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Revisiting Concepts of Thermal Physiology: Understanding Feedback and Feedforward Control, and Local Temperature Regulation

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ABSTRACT

Most experts agree that the dominant mechanism through which body temperature is regulated, under a thermal challenge, environmental or metabolic, is negative feedback control. However, some consider negative feedback to be too sluggish to account for the rapid speed of response. The impression of sluggishness is based on an assumption that the body temperature that is regulated is a core temperature, whereas we concur with those who have concluded that what is regulated is an integrated temperature compiled from inputs from multiple body parts, including the skin. Negative feedback control is supplemented, though, by feedforward control, which is initiated by cues about the predicted magnitude and timing of the thermal challenge. Feedforward control is anticipatory because it can excite thermo-effectors in advance of the thermal challenge impacting on body temperature. Feedforward control is improved by learning but always is supervised by feedback control. There is disagreement about whether the pro-active excitation of thermo-effectors by temperature receptors in the skin occurs by fast feedback control or by feedforward control. We show that skin temperature receptors can provide physiologically meaningful negative feedback within seconds. Both the feedback and the feedforward regulation of integrated body temperature can be modulated by regulation of the temperature of body parts that have special thermoregulatory needs, notably the scrotum.

1 | Introduction

Homeothermy, the maintenance of body core temperature within narrow limits despite large variations in microclimate, is physiologically costly for most animals. It requires the diversion of resources and physiological functions from other duties, like the redirection of cardiac output from the gastrointestinal tract, where it serves nutritional functions, to the skin for heat dissipation. For mammals and birds, the maintenance of homeothermy in the cold requires the diversion of energy to shivering and non-shivering thermogenesis, and often the acquisition of extra energy through increased food intake. The maintenance of homeothermy in the heat often requires the diversion of body water to evaporative cooling via panting and sweating, so competing with osmoregulation, a competition that will become increasingly problematic in a warming world [1]. That animals will incur those costs to maintain body core temperature within narrow limits implies that homeothermy must be important to their physiological welfare, although the physiological processes that have evolved specifically to function best in the homeothermic state are difficult to identify [2, 3].

The achievement of homeothermy requires the active regulation of body temperature. The many processes that animals use to control body heat balance and distribution (thermo-effectors) require activation and de-activation, and finely controlled coordination. If the body begins to gain or lose heat under a thermal challenge, whether that challenge be environmental or metabolic, corrective actions are initiated that seek to arrest the deviations in body temperature. Provided that the environmental conditions and the physiological capacity of the animal allow it, a new thermal steady state (a state where there is no net loss or gain of heat from the body) will be attained. Body temperature will restabilize but at a new value that will be sustained as long as the challenge persists.

The dominant process used by the central nervous system to achieve that regulation is considered by most in the field of thermal physiology to be negative feedback control [3, 4]. In negative feedback regulation of body temperature, temperature receptors alert the central nervous system to a deviation in body temperature caused by the body gaining or losing heat, and control centers in the brain then activate corrective thermo-effectors that seek to arrest the deviation, by restoring balance in the heat exchange between the body and the environment.

Negative feedback, however, does not account for all of the elements of body temperature regulation that are observed experimentally or in real life [3–6]. We agree with the statement that "it is overly restrictive to limit homeostasis to achieving regulatory control solely via the action of negative feedback" [7, p. 391]. For example, negative feedback control requires the activation of temperature receptors to generate a feedback signal, but human subjects resting in a warm environment and then exercising increased sweat rate within 1.5 s of starting exercise, long before any temperature receptor could have been activated sufficiently to stimulate the sweating response [8]. Such observations have led some researchers to conclude that negative feedback is too sluggish to be the foundation of thermoregulation [9], and that its real foundation is feedforward control, in which anticipatory thermo-effector activity is implemented before any deviation in body temperature [10–12]. We do not agree that the foundation of thermoregulation is feedforward control but do accept the need for feedforward augmentation of feedback control. Further, the activation of temperature receptors in certain body parts can induce responses that are apparently inappropriate for the regulation of whole-body temperature by negative feedback. For example, heating the scrotum of the ram can cause core body temperature to fall several degrees, an outcome that does not occur if the same area of skin on the trunk is heated [13, 14]. Why negative feedback does not correct that anomalous fall in core temperature is an open question.

In this review, we argue that the negative feedback control system for thermoregulation is far from sluggish. We contend that feedforward control aids, rather than displaces or outranks, negative feedback. We explore local thermoregulatory networks that function under the umbrella of a control system for the body as a whole, including the network controlling responses to scrotal heating. We also engage in some areas of uncertainty and disagreement that may confound our current understanding of how humans and other animals regulate body temperature, particularly concerning the role of skin temperature receptors in body temperature regulation.

2 | Negative Feedback Regulation of Body Temperature Is Not Inherently Sluggish

2.1 | Body Temperature Regulation Uses Proportional Control and Rate Control, but Not Integral Control

Transfer functions are essential constructs in any description of the performance of a control system. A transfer function is an algebraic or graphical expression of the relationship between the magnitude of an output of a control system (in our case a thermo-effector like respiratory evaporative heat loss, sweating, or shivering) and the input signal to the control system that is responsible for inducing that output (in our case body temperature). Such a transfer function is shown in Figure 1. That transfer function applies to a negative feedback control system that is operating in proportional mode. In a proportional control

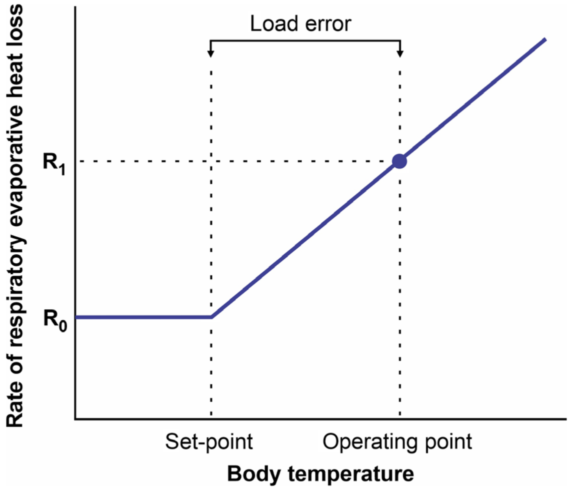

FIGURE 1 | A transfer function that relates the rate of respiratory evaporative heat loss to the regulated body temperature in an animal that pants. R_0 depicts the basal value of the output, which is the respiratory heat loss generated by breathing without panting. The body temperature at the point of inflection where panting starts is the set point or threshold for panting. Under heat stress, rising body temperature will elicit an increase in the rate of respiratory evaporative heat loss that is determined by the difference between body temperature and the set point (designated as the load error on the figure). R_1 depicts the rate of respiratory evaporative heat loss at which the rate of cooling is just sufficient to counteract the heat stress, thus arresting any further change in the regulated body temperature. A new steady state is attained, and body temperature restabilizes at the operating (or balance) point. Transfer functions may not necessarily be linear, as depicted here for simplicity. Indeed, they are likely to be sigmoid. See Mitchell et al. [3] for other transfer functions, including transfer functions for behavioral thermo-effectors.

system, the more that the input (the body temperature) deviates from the set point (or threshold) at which the output (rate of respiratory evaporative heat loss) first is induced, the greater is the output [3]. So the higher the body temperature, the greater is the activation of evaporative cooling. Strictly speaking, "proportional" is a misnomer because it implies a linear relationship as in Figure 1, but a transfer function can be nonlinear, and most, if not all, probably are sigmoid.

The proportional mode is not the only mode in which a negative feedback control system can operate. It can also operate in "rate" (or "derivative") mode, or in "integral" mode [15, 16]. The modes are not mutually exclusive, and engineering control systems often incorporate the simultaneous operation of all three modes: proportional, rate, and integral. In rate mode, the output is a function not of the magnitude of the input but of its rate of change. The faster the input is changing, the greater is the output. In the case of body temperature regulation under rate control, the output, say rate of respiratory evaporative heat loss, would be a function of $\Delta T_{b*}/\Delta t$, where t is time and T_{b*} is the regulated body temperature [3]. In combined proportional and rate control under a thermal challenge, the magnitude of the thermo-effector will depend simultaneously on how much body temperature exceeds the set point (ΔT_{b*}, indicated by the load error) and on its rate of change ($\Delta T_{b*}/\Delta t$).

In integral mode, the output of the control system is a function of the time integral of the input, which, in the thermoregulatory system, is equivalent to the area under a curve of body temperature plotted against time. Integral control of body temperature under a thermal challenge would implement thermo-effector activity until the area under the body temperature curve is eliminated, that is, when body temperature is restored to its value when not under thermal challenge. Therefore, in the case of integral control, and only in the case of integral control, could an operating point (i.e., the value of the input signal at which the system reaches a thermal steady state under a thermal challenge) be at the set point for a thermo-effector that is engaged in the response to the challenge [16]. While a thermal challenge remains, neither proportional control nor rate control could ever return body temperature to the set point.

