Journal of Thermal Biology 85 (2019) 102397

Contents lists available at ScienceDirect

Journal of Thermal Biology

journal homepage: www.elsevier.com/locate/jtherbio

The origin, significance and plasticity of the thermoeffector thresholds: Extrapolation between humans and laboratory rodents

Nigel A.S. Taylor[a,*], Christopher J. Gordon[b]

[a] Centre for Human and Applied Physiology, School of Medicine, University of Wollongong, Wollongong, NSW 2522, Australia
[b] 5018 Butternut Road, Durham, NC, 27707, USA

ARTICLE INFO

Keywords:
Evaporative heat loss
Non-evaporative heat loss
Thermoeffector thresholds
Thermogenesis
Sudomotor
Vasoconstriction
Vasodilatation

ABSTRACT

In this review, there is an overarching emphasis on the extrapolation of knowledge from one physiological regulator to another, with a particular emphasis on autonomic thermoregulation in humans and rodents. Through mammalian phylogenetics, one finds evidence for the gradual acquisition of an ability to maintain whole-body thermal stability, with discrete autonomic mechanisms arising for the generation, retention and dissipation of thermal energy. The sequential attainment of those thermoeffectors, over aeons, makes it unlikely that they are controlled by a common central processor, so the presence of a single activation switch is perhaps inconceivable. Instead, effector activation is associated with the arrival at lower and upper critical (threshold) body temperatures, with regions between those points defining zones of mammalian thermoneutrality. As thermal energy content deviates from thermoneutrality, there is a progression from purely passive (physical) heat exchanges through to autonomic (thermoeffector) recruitment. That activation is morphologically dependent, with an obligatory greater basal metabolic heat production evident in smaller individuals within both hypo- and normothermic states. Indeed, a first-principles, morphological case is presented for the existence of an effector recruitment cascade, with human observations providing the empirical support. That sequential activation is consistent with the presence of multiple central controllers, and both animal and human experiments supporting that possibility are reviewed. Finally, the case is presented that mammals possess multiple thermoreceptive fields, thermoeffectors with discrete neural pathways and several central, but independent, controllers of thermoeffector function. Those concepts are summarised in updated conceptual and neuronal models for human thermoregulation.

1. Introduction

Since "*temperature is the universal engine that affects all life processes*" (Gordon, 2012b: P. 286), then integrated physiologists are obliged to be conversant with both the principles of, and variations in, animal thermoregulation. In this regard, species can be loosely classified as thermal conformers or regulators, with respect to coincident changes in the temperatures of their bodies and their ambient environment. Whilst the body temperatures of conformers, including fish, amphibians and reptiles, generally track that of the *milieu extérieur*, those species use behavioural mechanisms (*e.g.*, thermotaxis [movement towards preferred ambient temperatures]) to maintain an optimal body temperature (Sullivan, 1954; Cowles and Bogert, 1944; Seebacher and Franklin, 2005). Mammals and birds are distinguished by utilising learned and well-developed behavioural, as well as acquired autonomic mechanisms, to defend a relatively stable thermal state (Hafez, 1964; Bligh, 1973; Crawshaw et al., 1985). The focus of this review is upon mammalian autonomic thermoregulation in general, but with a specific emphasis on the thermoeffectors utilised by humans and rodents to maintain stable body temperatures over a relatively wide range of ambient conditions.

In this contribution, our goal is to compare the differences, as well as exploring the similarities, between the thermoregulatory responses of laboratory mice and rats to those of adult humans. This information is crucial when biomedical researchers, working with rodents as their primary test species (animal model), are required to extrapolate and apply their observations to humans. While the mechanisms of thermoregulation in rodents are rarely the focus of such research, there are, nonetheless, treatment-induced changes in body temperature and thermoeffector activity that must be understood if one is to correctly predict human responses. For example, innumerable pharmaceutical preparations, genetic manipulations and induced pathological

* Corresponding author. Centre for Human and Applied Physiology, School of Medicine, University of Wollongong, Wollongong, NSW 2522, Australia.
E-mail address: nigelastaylor@gmail.com (N.A.S. Taylor).

https://doi.org/10.1016/j.jtherbio.2019.08.003
Received 2 June 2019; Received in revised form 5 August 2019; Accepted 5 August 2019
Available online 09 August 2019
0306-4565/

conditions in rodent models lead to changes in thermoeffector function and body temperature. It behoves researchers to assess how those thermoregulatory changes may influence data interpretation and applications to humans. On the other hand, human physiologists may observe a treatment-induced change in thermoregulation that requires the development of an animal model to replicate and study the mechanisms underlying that effect. In this case, they must understand how to extrapolate a thermoregulatory response in an 80-kg human to an animal several orders of magnitude smaller (0.03 kg). Hence, a review and analysis in which the temperature-dependent points of thermoeffector activation within humans and rodents are described, and their mechanistic relationships are discussed, is considered critical for biomedical researchers. Those points define the lower and upper limits of thermoneutrality, and they are known as the critical (threshold) temperatures.

