffectors is achieved through their common controlled variable, Tb. The described model incorporates Kobayashi’s views, but Kobayashi’s proposal to eliminate the term sensor is rejected. A case against the term set point is also made. Because this term is historically associated with a unified control system, it is more misleading than informative. The term balance point is proposed to designate the regulated level of Tb and to attract attention to the multiple feedback, feedforward, and open-loop components that contribute to thermal balance.

THERMOSENSORS

Central Thermosensors

A typical textbook chapter would say that brain temperature is detected by central thermosensory neurons (central “thermoreceptors”). Most of them are warm-sensitive, that is, they increase their activity with an increase in brain temperature. The abundance of warm-sensitive central sensors is consistent with the following two facts. First, our thermal physiology is “asymmetrical”: Tb is positioned very closely, within just a few degrees Celsius, to the upper survival limit (which is possibly determined by the denaturation of regulatory proteins) but relatively far, a few tens of degrees, from the lower limit (which is likely determined by the freezing of water). Therefore, core overheating is much more dangerous than overcooling. Second, humans are endothermic animals (meaning that their principal source of heat is their own body), as opposed to ectothermic animals (that receive heat primarily from the environment). Hence, sensors for limiting heat gain have to be located inside the body. Although much less common, cold-sensitive neurons (i.e., those that increase their activity with a decrease in brain temperature) also exist. However, the cold sensitivity of most of them seems to be due to inhibitory synaptic input from nearby warm-sensitive neurons.

Thermoregulatory responses in a variety of animal species can be elicited by local thermal stimulation of various areas in the central nervous system, including several brain stem neu-
In the present Call for Papers, these studies are represented by the invited review by Caterina (20), and, to a certain extent, the point-counterpoint exchange between Kobayashi et al. (57) and Boulant (11). While referring the reader to the review by Caterina (20) and several other recent reviews (30, 87, 102) for more detailed information, I would like to emphasize a few points.

First, activation of all thermoTRP channels results in an inward nonselective cationic current and, consequently, in an increase in the resting membrane potential. This mechanism agrees more readily with a role for these channels in peripheral thermosensitivity (83) rather than hypothalamic thermosensitivity (11, 129). Furthermore, the TRPV4 channel (which is likely to play a physiological role in thermoregulation; vide infra) does not seem to be expressed in the bodies of POA neurons (39), but it is expressed by the neuronal bodies of dorsal root ganglia (44).

Second, although each thermoTRP channel is activated within a relatively narrow temperature range, the range that they cover cumulatively is very wide: from noxious cold to noxious heat (Fig. 1). Furthermore, they cover this temperature range in an overlapping fashion, and their activities have different sensitivities to temperature. These features make the thermoTRP channels well suited to the job of peripheral thermosensors. It is important to note, however, that the temperature ranges shown in Fig. 1 were obtained in vitro. In vivo, a specific cell type on which a thermoTRP channel is expressed and concomitant activation with chemical ligands affect the temperature range in which the channel is activated and, in some cases, bring it closer to physiological values of deep $T_b$. Indeed, although the TRPV1 channel is widely thought to be

**ThermoTRP Channels**

The mammalian TRP superfamily consists of ~30 channels divided in six subfamilies known as the TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPML (mucolipin), TRPP (polycystin), and TRPA (ankyrin). Of these, the heat-activated TRPV1-V4, M2, M4, and M5 and the cold-activated TRPM8 and A1 are often referred to as the thermoTRP channels. Involvement of these recently cloned and characterized channels in thermoregulation has been studied intensively. In the present Call for Papers, these studies are represented by the original articles by Ni et al. (80) and Wechselberger et al. (123), the invited review by Caterina (20), and, to a certain extent, the point-counterpoint exchange between Kobayashi et al. (57) and Boulant (11). While referring the reader to the review by Caterina (20) and several other recent reviews (30, 87, 102) for more detailed information, I would like to emphasize a few points.

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activated at pain-inducing temperatures of >42°C (20, 30), Ni et al. (80) showed that increasing temperature within the normal physiological range (perhaps as low as 34.5°C) can exert a direct stimulatory effect on pulmonary sensory neurons, and this effect is likely mediated through the activation of the TRPV1 channel and other subtypes of TRPV channels. For some TRPV channels (namely, the V3 and V4), likely physiological roles have been established (63, 74). Other thermotransient receptor potential (TRP) channels are currently under investigation.