There is no evidence, however, that the thermoregulatory system of any animal ever functions in integral mode, or could do so. So the statements that negative feedback is a "reactive strategy whereby the perturbation of a regulated variable away from its optimal value was detected and consequently elicited corrective responses that served to return the variable back toward pre-perturbation levels" [17, p. 2], or that "as the corrective effector responses take effect, countering the effect of the perturbation, the regulated variable begins to return towards set point values" [17, p. 11], which would require the system to be operating in integral mode, do not apply to the thermoregulatory system of humans or of any other animal. Equally unlikely is a historical concept: "if measured temperature does not correspond to the set point, the control center orchestrates the coordinated activation of the appropriate temperature-increasing or temperature-decreasing mechanisms to bring the measured temperature back to the set point value" [18, p. 1]. The same proposition was echoed more recently: "The components of homeostatic systems include error detectors, controllers, effectors and sensors that act to maintain the set point for a physiological variable" [19] (Figure 1). Under a thermal challenge, body temperature, the regulated variable, is maintained at a value that is different to both the set point and to the pre-perturbation level. It is maintained at an operating point, and that operating point is not equal, except coincidentally, to the set point of any thermo-effector that responds to the thermal load [3, 16]. In Figure 1, if the body temperature were returned to its set point or threshold, panting would cease while the animal was still under the heat stress, with potentially disastrous consequences. Instead, what the thermoregulatory system does when faced with a thermal challenge is to "activate effector mechanisms that oppose further deviation of the regulated variable" [7, p. 391].

While the thermoregulatory system does not have access to integral mode, it does have access to rate mode. It is a characteristic of temperature receptors in the skin that they have a strong dynamic response, that is, they fire strongly when their temperature is changing [20–25]. Indeed, the peak firing rate during that dynamic phase typically is much higher than the peak static response that is elicited by any stable temperature [23, 26]. The strongest signal that the skin temperature receptors ever send to the thermoregulatory centers is a signal that local temperature is rising or falling fast [27]. It is the dynamic response that distinguishes between cold and warm receptors too. Cold and warm receptors can be active at the same temperature (there are cold receptors that are active at skin temperatures higher than 40°C) [28, 29], but the firing rate of cold receptors increases when skin temperature is falling, while the firing rate of warm receptors increases when skin temperature is rising.

The dynamic response that is evident in temperature receptors in the skin has not been shown for temperature receptors in the central nervous system, including those in the hypothalamus and spinal cord [30], but there is some evidence that is compatible with the dynamic sensitivity of central temperature receptors. Rapid heating, by diathermy, of the hypothalamic area of cold-exposed dogs abolished shivering within a minute [31], even though, at 1 min, the hypothalamus presumably was still above the threshold at which a static hypothalamic temperature would induce shivering. Rapid heating of the hypothalamic area of conscious rats with diathermy induced behavioral responses (grooming, body extension) within a minute and an autonomic response (tail vasodilatation) within 45 s, again presumably while the hypothalamus still was below the threshold for grooming, body extension, or tail vasodilatation [32]. It may be that, in the in vivo neurophysiological experiments that looked for a dynamic response of temperature receptors in the central nervous system, it was not possible to heat or cool the central temperature receptors fast enough to elicit a dynamic response because of the high thermal inertia of the tissues surrounding those temperature receptors.

2.2 | The Thermoregulatory System Responds to Dynamic Activity of Temperature Receptors by Fast Negative Feedback

That skin temperature receptors have a strong dynamic response does not necessarily mean that the dynamic response contributes a functional input signal to the thermoregulatory system. It could just be an epiphenomenon, occurring very quickly and without impact beyond the temperature receptors. However, humans, at least, are impacted by the dynamic firing of temperature receptors. Humans can distinguish between different rates of rapid change of skin temperature. That same range of rates elicits graded dynamic responses from skin temperature receptors. By applying a thermal stimulus that either increased or decreased by 5°C, at rates between 0.05°C and 1°C·s^{-1}, Davies et al. [20] explored the thermal sensations that human subjects experience during rapid changes in the temperature of their facial skin. The subjects experienced different thermal sensations at the different rates of change, particularly when skin temperature was declining. Davies et al. [20] then used the same thermal stimulus to explore the firing rates of temperature receptors in the facial skin of the cat, and observed dynamic responses increasing with the rate of change of skin temperature. That observation means that human thermal sensation is quantitatively responsive to different rates of change of facial skin temperature that are rapid enough to elicit a strong dynamic response in skin temperature receptors. Corrective thermoregulatory behavior often accompanies thermal sensation. For example, an icy wind generates a sensation of cold and simultaneously induces us to seek warmth. So the dynamic firing of skin temperature receptors indeed can provide a functional input signal to the system that initiates behavioral thermoregulation.

The rate of change of skin temperature influences autonomic thermoregulatory control too, including the control of metabolic rate [27] and sweat rate [33–36], but there is not yet evidence that it influences peripheral blood flow or panting [37]. The influence of a rapidly cooling skin is sufficiently strong to cause a paradoxical increase in core temperature at the beginning of cold exposure [38], when peripheral vasoconstriction reduces the flow of blood from the core to the periphery, trapping heat in the core.

Counterintuitively, though, the sensation of heat or cold is not necessary for the activation of thermoregulatory behavior [39]. The somatosensory pathways that convey information from temperature receptors in the skin, both static and dynamic, traverse the thalamus *en route* to the somatosensory cortex, where the neural substrate for thermal sensation is housed [40, 41]. It seems entirely plausible that a neural pathway should exist between the thalamus and the hypothalamus, or between the somatosensory cortex and the hypothalamus, either of which would allow information from temperature receptors in the skin to proceed to the hypothalamus and to activate autonomic thermo-effector responses. Such pathways have eluded neuroanatomists, and we now know that information from skin temperature receptors reaches the hypothalamus by a different route, at least in rats. The parabrachial nuclei, at the junction of the cerebellum and the brainstem, receive ascending neural information from the skin and viscera and distribute it to more-rostral sites in the brain [42]. Information from temperature receptors in the skin that arrives at the parabrachial nuclei is dispatched by parallel, but separate, pathways to the somatosensory cortex (via the thalamus) and to the thermoregulatory centers in the hypothalamus [39]. When lesions were made in the thalamus of rats, their somatosensory cortex showed no responses to cold or hot stimuli applied to the skin, but the rats made appropriate behavioral responses to changes in floor temperature [43]. This means that the rats reacted to cold skin apparently without being aware of the cold. If that pattern prevails in other mammals, including humans, it would be a misconception that thermal sensations are required to induce thermoregulatory behaviors. The behavioral responses and the perception of hot or cold can operate independently, but they rely on the same information from the temperature receptors in the skin.

The dynamic response of temperature receptors in the skin to a change in skin temperature is over within seconds or minutes [20, 44]. By the time that the body reaches a new steady state of body temperature after a thermal challenge, which can take hours in humans [45], the dynamic response has long ended, and so cannot then contribute to the regulation of body temperature. It is the static response of skin temperature receptors that then contributes to that input signal (see below). Rate control is functionally unimportant in a thermal steady state. In other words, no matter how fast body temperature changes during a thermal challenge, the rate of that change has no effect on the ultimate relationship between body temperature and thermo-effector activity. What the dynamic response will do is reduce the time that it takes to reach a steady state, and so the time that it takes for body temperature to restabilize at a new operating point. The dynamic response will activate thermo-effector activity before the static response of temperature receptors will do so, and it will activate that thermo-effector activity powerfully. If there is an advantage to body temperature being stable, or a cost to it being unstable, there will be a benefit to reaching stability quickly. So the dynamic response of temperature receptors will contribute to the efficiency of the thermoregulatory system, but without necessarily affecting the actual body temperature at equilibrium.

The rapid implementation of thermo-effector activity by changes in skin temperature during a thermal challenge sometimes has been considered to be “feedforward control” [5, 17, 39, 46], a view with which we do not agree. For reasons that we shall discuss below, we consider feedforward control to be a different process [4]. However, we do agree that the rapid implementation of thermo-effector activity may be termed “pro-active,” a term used by Romanovsky [6]. When resting men of European ancestry, who “were born and lived for a long time in a hot climate (their families had been living in hot climates for several generations)”, were moved abruptly from a neutral to hot environment, sweating was enhanced in 2–3 min, long before any change in core temperature was detected [47, p. 989], and the enhancement of sweating was correlated with an increase in skin temperature. Similarly, the cessation of sweating after transition from a hot to a cool environment correlated well with the rate of skin cooling [36, 48]. The dynamic neural signal from skin temperature receptors proceeds to the central nervous system via conventional thermosensitive pathways; they are the same pathways that convey the static signal after skin temperature has changed. That dynamic neural signal conveys information about a change in the temperature of body tissues that already has happened, not about a change that is imminent, so it is not an anticipatory signal. We believe that it is a fast negative feedback signal, serving to alert the regulatory centers rapidly that a change in body temperature has occurred, and so to help arrest further effects on body temperature by a thermal challenge. The outcome of thermoregulatory behavior like huddling, for example, initiated when ambient temperature falls rapidly (and consequently the temperature of temperature receptors in the skin also falls rapidly), is that body temperature does not fall as far as it would if there were no huddling. That is consistent with how classic negative feedback works.