1.1. The evolution and acquisition of mammalian thermoeffectors

As one moves up through the phylogenetic tree, it becomes apparent that a sequential overlaying of autonomically driven thermoeffectors has occurred across the animal *phyla*. That gradual acquisition commenced with the (primitive) behavioural strategies possessed by all sentient species, including some of the oldest (eukaryotic) life forms (Malvin and Wood, 1992), to defend body temperature or to avoid thermal stress (Cabanac, 1972; Nelson et al., 1984). Thus, a preference towards thermal stability is likely to have been a major driving force underlying the evolutionary heritage of all animals (Bligh, 1998).

The evolution of thermoeffector systems in birds and mammals most likely involved the utilisation of physiological systems that originally functioned for non-thermoregulatory purposes. For example, the cardiovascular system was refined to incorporate the control of non-evaporative heat exchange at the skin, the respiratory system provided an avenue for controlling evaporative heat loss (panting) and skeletal muscles could be activated asynchronously to produce heat (shivering thermogenesis). Of those, the first thermoeffector to appear probably involved cutaneous vasomotor activities that modulated peripheral heat exchanges (Templeton, 1970). That capability was already present in the ectotherms (Smith, 1979; Dzialowski and O'Connor, 1999), some of which also used behavioural strategies to take advantage of solar radiation and the thermal heterogeneity of their surroundings. The capacity to independently control blood flowing through their cutaneous vasculature was presumably acquired as reptiles evolved (> 300 million years ago; Carroll, 1970), thereby providing a mechanism through which thermal energy may be gained from and, to a lesser extent, lost to their ambient environment. Moreover, some reptiles also acquired an evaporative heat-loss mechanism; thermal panting (Tattersall et al., 2006).

To those attributes of the bradymetabolic amphibians and reptiles, mechanisms unique to the tachymetabolic endotherms (birds and mammals) were progressively added: non-shivering thermogenesis (Himms-Hagen, 1984; Jastroch et al., 2008; Nowack et al., 2017), shivering thermogenesis (Hohtola, 2004) and eccrine sweating for evaporative cooling (Jenkinson, 1973; Gelineo, 1964; Best and Kamilar, 2018). Since early egg-laying mammals (*monotremata*) evolved from amphibious reptiles > 110 million years ago (Phillips et al., 2009), it is reasonable to assume that they too possessed some level of cutaneous vascular control, although the control mechanisms may have differed considerably across species (Morgareidge and White, 1969). Nevertheless, the monotremes were endothermic, so the possession of cutaneous vascular control mechanisms provided a means through which they too could exchange thermal energy. The eventual appearance of *Australopithecus* (3–4 million years ago), which then gave rise to Old World monkeys, apes and humans (*catarrhini*) with their unique, whole-body distribution of eccrine sweat glands (Best and Kamilar, 2018), added another dimension to the existing evaporative heat-loss (thermolytic) mechanisms. As a consequence, evaporative cooling now existed in reptiles, birds and mammals (Robertshaw, 2006; Tattersall et al., 2006; Farmer, 2015).

Most endotherms inhabit climates that are cooler than their body temperatures, permitting passive (physical) heat dissipation. Therefore, the addition of an effective evaporative capability allowed those species to reside successfully in climates in which air temperatures exceeded those of the body tissues, particularly the skin, and thereby enabled heat loss, even when the prevailing thermal gradients would normally dictate heat gains. Rats and mice can survive for short periods in hot environments by increasing evaporative heat loss via the grooming of saliva on their fur and tail (Hainsworth and Stricker, 1971; Gordon, 1993). However, such a mechanism is inefficient for long-term survival in a hot environment.

On the other hand, primates, with well-developed eccrine sweating, can carry out their normal day-to-day activities without the restrictions that the constant grooming of saliva places on non-sweating rodents. Consequently, the capacity of primates to tolerate more extreme environmental conditions provided those species with the physiological possibility for migration beyond their temperate habitats. Perhaps the first human emigrants from Africa left about 70,000 years ago, and arrived in Sahul (the land mass encompassing Australia and New Guinea) over 65,000 years ago (Clarkson et al., 2017).