Afferent Pathways

**Discriminative sensation.** There is little doubt that afferent pathways start with primary thermosensory neurons. The bodies of these bipolar cells are located in the dorsal root ganglia, and the central axons project to the dorsal horn of the spinal cord (mostly lamina I), where they synapse with secondary monopolar neurons. Axons of these secondary neurons cross the midline and ascend in the lateral funiculus of the spinal cord. It was believed for a long time that the secondary neurons project directly to the ipsilateral ventrobasal complex of the thalamus, from where their signals are conveyed to the ipsilateral somatosensory cortex (postcentral gyrus) by tertiary neurons, and your textbook may hold this to be true. According to Craig (27, 28), however, this pathway, which is involved in tactile sensation, is uninvolved in temperature sensation. Instead, the lamina-I neurons carry temperature signals to the insular cortex (the island of Reil) with a relay in the postero-lateral thalamus (specifically, the posterior part of the ventromedial nucleus) or with two relays (in the parabrachial nucleus and the basal part of the ventromedial nucleus of the thalamus) (Fig. 2). These two branches of the spino-thalamo-cortical pathway are involved in discriminative temperature sensation. A functional magnetic resonance imaging study in humans by Hua et al. (48) published in this Call for Papers shows that this pathway is organized topically, as evident from the topical representation of skin temperature in the insula. This pathway allows for sensing temperature at a high spatial resolution (e.g., temperature of the surface under the tip of an individual finger can be assessed). Therefore, this pathway is important for making decisions about a wide range of issues related to interactions with the environment, but it appears to have little to do with Tb regulation, that is, with triggering thermoeffector responses to defend deep Tb. It should also be noted that the spino-thalamo-cortical pathway (as described here for humans) is not the same in other vertebrates, as several interspecies differences have been noticed (27).

**Homeostatic control.** Thermoeffector responses are triggered by thermal exposures massive enough to affect heat exchange between the body and the environment. Temperature-generated signals from large areas of the shell are sent to the brain through the spino-reticulo-hypothalamic pathway (Fig. 2), in which the secondary lamina-I neurons project to the reticular formation (medullar, pontine, and midbrain neuronal

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**Fig. 1.** Schematic representation of the dependence of the activity of cold-activated (blue) and heat-activated (red) thermoTRP channels on temperature. The thresholds of activation and temperatures of maximal activation are based on the activity of the channels in heterologous systems; some of the thresholds are means of values obtained in several studies. The figure is adapted from Patapoutian et al. (87). Information on the TRPM2 is added based on Togashi et al. (119); information on the TRPM4 and M5 is added based on Talavera et al. (114); the added lines are dashed. Please note that quantitative aspects of the relationships shown should be looked upon with great skepticism, as the figure does not account for several important factors (81). Nevertheless, this figure illustrates how well thermoTRP channels are suited for detecting physiologically relevant temperatures both in the shell and core.

**Fig. 2.** Afferent neuronal pathways for discriminative sensation/localization of a thermal stimulus and for homeostatic control of body temperature. DRG, dorsal root ganglion; PBN, parabrachial nucleus; POA, preoptic anterior hypothalamus; VMb, basal part of the ventromedial nucleus of the thalamus (formerly known as the parvicellular part of the ventroposterior medial nucleus); VMpo, posterior part of the ventromedial nucleus of the thalamus; ?, unknown location(s) within the medulla, pons, and midbrain.
groups). In this pathway, thermosensory “lines” converge at the level of lamina-I neurons (i.e., a single lamina-I cell receive inputs from multiple thermosensory neurons; see Ref. 82) and possibly at other levels, so that downstream neurons (e.g., brain stem neurons in thermoefferent pathways) can collect signals from large thermoreceptive fields (5, 6). The tertiary neurons of the afferent spino-reticulo-hypothalamic pathway project to hypothalamic structures (including the POA) either via the periventricular stratum passing along the wall of the third ventricle or via the medial forebrain bundle, which passes more laterally. As described above, warm-sensitive POA neurons have a dendrite orientation ideal for collecting information from both the periventricular stratum and the medial forebrain bundle. More precise delineation of this homeostatic, spino-reticulo-hypothalamic pathway, especially of the “reticulo” part of it, requires further study.