There is an apparent anomaly, although, in the peripheral vasomotor response to temperature signals. Falling skin temperature, when an animal enters a cold environment, will induce peripheral vasoconstriction by negative feedback, reducing the delivery of warm arterial blood to the skin, which will cause a further fall in skin temperature. However, the further fall in skin temperature will help to elicit stronger responses that arrest the fall in temperature of the body as a whole.

Thus, the evidence does not support the conclusion that negative feedback is too sluggish to account for the regulation of body temperature following an acute change in the thermal environment [5, 9]. The conclusion that it is too sluggish has been based on the assumption that core temperature is the regulated variable and that the system has to wait for a change in core temperature to occur before appropriate thermo-effector activity is implemented. If core temperature changes, the thermoregulatory system indeed is activated powerfully, and if core temperature did provide the only input to the control system, then the system indeed would be sluggish, especially in large animals. However, the impression of sluggishness erodes if the regulated body temperature is not the core temperature but is an integrated body temperature that includes skin temperature [3, 4, 16, 49]. One of the reasons that core temperature changes so little under a thermal challenge is that the negative feedback system, which receives signals from temperature receptors in both the core and the skin, is so fast. Through negative feedback originating from the dynamic response of temperature receptors in the skin, the human thermoregulatory system receives information that the thermal status of the body has changed within 30 s of the change occurring and perhaps within 2 s if the change is fast enough and is applied to a sensitive area like the face [20], and the system can act on that information. Given that the characteristics of temperature receptors are similar across diverse species [21, 25, 50–52], it is likely that in other animals the control system receives that thermal information equally quickly, with the proviso that insulative fur or feathers would attenuate the rate of change of skin temperature when the thermal environment changes and also change the equilibrium skin temperature.

3 | Feedforward Control Is Helpful, but Unreliable

3.1 | Feedforward Control Speeds Up Behavioral and Autonomic Thermo-Effector Activity

Those of us who have the resources to do so, dress for the weather. We institute thermoregulatory behavior that is based on the visual and cognitive cues that we receive in advance of any change in body temperature that results from exposure to those weather conditions. Dressing for the weather is an example of feedforward control of body temperature, and, if implemented properly, might result in body temperature not deviating at all under the thermal challenge of adverse weather [6]. The powerful dynamic responses of skin temperature receptors allow animals to respond rapidly to a change in their thermal environment [53] but do not allow them to avoid the effects of the thermal challenge. “Using feedforward mechanisms, organisms can exploit correlations in environmental variables to prepare for anticipated future changes” [54, p. 1]. That we will engage voluntarily in anticipatory thermoregulatory behavior, when a thermal challenge threatens, implies that we benefit from the achievement of homeothermy, or the avoidance of heterothermy [55].

The concept that feedforward control is a mechanism used in regulating body temperature, in addition to feedback control, was introduced more than half a century ago [56]. The concept gained sufficient traction for a distinguished neurophysiologist to announce that feedforward control alone accounted for how body temperature was regulated; feedback control played no role [12]. Feedforward control was omitted, although, from most models of thermoregulatory control until the concept was revived early in this century [5, 39, 57, 58]. Its revival has been sufficiently strong for some contemporary researchers to consider feedforward control to be more crucial than is feedback control in the regulation of body temperature [9, 17].

Although Romanovsky [6, 59] considered feedforward control of body temperature to be confined to behavioral thermo-effector activity, it can be implemented for autonomic thermo-effector activity too, as Huckaba et al. [56] had proposed in their original formulation. Rams that were waiting to start running on a treadmill initiated sweating from scrotal sweat glands before either core temperature or scrotal temperature had changed [60]. Feedforward control presumably underpins the phenomenon of “temperature contagion”; the temperature of skin on the hand of viewers dropped when they watched a video of another person immersing a hand in cold water [61]. People who were about to swim in ice water apparently initiated “anticipatory thermogenesis,” whereby they increased metabolic heat production before entering the water [62, 63]. Rats given alcohol develop hypothermia, but not if they are given advance warning of its administration by cues previously paired to its administration [64]. Feedforward control enables them to develop a preemptive increase in body temperature [7]. Mammals that were both hypohydrated and hyperthermic, including humans [65, 66], baboons [67], goats [68], sheep [69], and dogs [70], increased evaporative heat loss immediately after they drank, even if the water they drank was at core temperature. They did so long before any water was absorbed from the gastrointestinal tract, and without any preceding change in body temperature [67, 71]. The cue for the feedforward control following drinking seems to be mechanical stimulation of oropharyngeal receptors [69, 72–74], although in hypohydrated–hyperthermic humans, at least, anticipatory sweating may be induced merely by the sight of water [75]. So, although the thermoregulatory system relies on feedback control, it also uses feedforward control in the activation of both autonomic and behavioral effectors. Because the neural signals that activate behavioral feedforward control originate from the cerebral cortex [76, 77], some thermal physiologists have called them “central command” signals [78, 79], a term borrowed from cardiovascular physiologists [76, 80].

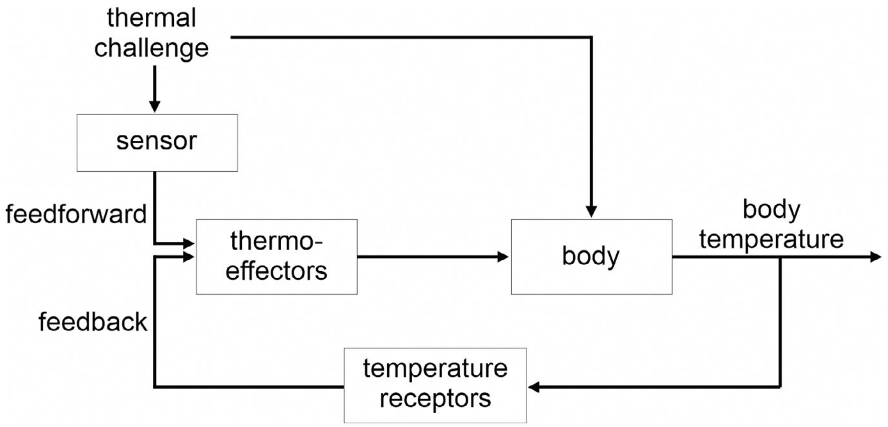

FIGURE 2 | Feedback and feedforward control of body temperature. Feedforward control uses cues about expected thermal challenges to initiate thermo-effector activity that can limit or prevent deviations in body temperature, even before the receptors that sense body temperature are activated. Dressing for the weather is an example [6]. Figure based on Kanosue et al. [5], for whom the temperature receptors were confined to the body core.

How feedforward control fits into the control systems model of body temperature regulation is shown in Figure 2. Feedforward regulation of body temperature uses cues about an expected thermal challenge, environmental or metabolic, to institute thermo-effector activity that will reduce or arrest deviations in body temperature before any tissue temperature has changed, so before any negative feedback resulting from that challenge has been initiated. Feedforward control might activate thermo-effectors directly, but it might also act on the set point or threshold, which would have the same effect [81]. The thermo-effector activities often are avoidance behaviors [6], which can reduce the temperature change of the body by a reduction of, or escape from, the expected thermal challenge. Avoidance behaviors stabilize the body temperature by preventing the thermal challenge impacting on the body or by reducing the extent to which other thermo-effector activity needs to be implemented after a thermal challenge has impacted on the body, so eliminating or reducing the deviation in body temperature (load error, see Figure 1) that is required to restore a thermal steady state. Feedforward interventions other than avoidance behaviors may not reduce the thermal load, but could remain active even after negative feedback has been implemented, and so help to reduce the deviation in body temperature. Feedforward control also could hasten the approach to a new steady state under a thermal challenge, as can the dynamic response of temperature receptors (see Section 2), so contributing to the stability of body temperature.

Autonomic feedforward responses can be extraordinarily fast. Human subjects resting in a warm environment, but not yet sweating, started to sweat within 1.5 s after they began to exercise [8]. That would be long before muscle temperature or any other core temperature had changed. Also, exercise would have no immediate effect on skin temperature, especially because, in the warm environment, the subjects already would have exhibited peripheral vasodilation. So feedback from temperature receptors, either static and dynamic, could have played no role in the response; it must have been a feedforward response, unrelated to skin temperature. Others have confirmed a rapid feedforward initiation of sweating at the onset of human exercise [82–87]. At the end of exercise, there can be an immediate, sometimes transient, reduction of sweating, again induced by feedforward control, even though body temperatures still may be increasing [78]. Feedforward autonomic control in human thermoregulation is not confined to the control of sweating. At the onset of exercise, presumably in anticipation of a potential fall in mean arterial blood pressure as blood is diverted to working muscles, cutaneous vascular beds constrict immediately [88–90]. That peripheral vasoconstriction helps to stabilize blood pressure, but it also compromises the dissipation of metabolic heat. It is reduced in due course, and even overridden, by the vasodilator effects that accompany the later rise of body temperature induced by the exercise [91].