In the absence of definitive neurological evidence, we do not yet know precisely how the thermoeffectors of rodents and humans are controlled, although it is highly likely that mammals evolved similar mechanisms of thermal reception, along with the central processing and integration of that information (Bligh, 1998). But do all mammals use the same sensors (thermoreceptors) to detect variations in ambient conditions and heat storage? Did they evolve with, and retain, separate control centres and neural networks? Was each control mechanism simply added to an already existing network? Perhaps two were integrated, but not all three? We simply do not know how the random choices of natural selection transpired, and we shall return to this point subsequently.

What is clear is that some of those effectors, if not all, were borrowed from, and shared with, other regulatory functions (von Euler and Söderberg, 1958; Simon et al., 1986), rather than being bespoke mechanisms, for "*it would be unnecessarily burdensome to require the evolutionary process to create a new system to solve a problem already solved by an existing system*" (Satinoff, 1978: P 21). As a consequence of this evolutionary progression, rodents and humans acquired a battery of tools with which to regulate (defend) the temperatures of their body tissues. Those effectors formed the essential components of mammalian thermoregulation, which, unlike most other systems, appears to be a collection of scavenged structures controlled centrally, and integrated into pre-existing regulatory systems. Indeed, those systems may even exist within an hierarchical configuration, such that, within (Satinoff, 1978) and among the various regulatory systems (Taylor, 2015), the regulation of some variables may take precedence over others.

The evolution and hierarchical control of mammalian thermoeffectors are likely to have been driven by species-dependent variations in morphological characteristics, natural history, habitats, behaviour and so on. For example, a major morphological difference between humans and rodents is the relatively spherical shape of the latter, when compared to the elongated human form. The furless tails of rats account for only ~7% of their body surface area, yet it is a critical site for the vasomotor control of dry-heat loss (Lin et al., 1979; Gordon, 1990). Under ideal ambient conditions (*i.e.*, between the lower and upper critical ambient temperatures), it has been estimated that the rat can dissipate ~25% of its total metabolic heat production through its tail (Young and Dawson, 1982). Moreover, most rodents are nocturnal. They avoid temperature extremes by foraging at night when it is cooler, and when they are also less likely to be preyed upon.

When housed in a temperature-gradient enclosure that permits movement to a more comfortable ambient temperature, rodents prefer relatively warm temperatures in the day, but move into a cooler

environment at night, when they are most active (Gordon, 1994, 2012b; Hankenson et al., 2019). Hence, for nocturnal rodents, there is generally not a significant impediment to heat dissipation during their active phase. On the other hand, the relatively large, persistence hunters (our ancestors; Bramble and Lieberman, 2004) were diurnal, and forced to rely on both evaporative and non-evaporative heat-dissipation to rid themselves of excess body heat, particularly during the heat of the day.

The first to elaborate on how the various mammalian effectors were integrated into systems for the physiological regulation of the chemical and physical properties of the cells, and the surrounding extracellular fluid (the *milieu intérieur*), were Bernard (1879) and Cannon (1929). We now recognise that, among other variables essential to our survival, mammals regulate blood pressure, the partial pressures of respiratory gases, blood glucose content and the thermal status of their bodies. Those regulatory processes are imperfect, and, as a consequence of the continual exchanges of matter and energy across cellular and vascular membranes, we exist in states of dynamic equilibrium (Cannon, 1929; Vendrik, 1959; Prosser, 1964). When those exchanges are most stable, well-rested individuals have a somewhat constant (neutral) thermal state, as reflected in their mean body temperature (Worthing, 1941; Taylor et al., 2014b). Deviations away from that thermoneutral state result in the initiation of corrective behavioural and autonomic responses, as described by Giaja (Fig. 1: 1938; Andjus et al., 2016), and Hardy and Soderstrom (1938). Moreover, when behavioural thermoregulatory options are available, mammals will often choose a behavioural strategy, before activating the energetically costly autonomic responses (thermogenesis and thermolysis: Cabanac, 1972; Satinoff, 1974), although that precedence does not apply to the more subtle cutaneous vascular responses of humans.

Giaja (1938) was perhaps the first to provide a schema for thermoregulation, which included four regulatory zones. He also identified the lower and upper critical temperatures (Fig. 1: *température critique inférieure* [*supérieure*]). Hardy and Soderstrom (1938) contemporaneously described three regulatory zones. Unlike the present-day use of critical temperatures to identify thermoeffector switches (thresholds), the thermal boundaries of Giaja (1938) represented transitions into hypo- and hyperthermia, ending in states no longer conducive to life (*température de la mort*). Between the points of basal and peak metabolic rate, homoeothermia was suggested to have been achieved through thermogenesis, with thermoneutrality (*neutralité thermique*) accompanying basal metabolism. Herein, the following deep-body (core) temperatures have been assigned to define the various thermal states that exist in humans (Taylor et al., 2008a, 2008b) and rodents (Gordon, 1990; 1993, 2012b, 2017; Yang and Gordon, 1996): normothermia (humans: 36.5–37.0 °C; rats: 36.5–37.5 °C; mice: 35.5–36.5 °C); moderate (humans: 33.0–25.0 °C; rats: 34.0–25.0 °C; mice: 34.0–22.0 °C) and profound hypothermia (humans: < 25.0 °C; rats and mice: 20.0–16.0 °C); and moderate (humans: 38.5–39.5 °C; rats: 37.5–39.0 °C; mice: 37.5–38.0 °C) and profound hyperthermia (humans: > 39.5 °C; rats and mice: > 41.0 °C). Note that the temperatures for rodents typically reflect values measured during the daytime.