Thermosensors or Thermostats?

Our views on how temperature is sensed have been challenged recently by Kobayashi and colleagues (56, 58, 83). The pre-Kobayashi models of $T_b$ regulation assumed that thermoreceptors code temperatures of different parts of the body (into neuronal activity codes) and that these codes of local temperatures are then integrated by a separate network (that consists of several neurons with different roles) into some mean temperature. The location of the integrating network was unclear (8a). Nevertheless, it was often assumed that this integrating network also compares the integrated temperature with an external or internal reference signal and, based on such a comparison, somehow generates individual orders to thermoeffectors.

Kobayashi and colleagues proposed a different scenario (56, 58, 83). According to them, a sensory neuron is wired through several layers of a reticulo-hypothalamic pathway to a particular thermoeffector cell. When the temperature to which the temperature-sensitive part of a sensory neuron is exposed reaches the activation threshold of this neuron, the neuron fires and, through its connections, sends a signal to the effector cell. If a large number of sensory neurons sends signals to their effector cells, a thermoeffector response occurs. In this model, a decision to trigger an effector is made “automatically” (principally, by sensory neurons) and involves neither a separate decision-making network nor operations with temperature codes (computation of a mean $T_b$). According to this model, a sensation is a “side product” of the activation of those neurons that are wired to cause certain effector responses (i.e., feeling cold means having activated those neurons that are wired to cause cold-defense responses). The same principle is used by Kobayashi and colleagues (58) to explain how we sense other modalities as well.

Kobayashi’s model also explains how deep $T_{bs}$ and peripheral (e.g., skin) $T_{bs}$ contribute to thermoregulation. Deep $T_{bs}$ are regulated variables, and they are very stable. From the point of view of the control theory, they serve as feedback signals. Peripheral $T_{bs}$, on the other hand, are not regulated; they are highly variable (97). They are feedforward signals that, according to the control theory, allow the body to respond to a thermal load “in advance,” that is, before deep $T_{bs}$ start changing. In Kobayashi’s model, both deep and peripheral $T_{bs}$ drive effector responses in a similar way. Which central and peripheral sensory responses are wired to a particular thermoef- fector determines which combinations of core and shell $T_{bs}$ activate this effector (see Thermoefector Loops).

Despite its conceptual strength, Kobayashi’s model has not become widely accepted yet, perhaps because the author favors rather drastic terminological changes: he proposes to call sensors thermostats (or comparators). Kobayashi is certainly right that, from the engineering point of view, the role of thermoreceptors in his model is that of thermostats, and not of sensors. However, in the minds of the majority of medical and biological scientists and students, the current terms (sensor, thermostensor, sensory, somatosensory, etc.) are associated with no particular engineering analog. Hence, biologists feel no urge whatsoever to get rid of the entire family of widely used biological terms or to start translating them to the engineering language. (Later in this review, I will discuss a different term, set point, which is associated with a false idea in the minds of most biologists and physicians and, therefore, must be replaced.) In the case of thermosensors, a more productive approach might be to save the term, but to provide it with a different meaning.

THERMOEFFECTORS

Effectors

Your textbook is likely to name various autonomic thermoef- fectors and possibly some behavioral ones, to discuss their anatomy, mechanisms of physiological control, and effects on heat balance. Various aspects of thermoregulatory skin vasoconstriction (29, 118) and vasodilation (4, 55, 71, 127), thermogenesis in brown adipose tissue (BAT) (79), shivering (62), and thermoregulatory behavior (41) have been addressed in the present Call for Papers. Some interactions between thermogenesis, energy metabolism, and body temperature regulation have been analyzed in several original articles (37, 45, 49, 124), two editorials (112, 113), and the invited review by Diepvens et al. (31). I would also like to refer the reader to the fundamental review on BAT by Cannon and Nedergaard (17) published in Physiological Reviews. What your textbook is unlikely to cover is the efferent neuronal pathways to thermoef- fectors.