As far as we know, thermoregulatory feedback signals that lead to the activation of both autonomic and behavioral thermo-effector activity are processed in the hypothalamus [92]. Feedforward signals that activate autonomic thermo-effector activity like sweating and vasoconstriction also will likely be processed in the hypothalamus. However, the processing of feedforward signals that lead to the activation of behavioral thermo-effector activity, and especially avoidance behavior, requires integration of cues about an impending thermal challenge with stored cognitive information about the success or failure of a particular behavior when it has been implemented previously. It requires prior learning [9, 17, 93]. To dress correctly for the weather, we need to know whether clothing that was worn previously, in anticipation of a particular type of weather, turned out to be appropriate for the weather that ensued. The integration of cognitive information about the environment with neural information about the outcome of previous thermoregulatory behaviors is not a traditional function of the hypothalamus. Such integration, and generation of directed efferent information, is a main function of the insular cortex, which has efferent connections with not only the hypothalamus but also the motor cortex, which are required to initiate locomotion in thermoregulatory behavior [94]. At least in humans, the insular cortex receives afferent information from temperature receptors, via spinothalamic pathways transiting the thalamus [95, 96]. The insular cortex also generates "central commands" that provide feedforward signals to the cardiovascular system at the initiation of exercise [97]. It seems to be a prime candidate as the neural seat for thermoregulatory behavior under feedforward control.

3.2 | Feedforward Thermoregulatory Control Is Answerable to Feedback Control

Some researchers have dismissed negative feedback entirely as a control process involved in thermoregulation, in favor of feedforward control, "because the organism makes accurate responses without guidance by identifiable error signals" [12, p. 184]. Those "accurate responses" arise because, it is contended, not just behavioral responses but also all the autonomic responses that are required to regulate body temperature are learnt during early infancy [12]. Others concur that feedforward anticipatory activation of thermo-effectors is implemented accurately based on experience [9, 17, 93]. If accurate activation of thermo-effectors is based on experience or learnt during infancy, a newborn infant should not yet have control of thermo-effectors. Yet, within a day of birth, newborn humans display all of the components of regulation of body temperature, including the full range of changes in peripheral vasomotor tone in response to ambient temperatures below and above the thermoneutral zone, the activation of non-shivering thermogenesis, and the ability to sweat [98, 99]. Sweating can be triggered soon after birth, even in infants born 3 weeks prematurely [100]. Weight is added to the story by the finding that, at least in sheep, brown adipose tissue develops in utero but cannot be activated in utero by a cold stimulus. As soon as the umbilical cord is severed, a cold stimulus can activate brown adipose tissue [100]. Similarly, newly hatched ducklings display competent defense against cold without having had any opportunity to learn about thermoregulation [101]. Thus, it is clear that not all thermo-effector activity requires prior experience, although, undoubtedly, thermoregulatory efficiency will be improved by learning.

If feedforward control were to operate perfectly, it should be possible to achieve a thermal steady state in the face of a thermal challenge without any deviation of body temperature, because, alert to the challenge, anticipatory thermo-effector activity would be elicited to prevent the challenge from having any effect on body temperature. While the concept may hold for minor challenges, it implies that endotherms never would experience deviation in body temperature as a result of a thermal challenge. Yet, as reported, famously, by Marius Nielsen more than 80 years ago, but discovered by Bardswell and Chapman 27 years earlier, during aerobic exercise, core temperature is elevated to a level that depends on the metabolic rate and is independent of the ambient temperature, and is sustained at that elevated level while the aerobic exercise continues [102, 103]. If anticipatory feedforward responses could be implemented sufficiently accurately to take full responsibility for the regulation of body temperature, core temperature would not rise during exercise. Ramsay and Woods, who have reinvigorated interest in feedforward control in body temperature regulation, do not take such an extreme view. Although they adhere to the primacy of feedforward control, they allow for negative feedback control too: "undoubtedly, negative feedback plays an important role in homeostasis as regulated variables are defended from unanticipated disturbances and emergency situations" [7, p. 391]. Others too have assigned a crucial role, but not total responsibility, to feedforward control in the regulation of body temperature [11]. Goldstein and Kopin [10] considered feedforward control to be more efficient than is feedback control in maintaining homeostasis.

Although the regulation of body temperature undoubtedly benefits from feedforward control, there are at least three reasons why it cannot be the dominant, and much less the sole, mechanism that underpins that regulation. The first is that the anticipatory thermo-effector activity that is implemented by feedforward control always at best is an educated guess because the feedforward system must estimate how much the anticipated thermal challenge will influence the heat balance of the animal but without any information about the animal's prevailing body temperature. That is because, under the proposed purely feedforward system, the control system is not informed about the actual temperature, because feedback about temperature is not supposed to be operating. That would be like estimating how much cold water to add to a hot bath to attain a desired bath temperature, but without knowing the temperature of the hot bath. Without feedback, there is no way of knowing whether a guess was right or wrong, and if wrong, by how much. The second reason that feedforward cannot be the dominant mechanism is that thermoregulatory control systems are fallible, as Somjen [12] acknowledged. Even if the feedforward system has estimated correctly, based on experience, how many watts of heat the thermo-effector activities must add to or take from the animal's body to arrest a change in body temperature, there is no guarantee that the system will add or remove that exact number of watts unless the response is monitored. Unlike feedforward control of the cardiovascular and ventilatory systems during exercise, where the requirements for perfusion and the demand for the supply of O_2 and removal of CO_2 are quite predictable from the level of muscle activation, the requirement for heat dissipation or conservation will depend on many factors, including, for example, fur, feathers, and clothing. Ramsay and Woods [93] confine the dominant role of feedforward control to predictable thermal challenges. Thermal challenges may be predictable, but we do not believe that the magnitude of responses to thermal challenges ever is fully predictable. The magnitude has to be monitored continuously. Feedforward systems do not monitor; they only anticipate. The third reason that feedforward control cannot be the dominant mechanism is that inappropriate feedforward control introduces frank errors in body temperature regulation. For example, young women not only had different thermal sensations but also different aural and toe temperatures when presented with, and ingesting, bowls of hot soup that differed only in the coloring added, namely yellow ("hot") and blue ("cool") [104]. Visual feedforward control induced an error in thermoregulation.

If body temperature were to deviate as a result of an error in feedforward control, that deviation would be permanent in the absence of feedback information, because, without any feedback, the regulatory system would not be informed that an error had occurred. Based on previous experience, the feedforward system may be able to estimate how much evaporative cooling is needed to compensate for a heat load, but it cannot estimate how much sweat will drip from the skin without evaporating, as would occur in a humid environment. A given level of activation of the sympathetic efferent activity that brings about peripheral vasoconstriction produces stronger vasoconstriction when core temperature is low than when core temperature is high [29]. Without feedback about core temperature, a feedforward system could not estimate accurately by how much to activate the sympathetic nervous system to induce vasoconstriction. Even at steady state, core temperature in humans depends on body posture [29, 105], but posture changes frequently, and there may not be information available to the feedforward system about what someone's posture will be when its anticipatory thermo-effector activities take effect.

So a feedforward mechanism will initiate an educated guess as to what is the right thermo-effector activity, and, even if the guess is correct, the consequences for body temperature are unpredictable, because the thermoregulatory system is fallible: "The disadvantage with feedforward mechanisms is that if the cue becomes uncorrelated with the future environmental state (i.e., the cue becomes an inaccurate indicator of the future state) then organisms may initiate an anticipatory behaviour that is no longer beneficial in the later selective environment" [54, p. 2]. Feedforward control is fast but unreliable, and is, indeed, prone to error. Only by sensing body temperature and implementing corrections via negative feedback can precise regulation be achieved. So negative feedback must be the dominant control process in thermoregulation, while feedforward plays an important ancillary role, supervised by feedback control.

Other researchers, as we have said, have maintained a contrary view, arguing that feedforward control is more precise than negative feedback for the regulation of body temperature [9, 10, 17]. As evidence for the failure of negative feedback control, authors have cited Johansen's observation that when armadillos were exposed to cold, their core temperature increased [106]. However, Johansen's observations on the armadillo are entirely compatible with a negative feedback control system that has skin temperature as part of the regulated variable. The concerns of Ramsay and Woods [17] derived from the assumption, with which we and others do not agree, that skin temperature was not part of the regulated body temperature [3]. They also regarded inaccuracies in the guesses of the feedforward system to be signs of temporary incompetence that could be overcome by learning. Learning certainly occurs in the thermoregulatory system. It underlies the changes in the system that occur during acclimation, when environmental changes are experimentally induced, and acclimatization, when environmental changes occur naturally. Thermal acclimation and acclimatization are the processes of adjustment of the thermoregulatory system to a thermal environment that is different from the one in which the system has been operating, and so qualify as learning [107–110]. The changes are brought about by repeated exposure to the new thermal environment. Acclimation and acclimatization induce an improved stability of core temperature in the new thermal environment, with smaller load error. The thermoregulatory system "learns" how to function better in the new environment.