2. Thermoeffector thresholds

2.1. Thermoeffector switches: thresholds

In addition to endogenous thermogenesis (non-shivering and shivering), mammals modulate (sensible or dry) heat exchanges by varying cutaneous blood flow, resulting in changes to both tissue and ambient (microclimate) temperatures. Mammals also use evaporative heat exchanges (panting, salivation and sweat secretion) to cool their body tissues, but those exchanges do not modify microclimate temperatures (insensible heat loss). Instead, thermal energy is used to change water from a liquid into an its isothermal gaseous phase. Those thermoeffectors must now be added to Giaja's schema (1938).

Since natural selection almost invariably eliminated design inefficiencies, then we do not observe the simultaneous (single-switch) activation of the complete repertoire of behavioural and autonomic regulatory mechanisms to their full capacity when each critical temperature is reached. That is, a single switch (threshold) with on-off control does not exist. Instead, selection pressures favoured the acquisition of proportional control characteristics for mammalian thermoregulation (Burton, 1941; Hardy, 1961; Hammel et al., 1963; Werner, 2010; Stolwijk and Hardy, 2011; Wissler, 2018), as illustrated in a revised schema of human thermoregulation (Fig. 2: Werner et al., 2008), with evaporative and non-evaporative heat exchanges intensifying in proportion to body temperature changes.

Nevertheless, while Fig. 2 shows a clear separation of the lower (thermogenic) and upper (sudomotor) critical temperatures, it

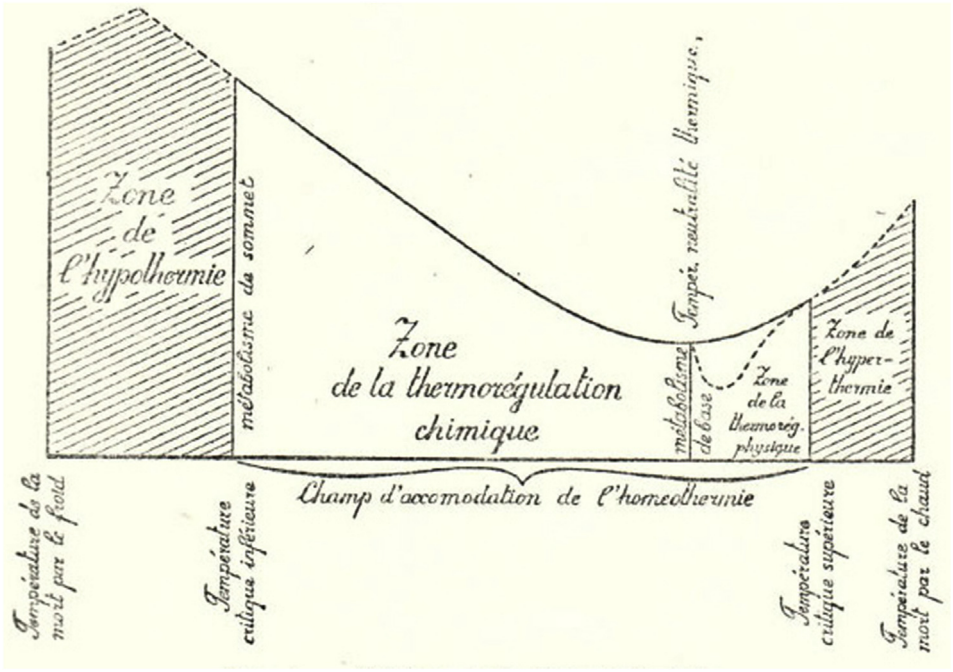


Fig. 1. A schema of thermoregulation (reproduced from Giaja, 1938). Translations (left to right): (a) *Température de la mort par le froid*: lethal temperature due to hypothermia; (b) *Zone de l'hypothermie*: region of hypothermia; (c) *Température critique inférieure*: lower critical temperature; (d) *Métabolisme de sommet*: peak metabolic rate; (e) *Champ d'accomodation de l'homéothermie*: region of homoeothermic accommodation; (f) *Zone de la thermorégulation chimique*: region of chemical (metabolic) thermoregulation; (g) *Métabolisme de base*: basal metabolic rate; (h) *Température neutralité thermique*: thermoneutral temperature; (i) *Zone de la thermorégulation physique*: region of physical thermoregulation; (j) *Température critique supérieure*: upper critical temperature; (k) *Zone de l'hyperthermie*: region of hyperthermia; and (l) *Température de la mort par le chaud*: lethal temperature due to hyperthermia.