Efferent Pathways

Autonomic effectors. Efferent pathways to thermoef- fectors have not been well characterized in humans, although this topic has recently started receiving attention (34). Even in the rat, the most studied laboratory species, not all thermoefector pathways have been mapped. Some of the neuronal circuitries connecting the warm-sensitive hypothalamic neurons to autonomic thermoefectors in the rat, particularly the BAT and skeletal muscles (heat-production effectors) and the vasculature of the tail (a specialized heat-exchange organ), have been characterized during the past decade (Fig. 3). Studies of these pathways have been propelled by the development of transsynaptic retrograde tracing techniques using pseudorabies virus, along with the refinement of techniques for discrete lesioning and pharmacological stimulation and inhibition of neural structures. The revealed pathways appeared complex, and their detailed description is beyond the scope of the present paper; see the invited review by DiMicco and Zaretsky (32) in the present issue, as well as the reviews by Nagashima et al. (78).
and Morrison (75) published elsewhere. However, a few points deserve elaboration.

As shown in Fig. 3, both the BAT and skin vasculature are controlled by sympathetic ganglia, with the bodies of preganglionic neurons located in the intermediolateral column of the spinal cord. These spinal neurons receive direct input from cells located primarily in the raphe/peripyramidal area of the medulla. These medullary cells are under the control of hypothalamic (dorsomedial and paraventricular nuclei), midbrain (periaqueductal gray matter, retrorubral field, and ventral tegmental area), and possibly pontine (locus coeruleus) neurons that receive input from warm-sensitive POA cells (8, 18, 84). Although the efferent pathways for skin vasomotor tone and nonshivering thermogenesis have some similarities, they are not identical, and both differ substantially from the pathway controlling shivering. Within the shivering pathway, \( \gamma \) and \( \alpha \) motoneurons of the ventral horn receive direct and indirect inputs from the midbrain and brain stem, including the raphé/peripyramidal area of the medulla (116). Axons of the midbrain neurons descend the spinal cord with the reticulospinal and rubrospinal tracts. These midbrain neurons are under control of posterior hypothalamic neurons, which, in turn, receive inhibitory input from warm-sensitive POA cells.

The efferent pathways described are to a large extent inhibitory. Consequently, thermoeffector activation involves disinhibition of tonically inhibited neurons. Importantly, thermoeffectors are controlled relatively independently of each other (69, 78), and certain portions of the pathways may be recruited in a thermoregulatory response in a stimulus-specific fashion. The latter speculation is supported by findings that the paraventricular nucleus (16, 47, 67) and locus coeruleus (3) seem to mediate a thermogenic response to bacterial lipopolysaccharide or prostaglandin E\(_2\) but not cold-induced thermogenesis or a nocturnal Tb rise in rodents. In the present Call for Papers, neural circuitries of autonomic thermoeffector responses have been subjects of original articles by Nakamura and Morrison (79), Ootsuka and McAllen (85), Tanaka and McAllen (115), and editorial foci by DiMicco and Zaretsky (33) and McAllen (68a).

**Behavioral effectors.** Evidence (mostly from stimulation experiments) suggests that different thermoregulatory behaviors in the rat (e.g., relaxed postural extension, thermoregulatory grooming, and locomotion) use distinct neural circuitries (92). However, the neuroanatomic substrate of no thermoregulatory behavior has been studied extensively, and little is known about the neuroanatomy of behavioral thermoregulation (78). This situation is likely to change, as behavioral thermoregulation is becoming a subject of keen attention (1, 2, 59, 60, 68). In the present issue, Konishi et al. (59) report that neurons in the median preoptic nucleus are involved in the intensification of an operant thermoregulatory behavior (moving to a reward zone during heat exposure to trigger a breeze of cold air) caused by hypertonic saline. For a different behavioral response (moving to a cold environment during bacterial lipopolysaccharide-induced shock), two other substrates have been recently identified by Almeida et al. (2): neurons of the dorsomedial hypothalamic nucleus and fibers passing through the paraventricular hypothalamic nucleus. By studying warmth- and cold-seeking behaviors of rats in six different tests, Almeida et al. (2) also showed that these behaviors do not require an intact POA, whereas autonomic thermoregulatory responses do.