Ramsay and Woods did not discuss those phenomena when they proposed that thermoregulatory control is learned; they were concerned with cognitive learning. But others have done so (e.g., Armstrong and Stoppani [111]). What Ramsay and Woods proposed is a process by which past experience enables the feedforward control system to make progressively more accurate estimates of the anticipatory thermo-effectors that are required in the face of a thermal challenge, so reducing dependence on negative feedback control. Past experience may well allow the feedforward system to make a better guess about what anticipatory thermo-effector needs to be implemented, and at what strength, based on feedback from temperature receptors, but it cannot counteract the intrinsic fallibility of the thermoregulatory system. Past experience reduces, but does not eliminate, the unreliability of feedforward control.

Apart from their inherent unreliability, learned feedforward thermo-effector activities have the potential to make the control system unstable, although some refute that learned responses ever overcompensate [17]. A behavioral response is more likely to be repeated if it has a favorable outcome rather than an unfavorable outcome. So if dressing warmly makes a person feel more comfortable when they venture out in cold weather, that person is likely to keep dressing more and more warmly. However, in the absence of feedback, the person would not be aware of having dressed too warmly. Because the anticipatory response is rewarded, the system is in a state of positive feedback. Dressing warmly makes the person dress more warmly, and instead of arresting a potential fall in body temperature, the response could cause an increase in body temperature. When a thermo-effector has the opposite of the intended effect, the control system is unstable. For the feedforward thermo-effector to have a net benefit, the control system has to have the capacity to override the thermo-effector if it exceeds its intended goal, and that is a function of a negative feedback system.

3.3 | Do Skin Temperature Receptors Participate in Thermoregulatory Feedforward Control?

What are the sensors that initiate feedforward thermoregulatory control? The cues that induce us to dress for the weather could be visual cues (what the weather outside looks like) or auditory cues (what the weather forecast says), so the sensors then would be those in the eyes or the ears. For predictable thermal challenges, the cue also could be an internal cue associated with learning from past experience of similar challenges [93]. As we have noted, the sensors responsible for immediate panting or sweating when hypohydrated–hyperthermic animals drink are oropharyngeal mechanoreceptors that are stimulated by the act of drinking [69, 72, 74, 75]. Mechanoreceptors that respond to muscle and joint tension may be involved in the enhancement of sweating that can occur within 1.5 s of the start of human exercise [8], but metaboreceptors will detect the changes in oxygen and carbon dioxide partial pressures and concentrations of other metabolites more quickly at the start of exercise and induce an anticipatory enhancement of sweat rate [79, 83, 87]. The feedforward control of peripheral vasomotion is initiated by muscle metaboreceptors [112]. The anticipatory decline in sweat rate at the cessation of exercise appears to be induced by altered baroreceptor activity [78].

However, many researchers in thermal physiology have concluded that temperature receptors in the skin provide a cue for feedforward control by detecting changes in ambient temperature, warning of an impending thermal challenge, and initiating anticipatory thermo-effector activity intended either to prevent the thermal challenge impacting on the body or to reduce the thermal consequences for the body if it does impact [5, 39, 57, 58, 113–116]. This proposition has a long history. When Huckaba et al. [56] introduced the idea of feedforward control in body temperature regulation, they were working under the conviction that there was a master controller for thermoregulation, that there was a single hypothalamic set point acting as the threshold for all thermo-effectors, and that all negative feedback originated from temperature receptors in the hypothalamus [3]. They conceived of feedforward control as a process to account for the then newly discovered influence of skin temperature in the control of human sweating [33, 34, 117]. The role of skin temperature receptors has been expanded beyond sweating and beyond humans, and its power expanded to the extent that it can ensure homeothermy in the face of environmental thermal challenges: "cutaneous thermal afferents elicit heat-defensive, autonomic effector functions in response to elevated environmental temperature to prevent increases in body core temperature" [113, p. 8850].

Although we contest that maintaining a constant core temperature is either possible or desirable [3], we agree with Romanovsky [6, 59] that skin temperature provides the control system with early ("pro-active") information about the thermal state of the body. That early information can be used to reduce deviations in core temperature under a thermal challenge. However, as we have argued above, we believe that the early information arises from fast negative feedback, and not from a feedforward process. We have two main reasons, one theoretical and one practical, for disagreeing with supporters of skin temperature involvement in a feedforward process. The theoretical reason relates to the nature of feedforward control: "to prepare for anticipated future changes" [54, p. 1]. By definition, feedforward control is anticipatory. Thermoregulatory feedforward control warns the body about the potential thermal effects of a challenge before the challenge actually has thermal effects on the body. However, skin temperature receptors are embedded in the skin. They work by detecting and reacting to the temperature (or rate of change of temperature) of the immediately surrrounding tissue however caused, including by ambient thermal conditions, but also, for example, by changes in peripheral blood flow. They are not activated until skin temperature has changed, so the challenge is not imminent but has impacted already.

The practical reason relates to the question of whether skin temperature receptors can give the thermoregulatory system a meaningful assessment of an environmental thermal challenge. A meaningful assessment is necessary because the magnitude and timing of the challenge will determine the strength and timing of the thermo-effector activity that is required. The protagonists for skin temperature receptors providing an assessment competent to initiate appropriate thermo-effector activity base their arguments on the proposition that "in thermoregulation, the disturbance (T_a [air temperature]) is detected in the periphery as skin temperature" [5, p. 7]. The only environmental thermal challenges considered are those that reflect as a change in air temperature. In the cold, skin temperature correlates well statistically with air temperature in humans and some other animals, but only in the absence of solar radiation. Skin temperature still may correlate with air temperature in animals with thick fur, feathers, or scales, and so skin temperature receptors may still be influenced by a change in air temperature in animals with a thick pelage, but the influence of air temperature on skin temperature will be weak [59], particularly in comparison to the effect of peripheral vascular changes. Also, in the cold, wind speed is a massive contributor to the magnitude of a thermal challenge, even at a fixed air temperature [109].

The greater problem, although, concerning the question of whether skin temperature receptors can give a meaningful assessment of an environmental thermal challenge relates to thermal challenges of heat, for which skin temperature receptors also are considered to provide anticipatory feedforward signals [113]. Threatening thermal challenges of heat arise much more from solar radiation and high water vapor pressure than they do from high air temperature [118]. In contrast with the situation in the cold, skin temperature in the heat correlates poorly with air temperature, at least in humans and other animals that use cutaneous evaporative cooling [119]. In near-naked men resting and exercising in a wind tunnel and sweating freely, mean skin temperature at a wet-bulb temperature of 24°C (not dangerous) was identical to that at a wet-bulb temperature of 34°C (dangerous) [120]. Skin temperature receptors would have had no capacity to warn the body of the danger.

Our doubts about whether "in thermoregulation, the disturbance (T_a [air temperature]) is detected in the periphery as skin temperature" might be resolved, at least for those thermal challenges defined by air temperature, by convincing experimental evidence that the neuronal activity of skin temperature receptors follows air temperature changes faithfully. Those who have proposed that skin temperature receptors generate a cue for feedforward control by detecting changes in air temperature do not seem to have provided such evidence. The landmark paper of Huckaba et al. [56] and the revival paper of Kanosue et al. [5] do not contain experimental data. In the keynote papers of Nakamura and Morrison [39, 113], for which the experimental animals were rats, the "trunk was wrapped with a plastic water jacket to cool and rewarm the skin".

There is no doubt that skin temperatures influence thermo-effector activity in both the heat and the cold. If, as we contend, generating a feedforward signal about an impending thermal challenge is not one of their functions, what is their role? The dynamic response of the receptors could initiate corrective thermo-effector activity as an environmental challenge impacts on the body, by the fast negative feedback mechanism that we have envisaged. Indeed, the consequences for thermo-effectors would be indistinguishable, probably, from the consequences of the anticipatory feedforward process proposed by others. However, that fast negative feedback could not control the thermo-effector activity, that is, determine its magnitude and time course, any more than feedforward control could do. The dynamic activity would be over in seconds or minutes while reattaining a steady state in the presence of the thermal challenge could take hours, especially in cold environments. Any influence of skin temperature receptors on sustained thermo-effector activity must be mediated by the static response of the receptors, that is how their firing rate changes with sustained change to their temperature.

We concur with those who have concluded that, in principle, the role of the static response of skin temperature receptors is no different to that of any other temperature receptors in the body, including sites in the body core: they contribute to an integrated signal that reflects whole-body temperature. It is the integrated temperature that is regulated, not the core temperature, and certainly not the skin temperature itself. That concept is far from new. In his 1973 paper, neurophysiologist Herbert Hensel said "the regulatory system tends to maintain the constancy of an integrated value of multiple temperatures more than that of a limited area of the body core", and followed that statement by "from the concept of a multiple-input system it follows that any temperature in the body that gives rise to a feedback signal is part of the controlled variable" [49, p. 988]. What he called the "controlled" variable would be called the "regulated" variable today (see [16] for a discussion of "controlled" and "regulated" variables in thermoregulation). The thermoregulatory system operates in a manner that achieves a new steady state under a thermal challenge, that is, when there is no net loss or gain of heat in the body. To achieve this goal, the system must assess what is happening to heat throughout the body, since heat may be stored in one body tissue but lost from storage in another tissue simultaneously. On its own, the skin is a large organ in mammals, and perhaps all vertebrates, and we do not think that the thermoregulatory system can ignore its thermal state. Also, as the schematic of Figure 3 shows, in cold conditions when there is very little peripheral blood flow, the peripheral "shell" can make up an fraction of the body mass far bigger than that of the skin itself. We cannot measure what the temperature of any receptors present in that peripheral shell is, but it will be closer to skin temperature than to core temperature. It is difficult to envisage how a thermoregulatory system could manipulate thermo-effector activity accurately enough to achieve a steady state without receiving any information about the rate at which heat is being stored or lost from that shell, particularly because, especially in the cold, the insulation provided by the shell delays the response of core temperature to an external thermal challenge. That is, the shell insulates the core from ambient conditions. To elaborate that point, consider a mammal swimming vigorously in cold water, for example, a fur seal in Antarctic waters [122]. To attain a thermal steady state, while dissipating the metabolic heat of muscular exercise and counteracting excessive heat loss to the cold water, the thermoregulatory system needs to assess whether the seal's body as a whole, including the shell, is storing heat or losing heat. So, as Romanovsky [59] put it: "the regulated variable in the thermoregulation system is an integrative, spatially distributed temperature signal, which incorporates deep (core) body temperatures (those of the brain and viscera) and shell (peripheral) temperatures (those of the skin and subcutaneous tissues)".