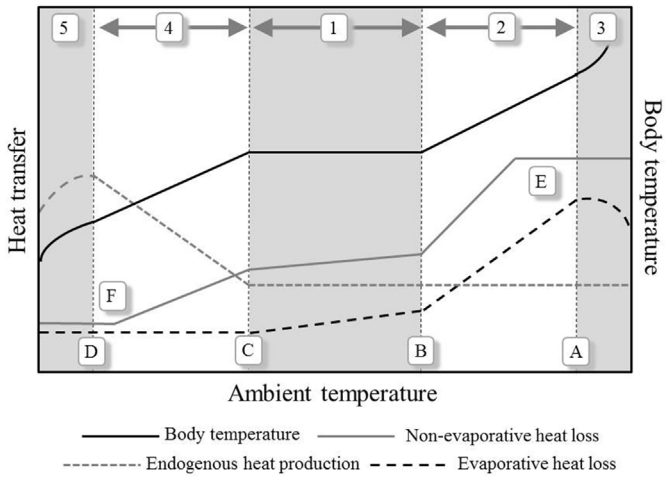


Fig. 2. Human thermoregulatory zones. The thermoneutral (cenothermic) zone (1) lies between the thresholds for sweating (B: upper critical temperature) and shivering (C: lower critical temperature), with the regions of sudomotor (2) and thermogenic regulation (4) situated beyond those critical points. Bordering those zones are the maximal limits of sweating (A) and shivering (D), beyond which thermoregulatory failure will eventually occur (zones 3 and 5, respectively). Plateaux E and F show maximal vasodilatation and vasoconstriction (respectively). This schematic is based on concepts first described by Giaja (1938), then embellished by Stanier et al. (1984), Bligh (1987) and Mekjavic et al. (2003), before being redrawn by Werner et al. (2008; reproduced with permission of ©Elsevier [all rights reserved]).

unintentionally implied the simultaneous recruitment of cutaneous vasoconstriction and thermogenesis (point C), as well as concurrent vasodilatation and sweating (point B). Those changes in thermoeffector function with ambient temperature raise many fundamental questions. For example, is there really a single switch (threshold) for each of those thermoeffector pairs? How do temperature changes in the deep-body and peripheral tissues contribute to the overall control of thermoeffector function? These questions are especially relevant for comparisons between humans and rodents. Typically, thermal responsiveness to central temperature changes predominate over peripheral sensitivity in smaller species (Gordon, 1993), which have a greater specific surface area (surface area-to-mass ratio; Royal Society, 1975). Thus, as body mass increases, thermoeffector activation tends to be more reliant upon changes in surface temperatures (Section 2.1.2).

2.1.1. The set-point concept

At this point, it is necessary to revisit set-point theory. Set points have been used in psychology and dietetics to imply that, following disturbances, humans are programmed to move back towards some predetermined level of well-being or body mass. Similarly, it was suggested that mammalian thermoeffectors are activated when body temperatures deviate from a fixed reference (set) temperature, and thereby creating an error signal (Hardy, 1961; Hammel et al., 1963; Nakayama et al., 1963). The thermal set point was deemed to be the preferred or regulated body temperature, with deviations in heat storage on either side of thermoneutrality eliciting autonomic responses designed to defend that temperature. Early proponents of the set-point concept used the thermostat, and the language of control-systems engineering (LaJoy, 1954; Hardy, 1965), to illustrate how, in the absence of sufficient empirical evidence, mammalian temperature regulation might operate and be simulated (modelled). Indeed, Hardy, a collaborator of Hammel, used his expertise in ventilation engineering to create a physical control analogue of physiological regulation, but, supposedly, he did not insist that the set point was the only way in which thermal homoeostasis could be achieved (Bligh, 1998). While Hammel (1972) claimed the concept to be defensible, he acknowledged that it awaited experimental proof, as it was currently "*unhampered by facts about how neurons act and interact upon each other to yield regulation*" (Hammel, 1965: P. 72). He also believed that the set point was not an invariant characteristic of the central regulator (Hammel, 1965, 1972).