**FUNCTIONAL ARCHITECTURE OF THE THERMOREGULATORY SYSTEM**

“Think simple” as my old master used to say—meaning reduce the whole of its parts into the simplest terms, getting back to first principles.

—Frank Lloyd Wright (1868–1959)

“The ability to simplify means to eliminate the unnecessary so that the necessary may speak.”

—Hans Hofmann (1880–1966)
Thermoeffector Loops

Thermoregulatory pathways form distinct thermoeffector loops. The efferent parts of the loops clearly differ, because each effector has its own efferent pathway (Fig. 3); the article by Ootsuka and McAllen (85) in this Call for Papers provides further support for this thesis. The afferent parts are also not identical, as each receiver receives a unique combination of signals from peripheral and central thermosensors. The question as to which temperatures (thermosensors in which parts of the body) trigger which effectors has been recently revisited in several studies (14, 116), including the one by Nakamura and Morrison (79) in the present issue.

In general (although fully realizing that generalization may not be the best approach in this particular case), behavioral responses depend more on signals from peripheral thermosensors (shell temperatures) than central thermosensors (core temperature) (92), whereas deep Tb is relatively more important for triggering autonomic responses (52, 103). Such an organization reflects the fact that behavioral responses are often aimed at escaping the forthcoming thermal insult. In contrast, autonomic cold-defense responses (energetically expensive) and heat-defense responses (water-consuming) are often recruited only when deep Tb starts changing because behavioral mechanisms were ineffective or could not be used (e.g., due to competing behavioral demands). Even within the autonomic responses, different thermoeffector responses are triggered by different combinations of peripheral and central Tbs. Because peripheral thermosensors are mostly cold sensors, information from peripheral sensors is relatively more important for triggering cold-defense effectors (14, 79, 103, 116) than heat-defense ones (103). Because central thermosensors are mostly warm sensors, information from central sensors is relatively more important for triggering heat-defense responses (103).

Combinations of shell and core Tbs that trigger the same thermoeffector response in different species are also likely to differ. The great thermal inertia of large animals makes transient thermal exposures less threatening, which decreases the importance of feedforward regulation. Indeed, peripheral thermosensitivity is relatively more important in smaller animals, whereas central thermosensitivity is relatively more important in larger animals (72). Therefore, caution should be exercised while extrapolating results obtained in rats (this section of the present review is based primarily on such results) to human thermophysiology.

Thermoeffector Coordination

Usually, the recruitment of thermoeffectors into a thermoregulatory response looks like a highly coordinated event. Those effectors that affect heat balance in the opposite directions are typically not activated simultaneously. Energetically expensive and water-consuming responses are typically triggered after those that do not consume a lot of energy or water. For a long time, such coordination between thermoeffectors was explained with the help of a complex neuronal network (coordinator) within a single integrated system, the same (or a similar) network that was thought to be responsible for the formation of thermal sensations (see Thermosensors or Thermostats?). However, the coordinator has never been found experimentally. Furthermore, each effector was found to be controlled by a distinct group of neurons (see Thermoeffector Loops).

It is also accepted now that the anatomically distinct thermoeffectors function largely independently (105), and a body of experimental data has been accumulated showing that different effectors sometimes defend drastically different levels of Tb (for a review, see Ref. 94). An example of differential responses of thermoeffectors is endotoxin shock: it is accompanied by a large (2°C) decrease in the threshold hypothalamic temperature for activation of cold-induced thermogenesis, but a small (a few tenths of a degree) or no decrease in the threshold hypothalamic temperature for triggering tail skin vasodilation (98). Data showing independent effector responses are often questioned (e.g., Refs. 15 and 19) based on the fact that a thermoeffector can be recruited by another homeostatic system to meet a competing demand and, hence, can become unavailable for thermoregulation. In the example with endotoxin shock (98), skin vasoconstriction is needed to maintain blood pressure, thus preventing thermoregulatory skin vasodilation. The real question, however, is not whether an “unusual” thermoeffector response has a compelling teleological explanation, but whether the thresholds of different thermoeffectors can change independently of each other. The data accumulated (reviewed in Ref. 94) clearly show that thermoeffector thresholds often change independently, and this is a rather strong argument against a unified model of the thermoregulatory system with a single controller. Models of the thermoregulation system with multiple controllers (relatively independent thermoeffector loops) to replace the unified system have been proposed (e.g., Ref. 53).