In Werner's model of thermoregulation [4], skin temperature is an intrinsic component of the regulated variable, as it was in the construct of Woods and Ramsay [7]. In the two-component simplification for quantifying the negative feedback signal, body temperature is calculated as $wT_{\text{core}} + (1 - w)\,T_{\text{skin}}$, where w weights for the relative influence of core versus skin temperature ($0 < w < 1$) in the integrated body temperature, confirming the legitimate role of skin temperature in the regulated variable [3, 16]. Some have argued that because core temperature is more stable than any peripheral temperature, core temperature must be the regulated variable. However, stability does not necessarily imply regulation. We have given the example of an insulated flask in a water bath; the contents of the flask have the more stable temperature, but it is the water bath temperature that is regulated [3, 123]. Nor is the concept that the thermoregulatory system seeks to attain or defend a core temperature valid [3]. It has been known for more than 70 years that, during exercise in humans, core temperature is not defended but stabilizes, in the steady state, over a wide range of thermal environments, at a level that depends on exercise intensity [124]. Core temperature is an emergent temperature of thermoregulatory processes, not a regulated or a target temperature of the thermoregulatory system [3].

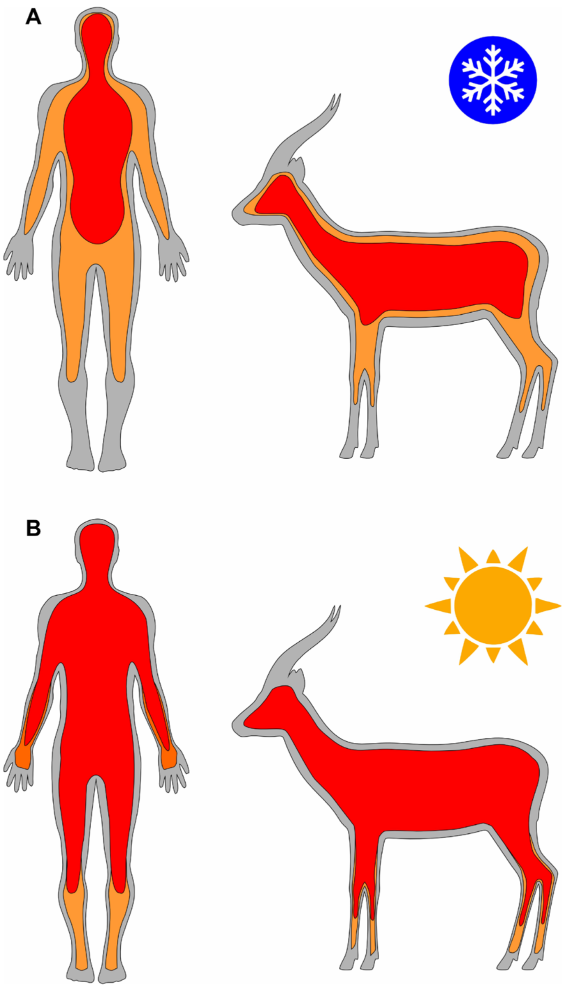

FIGURE 3 | Core and shell model of temperature distribution in a human and an antelope, with the relative size of the core and shell dependent on the degree of peripheral vasoconstriction during thermoregulation in the cold (A) and peripheral vasodilation in the heat (B). In the cold, the shell makes up a substantial part of the body mass, and its temperature cannot be ignored in the regulation of body temperature. In the heat, the shell is diminished, as would occur also during heavy exercise, but its temperature still cannot be ignored. Based on Romanovsky [6], but with the concept originating from Aschoff and Wever [121].

What still is lacking is an adequate anatomical and physiological description of how the input signal that conveys an integrated body temperature is constructed in thermoregulatory pathways. Those pathways must account for the role of skin temperature receptors not just in transient states following changes in the environment but also in steady states. An example is the role of skin temperature receptors in influencing steady-state sweat rate in humans [125], a role that clearly is not an anticipatory feedforward role. Some potential neural substrates for those pathways are known. Neural signals from temperature receptors in the core and skin converge on hypothalamic neurons presumably involved in controlling thermo-effectors [126, 127]. Recent research has revealed the neurobiological pathways responsible for the projections from skin temperature receptors onto hypothalamic neurons, at least in rats [39, 113]. However, how the full integrated signal is constructed remains unknown.

4 | Subsystems Within Systems

4.1 | A Thermoregulatory Subsystem Regulates Scrotal Temperature

As we contended in our introduction, thermal challenges to some body parts, apparently with special thermoregulatory needs, can produce anomalous changes in body temperature that seem to elude negative feedback control. Figure 4 is a diagram of the thermoregulatory control system that includes the concept of subsystems, not usually included in such systems-engineering diagrams, for which the regulated variable is not the integrated temperature of the whole body, but the temperature of a particular part of the body. The input to those subsystems includes information from temperature receptors that measure whole-body temperature, but also includes information from temperature receptors that measure the temperature of the specific part of the body for which the control subsystem is responsible. Since the temperatures that are regulated by each subsystem contribute to the integrated temperature of the whole body, thermo-effector activities that are implemented by one local subsystem can change the overall body temperature. The figure also endorses the concept of a separate system for each different thermo-effector activity, each of which acts autonomously. It assigns to all thermo-effector activities the common target of the regulation of body temperature. In the scenario depicted, the afferent signal, and so the regulated variable for each thermo-effector, is the same. For simplicity, the diagram does not depict the real possibility that the input signal might be different for each thermo-effector activity [3].

The best explored of such subsystems is the one responsible for the regulation of scrotal temperature. That subsystem functions to improve the stability of the temperature of the scrotal contents, the testes [129]. Scrotal temperature in rams can be more than 3°C lower than core temperature [60, 130]. Spermatogenesis is compromised by testicular hyperthermia, providing strong selection pressure for a system that regulates testicular temperature [131–134]. Lovegrove [135] contended that the scrotum evolved in mammals as the regulated level of body core temperature increased during the Cenozoic. In species that have an open inguinal canal that allows movement of the testes between the abdomen and scrotum, such as rats and rabbits, experimentally confining the testes to the abdomen caused the testes to degenerate [129].

The scrotal skin is richly endowed with temperature receptors, studied well in the rat [136–138], and those receptors contribute more to afferent thermoregulatory signals than the relative surface area of the scrotum would justify. In an operant conditioning paradigm, heating the scrotum of a pig in a cool environment, but not the same area of skin on any other part of the body surface, reduced the willingness of pigs to work for heat [139]. Heating the scrotum of rams has consequences for whole-body thermoregulation, inhibiting metabolic heat production and stimulating whole-body heat loss, including panting, such that core temperature can fall by as much as 2°C [13, 14, 60, 140], equivalent to or even exceeding the fall in core temperature that is observed under severe whole-body cold exposure.

In addition to contributing disproportionately to the input signal that stimulates whole-body thermo-effectors, the scrotum regulates its own temperature. It has sweat glands that are capable of reducing scrotal temperature substantially by local evaporative cooling [141, 142], including in humans [143]. A garment for cyclists that was designed to improve scrotal cooling significantly improved semen quality, even though it reduced scrotal surface temperature by <1°C [144]. There is also thermally induced control of the tone in the tunica dartos and cremaster muscles. Relaxation of those muscles lengthens the pampiniform plexus, increasing heat exchange between warmer arterial blood entering the scrotum and cooler venous blood leaving it, thus reducing the delivery of heat from the body core to the scrotum [145]. Tight male underwear, which interferes with scrotal relaxation, reduces semen quality [146]. Some of the afferent input for those thermo-effector activities comes from temperature receptors distributed around the body, so that whole-body warming causes relaxation of the tunica dartos muscle, but stronger input comes from the scrotal temperature receptors themselves. The subsystem behaves as if there is a reflex arc, but a local reflex arc is not the entire explanation, because the activity from the scrotal temperature receptors projects to the brain [137, 147, 148]. The control elements for the tone of the tunica dartos muscle are likely to be dedicated circuits in the central nervous system [149, 150]. Although there is a direct effect of local temperature on the contraction of the tunica dartos muscle that local activation cannot account for the changes seen in vivo [151]. The system achieves local control of scrotal temperature; heating the scrotum of rams at rest led to relaxation of the tunica dartos and cremaster and increased scrotal evaporative cooling, even though body temperature was not rising and core temperature actually was falling [60]. When the rams exercised on a treadmill, their scrotal temperature fell slightly (by about 0.3°C) while core temperature rose progressively by more than 1°C [60]. That local control can make scrotal temperature more stable than is core temperature.