Unfortunately, those simplifications, which were helpful at the time, are now widely agreed to have misled some physiologists by giving the illusion of knowledge (Cooper, 1972; Hensel, 1973; Werner, 1980, 2010; Bligh, 1998; Gordon, 2001; Mekjavic and Eiken, 2006; Kanosue et al., 2010). Nonetheless, the term 'set point' still remains in use (*e.g.*, Commission for Thermal Physiology, 2001; Cabanac, 2006), despite some 50 years of opposition. For a while, it was believed that a single set point existed for the activation of shivering and sweating (Cabanac and Massonnet, 1977), although those observations were eventually disproved (Mekjavić et al., 1991; Bligh, 2006). It has sometimes been implied (Fig. 2), if not directly stated (Benzinger et al., 1963), that the lower and upper critical temperatures represented thresholds (set points) for the simultaneous activation of appropriate thermoeffector pairs (vasoconstriction and thermogenesis; vasodilatation and sudomotion). The term 'set point' has also been used to refer to steady-state body temperatures accompanying zero heat storage (Commission for Thermal Physiology, 2001).

The theory of set-point thermoregulation is also confounded when one compares the stability of the deep-body temperatures in the large mammals, with those of smaller mammals, especially the rodents (Gordon, 2012a). With the development of radiotelemetry to monitor deep-body temperatures in undisturbed and unstressed mice and rats (Section 2.3.1.3), it is now clear that those temperatures exhibit marked variations (Fig. 3A and B). One wonders how the central regulatory mechanisms of small, thermally labile mammals might be responding to those natural temperature variations, if at all. If one compares the frequency distributions of the deep-body temperatures of mice and men (Fig. 3C), the very considerable instability of the former becomes evident. Those differences illustrate the challenges of comparing the thermoregulatory responses of small and large mammals, principally because the temperature of the most thermosensitive tissues (*i.e.*, the body core) is rarely stable in free-ranging, smaller mammals. In other words, if there is a set-point temperature, then one is compelled to conclude that considerable inefficiency must exist within the thermoregulatory systems of species that experience the continual waxing and waning of their deep-body temperatures. An alternative hypothesis is that those short-term oscillations are disregarded in small mammals, and that possibility can make inter-specific (inter-species) extrapolation exceedingly difficult.

Prior to telemetry, most deep-body temperature measurements in rodents were made using colonic probes, or surgically implanted devices and tethered measurements. Those techniques did not reveal the marked variations of temperature that occur in unrestrained rodents (Fig. 3), and that stands in marked contrast to the thermal stability of larger mammals (Kinahan et al., 2007; Taylor et al., 2014b). With that said, the characteristics of the rodent thermoregulatory system are most apparent when telemetric data are averaged over relatively long periods. For instance, if the deep-body temperature of unrestrained rodents is averaged over 12 h, one sees a regulatory pattern with clearly defined nocturnal and diurnal limits of normothermia (Fig. 4). How do those boundaries relate to a set point?

Notwithstanding some persistent confidence in the set-point theory, neurological and anatomical evidence for the existence of reference signals, or structures in which such information might reside, is lacking (Mitchell et al., 1970; Snellen, 1972; Werner et al., 2008), although Hardy (1965) hypothesised the existence of a reference in the form of thermally insensitive hypothalamic neurones (Nakayama et al., 1963); a concept that Boulant (2006) subsequently supported. However, it is unlikely that natural selection and control systems engineers would have arrived at the same solution for to mammalian temperature regulation (Partridge, 1982), even if neurones could transmit negative error signals (Bligh, 1998).