Furthermore, it has been realized that any regulatory system can exist, using the words of Partridge (86), as a group of relatively autonomous controllers, acting in a common environment with generally compatible rules, but at any particular time, operating with only limited active coordinating linkages, and at no time acting as a unified system with a single controller. In fact, almost any regulated variable in the body, for example, arterial blood pressure (39), is likely to be an emergent product of a decentralized control system.

Coming back to the thermoregulatory system, basic coordination between thermoeffectors is likely to be achieved through their dependence on a common variable: Tb. Such coordination can be explained, in a simplified way, as follows. When one thermoeffector is activated, its activity changes Tb, which changes the position of Tb relative to the thresholds of other thermoeffectors, which, in turn, triggers activation or cessation of other thermoeffector mechanisms (for a more detailed description, see Ref. 93).

What To Do with the Term Set Point?

On a related issue, there has been a recent upsurge of interest in the term set point (12, 15, 19, 93, 94, 96). The original meaning of the term—a physical (thermal, electric, etc.), externally originated reference signal in a unified control system—is now considered invalid almost unanimously. However, the term is still used widely, mostly in the following three meanings. First, it is used to designate some internal property of the unified thermoregulatory system that substitutes for an external reference signal. Needless to say, such a usage is obviously wrong as it refers to the same unified system.
Second, it is used to designate some internal characteristics (usually thresholds) of individual thermoeffector loops or their subcomponents (e.g., Kobayashi’s “thermostats” or individual thermoTRP channels). There is nothing wrong with such a usage of the term, except that it creates confusion: this usage refers to a set point as a property of an individual component, whereas all definitions of thermoregulatory responses (see next paragraph) use the term set point while referring to the entire system.

Third, many colleagues use this term to designate a regulated level of $T_b$ (e.g., Refs. 12, 15, 19). Such a usage is in accordance with the most recent thermophysiological glossary (25), and many definitions of thermoregulatory responses (fever, anaptyrexia, hypothermia, hyperthermia) are built upon this definition of the set point. However, in the minds of biologists, physicians, and students, the term set point is strongly, perhaps inseparably, associated with the reference signal of a unified thermoregulatory system. Even today, it is not unusual for scientists outside the thermoregulation field to talk about the set point temperature (117) or about neurons that detect the error signal (26). Even for scientists within the thermoregulation field, it is rather typical to seemingly accept the relative mutual independence of individual thermoeffector loops, but to use (whether intentionally or not) the unified model with a single controller while describing how $T_b$ is regulated (12, 15), to still conclude that all thermoeffectors operate according to a common plan (15), and to propose a neuronal model of a set point of a unified thermoregulation system (12).

In other words, the intrinsic association of the term set point with nonexistent physical signals (a computed mean $T_b$ and reference $T_b$) within the nonexistent unified thermoregulatory system complicates the usage of this term. It provides reference to the engineering analogies that are more misleading than informative. To eliminate this often unintended reference, I have proposed to use the term balance point when talking about the regulated level of $T_b$ (93, 94, 96). The balance point-based definitions work for all cases where the set point-based definitions of thermoregulatory responses work (25). More importantly, they also work for all cases where the set point-based definitions may not work (94). As an added benefit of such a substitution, the term balance point redirects the scientific search from looking for the location of the set point (or building a new model of it) to studying the multiple feedback, feedforward, and open-loop components that contribute to thermal balance in the thermoregulatory system operating as a federation of independent thermoeffector loops. Interestingly, many scientists in the field are already avoiding using the term set point altogether or replacing it with different terms (e.g., Ref. 10). In his editorial about the regulation of body fat content, Wade (122) suggests to put the notions of lipostats and individual thermoTRP channels. In his editorial about the regulation of body fat content, Wade (122) suggests to put the notions of lipostats and individual thermoTRP channels. In his editorial about the regulation of body fat content, Wade (122) suggests to put the notions of lipostats and individual thermoTRP channels. In his editorial about the regulation of body fat content, Wade (122) suggests to put the notions of lipostats and individual thermoTRP channels.

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