Particularly illuminating for our understanding about how stable temperatures are reached by the thermoregulatory system is the effect of pyrogens on the scrotal subsystem [14, 60]. Rams given the pyrogen lipopolysaccharide developed the expected fever, with a core temperature rise of 2°C, but the scrotal temperature did not rise. The relationship between scrotal

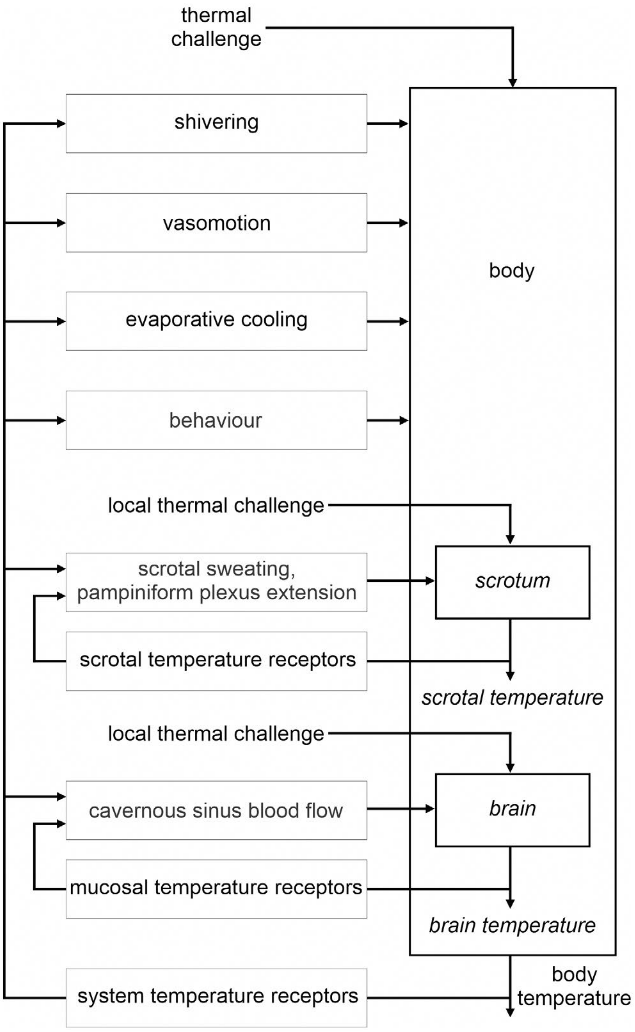

FIGURE 4 | Outline of a negative-feedback system that regulates body temperature, with parallel controllers of thermo-effector activity that affect whole-body heat exchange or distribution, and with two illustrative subsystems that are responsible for the regulation of the temperature of a specific part of the body (e.g., the regulation of scrotal temperature). The subsystems receive information about both overall body temperature and the temperature of the specific parts of the body. Any activity of thermo-effectors in a subsystem will affect the temperature of its part and also the whole body (e.g., scrotal evaporative cooling cools the scrotum, but also extracts heat from the body). Updated from Mitchell and Laburn [128].

temperature and the tone in the scrotal muscles was the same when the rams were febrile and afebrile. So, in the face of a pyrogen-induced change in set points elsewhere, the set points for thermo-effector activities of the subsystem responsible for scrotal temperature regulation did not change. In addition, there was no change in either the set point or the sensitivity of the relationship by which inputs from scrotal temperature receptors influenced breath frequency (panting) during fever, even though there was a change in the set point in the relationship between core temperature and breath frequency. This means that the neural circuits that regulate body temperature during fever can integrate afferent information from temperature receptors all over the body but can isolate the afferent information coming from scrotal temperature receptors. Thus, during fever, thermal protection of the testes is prioritized, at least in rams.

Thermal information from scrotal temperature receptors is unique in other ways too. Warming the scrotum of anesthetized rats, but not the warming of an equivalent area of other parts of the body surface, increased blood pressure, a response apparently unrelated to thermoregulation [152]. Thermal information from the scrotum is processed in a unique way in the central nervous system, which is equivalent to analogue-to-digital conversion. While the firing rate of neural afferents from the scrotum increases or decreases progressively with scrotal warming or cooling, the firing rate of neurons in the central nervous system that receive input from those scrotal afferents flips between low to high firing rate at a given scrotal temperature: there is no graded response [137, 153, 154]. So we think it unlikely that "information processing from the scrotum, is not a special system, but part of the general thermo-and noci-afferent system" [155, p. 181]. The scrotum has special thermoregulatory requirements that have no doubt resulted in strong selection pressure for a special subsystem that meets those requirements.

4.2 | Selective Brain Cooling Is Controlled by Its Own Thermoregulatory Subsystem

The brain is another part of the body that has special thermoregulatory arrangements, not because there is a special need to protect brain tissue from hyperthermia [156], but because of the special requirements for the control of selective brain cooling. Selective brain cooling is a phenomenon that is evident in artiodactyls, felids, and some other mammals that have a carotid rete, a vascular heat exchanger that lies within the venous cavernous sinus at the base of the skull [157]. Primates, including humans, do not have a carotid rete [158]. In the heat exchanger, arterial blood destined for the brain can be cooled by venous blood returning from evaporating mucosal surfaces of the nose and mouth. When selective brain cooling is implemented, hypothalamic temperature decreases, and more so in hypohydrated animals than in euhydrated animals [159]. Even in euhydrated animals, the decrease is enough to reduce the drive of hypothalamic temperature on sweating and respiratory evaporative heat loss, so reducing the rate of evaporative water loss and thus preserving body water [157, 159–161]. When selective brain cooling is switched off, which can happen in seconds under the influence of the sympathetic nervous system, hypothalamic temperature rises rapidly and activates evaporative cooling, resulting in a temporary reduction in whole-body temperature [156]. In bovids, selective brain cooling can be abolished, and the brake on evaporative cooling released, by high activity in the sympathetic nervous system, even though the result is a brain temperature that is several degrees higher than normal. Such activity in the sympathetic nervous system is associated with stressful situations, including intense exercise, as would occur in a predator–prey interaction [162].

The magnitude of selective brain cooling is determined primarily by the rate of blood flow in the *angularis oculi* and other cranial veins that convey blood from the evaporative mucosa to the cavernous sinus [163–165]. The inputs to the system that control that flow rate are complex and historically underappreciated. Originally, the input was considered to derive mostly from temperature receptors in the hypothalamus itself [166], providing the basis for a local control system with hypothalamic temperature as both the sensed and the regulated variable, much like the subsystem for the scrotum. However, it was later realized that the concept of hypothalamic temperature as both the sensed and the regulated variable created some issues with the stability of the control system: a rise in hypothalamic temperature would activate selective brain cooling, causing cool blood to flow to the heat exchanger, resulting in a fall in hypothalamic temperature, which would deactivate selective brain cooling by causing a decrease in the flow of cool blood to the heat exchanger, and so on, *ad infinitum*.

However, there is another possible mechanism of local control. Experimental manipulation of the temperature of the nasal mucosa in sheep showed that, above a threshold hypothalamic temperature of 39°C, blood flow in the *angularis oculi* vein, and consequently the magnitude of selective brain cooling, varied inversely with the temperature of the nasal mucosa [165]; the hotter the mucosa, the lower was the magnitude of selective brain cooling. The magnitude was lower not just because, with a warmer mucosa, the venous blood perfusing the cavernous sinus would be warmer, but also because the rate of blood flow from the mucosa to the sinus in the angularis oculi vein decreased. An advantage of that interaction between local temperature and selective brain cooling would be that the flow of venous blood to the cavernous sinus would be switched off if the temperature of the venous blood returning to the cavernous sinus was too high to cool the arterial blood in the carotid rete that was destined for the brain. This proposed local subsystem requires input from temperature receptors that respond to warming in the superficial nasal mucosa, and such receptors have not been found yet. Cold receptors have been found in the superficial mucosal tissue of cats and dogs [167], both of which are mammals that have a carotid rete, although the rete is rudimentary in dogs [168]. It is feasible that a decrease in input from cold receptors could account for the local effect of mucosa temperature on blood flow in the *angularis oculi* vein.

Inputs from the nasal mucosa are not the only inputs that are involved in the control of selective brain cooling. As with control of scrotal temperature, there is substantial input from temperature receptors elsewhere in the body [166], and also substantial nonthermal input into the control, the latter apparently related to the overall level of activity of the sympathetic nervous system. Indeed, in pigs, which exhibit potent intermittent selective brain cooling, there was no evidence for any thermal input to its control [169]. Congruent with the role of selective brain cooling in the saving of body water, a powerful input into the control subsystem arises from plasma osmolality, plasma volume, or some other variable that is associated with body water deficit. That signal is independent of core temperature, at least in sheep [161, 170].