Indeed, both neural and control-systems mechanisms have been

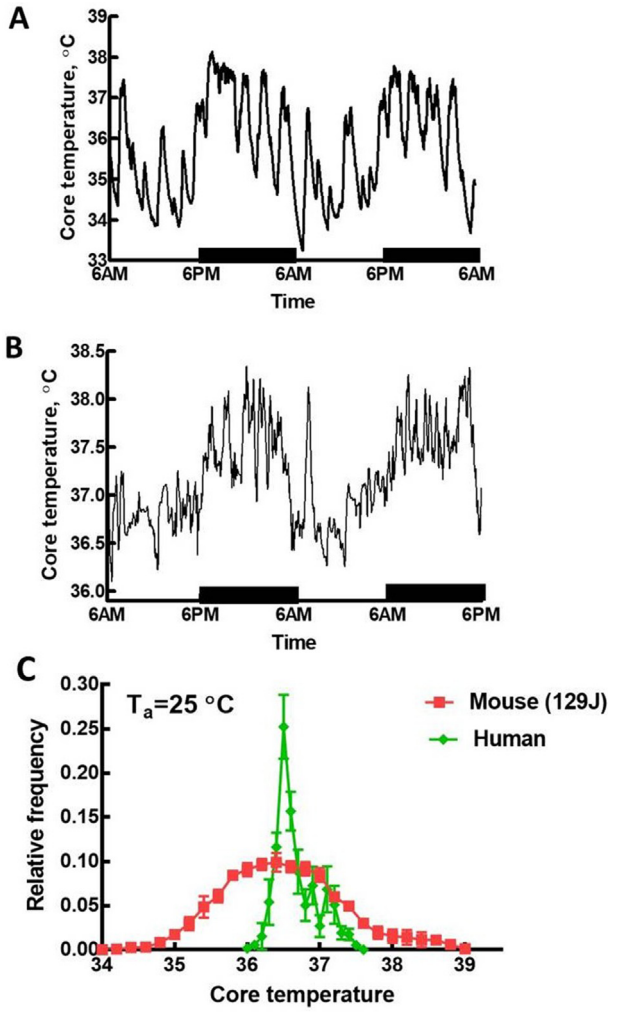


Fig. 3. Examples of the normal variability of deep-body temperature of a mouse (Fig. 3A; C57/Bl6) and rat (Fig. 3B; Long-Evans) when monitored using radiotelemetry (modified from Gordon, 2012,Gordon, 2012b and used with permission of ©Elsevier [all rights reserved]). Fig. 3C shows the frequency distributions of deep-body temperature, measured at 60-s intervals for 48 h, in one human (the narrower temperature range) and in mice (129J strain). Human data (unpublished) were collected using an ingested radiotelemetry pill. The mouse data were collected from surgically implanted radiotelemetry transmitters (modified from Gordon [2017] and used with permission of ©Elsevier [all rights reserved]).

hypothesised to explain temperature stability. From a neural perspective, a dynamic point of thermal stability was proposed to occur when feedback (afferent flow) from the counteracting warm- and cold-sensitive thermoreceptors was equal and opposite (Bazett, 1927, 1949; Vendrik, 1959; Mitchell et al., 1970). In addition, reciprocal cross inhibition can prevent the simultaneous activation of heat-loss and heat-production mechanisms (Bligh, 1976, 1998).

On the other hand, thermal stability can be achieved simply by the balance between the inherent properties of the controlled sub-systems (heat-transfer processes; thermogenesis, vasomotion and evaporation) and the controlling sub-systems (sensors, afferent and efferent pathways and control networks) in a feedback loop. Therefore, reference signals (set points) are not necessary within proportional, negative-feedback control systems (Werner, 1980, 2010). Instead, the gain of the controlling element, which is opposite that of the controlled system, results in the control loop converging towards the one (and only) state of compatibility. That point is the balance (or operating) point of the system (Werner, 1980, 2010), which can vary due to changes in the characteristics of either sub-system, and that interpretation replaces the view that "*two input signals with different temperature coefficients*" (Hensel, 1973: P. 950) were necessary to achieve negative feedback. Modifications to those characteristics can also alter the activation thresholds and sensitivities (or gains) of the thermoeffectors (Werner et al., 2008).

Subsequently, and as a result of either threshold or sensitivity changes, evidence will be presented that several thermoregulatory activation points exist. Moreover, those activation thresholds appear capable of independent movement (*i.e.*, they are not set points). Accordingly, use of the term 'set point' should be discontinued in thermal physiology, and replaced with the much less misleading term: 'thermoeffector threshold(s)' (Mekjavić et al., 1991; Mekjavic and Eiken, 2006; Werner, 2010; Romanovsky, 2018).

2.1.2. Morphological influences on thermoeffector recruitment

The sequential, phylogenetic acquisition of the thermoeffectors makes it unlikely that those effectors are controlled by the same central processor, so the possession of a single switch (threshold) becomes almost inconceivable (Satinoff, 1978). Since the autonomic effectors are only recruited when the passive (physical) heat exchanges (conductive, convective and radiative pathways), which are present even in inanimate objects, are overwhelmed, then a cascading recruitment of thermoeffectors may perhaps more closely reflect reality (Jessen and Ludwig, 1971; Satinoff, 1978; Kanosue et al., 2010; Notley et al., 2017; Romanovsky, 2018; Taylor et al., 2019). Furthermore, before the activation of either behavioural or autonomic strategies occurs, one's morphological configuration dictates the extent to which those physical heat exchanges can defend body temperature, so it is essential to revisit that principle.

This old, yet often misremembered, fact was a cornerstone of the ecological generalisations of Bergmann (1847; body mass) and Allen (1877; surface area), with respect to the dependency of animal body size on environmental temperatures. Those generalisations interact decisively with the first principles of thermodynamics; heat exchanges are functions of the size of existing thermal gradients and the physical characteristics (density, specific heat capacity, thermal conductivity) of objects and their ambient media. Since it is an object's volume that dictates its capacity to store thermal energy, whilst it is its surface area through which heat is exchanged, then morphological configuration has a pivotal influence on the potential for passive heat fluxes.