The influence of the sympathetic nervous system on selective brain cooling occurs at the effector end of the control system, through cardiovascular activity that controls the rate of blood flow in the *angularis oculi* vein and other veins that convey blood to the cavernous sinus from the mucosa [163]. Where, in the nervous system, the control elements that interpret and integrate the inputs to the subsystem are, and how they operate, is not known. The control elements need to accumulate afferent activity from temperature receptors in the nasal mucosa and elsewhere in the body, and they need to integrate that thermal information with afferent activity related to hypohydration, giving priority to the nonthermal inputs that are related to body water balance. Although the control action of the subsystem is entirely cardiovascular, it is not necessarily confined to the control of the diameter of veins that drain from the mucosa and enter the cavernous sinus. For example, it may also act on the determinants of arterial blood flow to the head generally, and so act via manipulation of the pressure and amount of blood that is available to those veins [165].

Does the subsystem that is responsible for the control of selective brain cooling have an independent response to pyrogens, as does the subsystem that is responsible for the control of scrotal temperature? There have been very few investigations on selective brain cooling during fever, and those studies were done in animals of unspecified hydration status, before the effect of hydration status on selective brain cooling, or the role of selective brain cooling in the modulation of evaporative heat transfer, had been identified. Does the rise in core temperature that occurs during fever activate selective brain cooling in animals with a carotid rete, or does an upward shift in set point during fever inactivate selective brain cooling at high core temperature? Selective brain cooling was active during experimental lipopolysaccharide-induced fever in sheep [171] and during naturally acquired fever in free-living kudu *Tragelaphus strepsiceros* [172]. In goats injected with lipopolysaccharide, selective brain cooling was active in the second phase, but not the first phase, of the characteristic biphasic fever, although the sensitivity of the subsystem in that second phase was much lower than it was in afebrile goats [173]. In the one goat in which it was measured, the set point (threshold) for selective brain cooling was elevated during fever, just as was the set point for whole-body thermoregulation [173]. Similarly, in oxen at an ambient air temperature of 7°C, selective brain cooling was not evident in the first phase of a biphasic experimental lipopolysaccharide-induced fever, but was potent in the second phase [174]. Because of the absence of selective brain cooling in that first phase, hypothalamic temperature rose precipitously. In the goats, hypothalamic temperature reached nearly 41°C at an arterial blood temperature that would be associated with a hypothalamic temperature of 39°C in afebrile goats [173]. That high hypothalamic temperature may have accounted for the anomalous increase in respiratory rate that was observed in both the goats and the oxen, at a stage of fever generation during which respiratory evaporative heat loss should have been suppressed. So, although proper experiments still need to be done in animals of known hydration status, pyrogens appear to have an effect on the subsystem that is responsible for selective brain cooling that is different from the effect of pyrogens on whole-body thermoregulation, and also different from their effect on the subsystem that is responsible for the control of scrotal temperature. In the subsystem for selective brain cooling, pyrogens appear to increase the set point and to reduce the sensitivity.

4.3 | Are There Other Thermoregulated Subsystems?

There may well be other thermoregulatory subsystems that serve organs or tissues that have special thermoregulatory needs, with a regulated local temperature that is at least partially independent of body temperature. Although Schmidt et al. [175] thought that the temperature of the pectoral muscles was regulated in king penguins *Aptenodytes patagonicus* during dives, we believe that there is insufficient evidence to conclude that regional hypothermia in diving birds and mammals is a third example of thermoregulation by a local subsystem. There is no doubt that diving birds and mammals exhibit regional heterothermy, with some body parts having a temperature very different during dives than when the animals are on the surface [176–178], but it would require evidence other than just that the temperatures are different to conclude that a temperature is regulated. The avian brood patch is another possible example [179, 180]. If the brood patch is another thermoregulatory subsystem and has characteristics similar to those of the subsystems that have been identified, then we would expect it to have local temperature receptors and local thermo-effectors. We expect the subsystem to receive input not just from those local temperature receptors, however, but also from temperature receptors elsewhere in the body. Pyrogens may affect the subsystems in a way that is different from the way that pyrogens affect whole-body thermoregulation. We do not expect there to be a local regulatory center; we expect the integration of inputs and the activation of appropriate thermo-effector activity to be the responsibility of remote sites in the central nervous system. Identifying those neural sites and how they function will be a challenge. Neither the sites nor the mode(s) of operation of the regulatory centers are known for the two subsystems that we have identified.

5 | Conclusion

In this review, we reaffirm that negative feedback control is the dominant process by which body temperature is regulated. It is negative feedback that determines which thermo-effectors are activated, and by how much, when body temperature is stabilized under an environmental or metabolic thermal challenge. We point out that negative feedback is not intrinsically sluggish, as some others have suggested based largely on the assumption that it is core temperature alone that the thermoregulatory system regulates. Rather, we argue that negative feedback can be very fast. The feedback signal arises from temperature receptors distributed throughout the body, including the skin. We concur with those who have concluded that the thermoregulatory system regulates the integrated temperature of all body tissues.

We discuss how events can happen in the thermoregulatory system too quickly for even the fastest negative feedback to arrest body temperature deviations, or indeed before any change in body temperature has occured, such as behaviors that are implemented before a thermal challenge has impacted the body. The control system involved then is feedforward control, a powerful supplementary control system that aids in stabilizing body temperature. Implementing feedforward control requires the body to identify that a thermal challenge is imminent. There are many potential cues by which it could identify a challenge, but we disagree with those who consider that activation of skin temperature receptors is such a cue. Because feedforward is anticipatory, it does not monitor the outcome of its actions. Rather, it is feedback that monitors the outcome of any action that affects body temperature and so can inform the feedforward system of the success or failure of feedforward actions, allowing the accuracy of feedforward control to improve with experience. That does not mean that all thermo-effector activity is learned, however. If it all were learned, neonates would not be able to regulate body temperature, and they can do so. We would expect feedforward control to operate best in environments with predictable and highly stressful thermal challenges, like hot deserts.

We also discuss body parts that have unique thermoregulatory needs and which sometimes exhibit unusual thermosensitivity. That unusual thermosensitivity can override the negative feedback control of integrated body temperature, at least temporarily. We identify two such subsystems, namely those responsible for the regulation of scrotal temperature and for the phenomenon of selective brain cooling in animals with a carotid rete. We also discuss how local feedback loops involved in subsystem temperature control may be exempt from some broader thermoregulatory processes engaged in the regulation of integrated body temperature, notably in the response to pyrogens.

So this review has addressed three complexities of thermoregulatory function, namely the apparent sluggishness of control, more rapid attainment of a thermal steady state when feedforward control anticipates a thermal challenge, and local regulatory circuits. The view has been expressed that "Students and residents and physicians cannot get lost in details that are of interest only to the specialists. Which (sic) is the practical relevance of the "thermoregulation without a thermostat" model for somebody working in an emergency department and treating for instance a heat stroke? This is the important message to deliver; the details of the theory can be skipped" [18, p. 7]. It may be the case that physicians, veterinarians and those engaged in the welfare of sportspeople and military personnel can skip our details. However, we hope that we have made the details more accessible for those who cannot afford to skip them, namely the thermal physiologists whose research informs best practice.

While our review has extended thermoregulatory systems well beyond the operation of a simple domestic thermostat, there are other complexities and unknowns that still need attention. There is much to be understood with regard to circumstances in which there are changes in the parameters of the transfer functions, leading to sometimes more powerful, or more often less powerful, effector responses than expected by the thermoregulatory system. Those changes can occur because there have been programmed changes in the set point (threshold) or gain (sensitivity) of thermo-effectors, as occur during fever or hibernation, or with lifecycle events like menopause. Animals with a carotid rete can implement selective brain cooling, but whether or not they do depends on an interaction between the thermoregulatory system and the osmoregulatory system, as well as other systems such as the fight-or-flight activation of the sympathetic nervous system. It is not only in hypohydrated animals in the heat that thermoregulation may concede to the competing demands of other homeostatic processes. For example, thermoregulation may compete with the regulation of blood gases and with sleep. Animals, unconsciously, decide what priority to assign to the regulation of body temperature when that regulation requires resources that are shared with other systems that are seeking to maintain their own homeostasis. Sometimes, a thermal steady state still can be achieved in the face of that competition, but at a body temperature at which physiological processes do not function optimally. What physiological responses humans and other animals implement when faced with competitive threats to their homeostasis, and what the consequences are of those decisions, are tales still to be told.

Author Contributions

Duncan Mitchell: conceptualization, project administration, writing – original draft, writing – review and editing. **Shane K. Maloney:** conceptualization, writing – original draft, writing – review and editing. **Edward P. Snelling:** conceptualization, writing – original draft, writing – review and editing, visualization. **Robyn S. Hetem:** writing – original draft, conceptualization, writing – review and editing. **Andrea Fuller:** conceptualization, writing – original draft, writing – review and editing.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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