The allometrically configured bodies of mammals adhere to those principles. Furthermore, during growth, we experience disproportionate changes in our linear dimensions, surface areas and volumes (Schmidt-Nielsen, 1984), with the result being that smaller individuals have a larger specific surface area. However, there exist significant inter-specific variations within that generalisation. For instance, rodents are ball-shaped with relatively short limbs, with the forelimbs, hindlimbs and tail of mice accounting for ~21% of their body mass (M.A. Serrat, personal communication). On the other hand, the limbs of humans, notwithstanding those participating within the obesity epidemic, represent a much greater proportion of our total mass (~46%; Clauser et al., 1969; Plagenhoef et al., 1983), and contain about 60% of the total skin surface area (Tikuisis et al., 2001; Yu et al., 2010). Those morphological differences may have an impact on thermoeffector recruitment, but our understanding of that allometric relationship has, thus far, not been extrapolated to thermoeffector function, although some have started down that path (Taylor and Notley, 2018).

When in a normothermic state, tachymetabolic mammals, which typically have basal metabolic rates nearly ten times that of bradymetabolic species of the same body mass (Bligh, 1998), maintain an elevated enthalpy (total thermal energy content). This is reflected in their higher basal body temperatures, which are remarkably similar across healthy individuals within each species, regardless of changes in body size. However, the larger specific surface areas of smaller individuals, both within and among species, means they are better able to dissipate

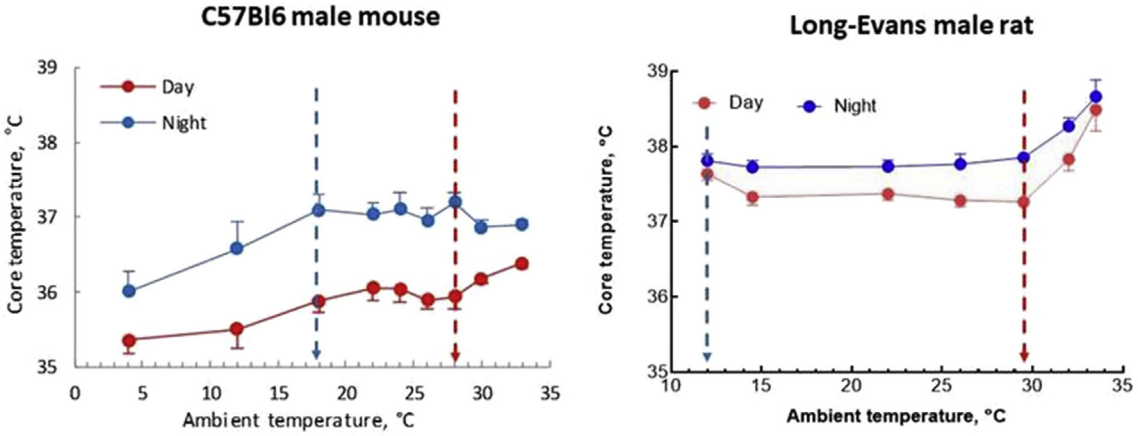


Fig. 4. The ambient temperature limits of normothermia for mice (Fig. 4A) and rats (Fig. 4B) monitored using radiotelemetry. Data were averaged separately over the 12-h light and dark phases. The dashed blue line indicates the lower limits of normothermia, although the lowest limit for the rat was not attained in that study. The dashed red line indicates the upper limits of normothermia. No upper limit was observed in mice at night. Mouse data were modified from Abreu-Vieira et al., (2015), while the rat data were extracted from Yang and Gordon (1996).

heat passively, even when heat conservation is required. Indeed, such heat loss is inexorable when ambient temperatures are less than body temperature. Therefore, according to the first ***Law of Thermodynamics***, the mass-specific basal metabolic rate required to offset those heat losses, and to regulate a constant body temperature, must be greater in smaller mammals. If different species regulate at dissimilar body temperatures under basal (thermoneutral) conditions, then those temperature variations can explain inter-specific variations in the mass-specific metabolic rate, with that linkage holding even when birds and mammals are compared (Clarke et al., 2010).

Consequently, under basal conditions, the relationship between mammalian metabolic rate (Y) and body size (X) is not a linear, but a power function ($Y = kX^b$; Rubner, 1883; Kleiber, 1932; Brody, 1945; Tanner, 1949; White and Seymour, 2003; White and Kearney, 2014; Bowes et al., 2015). The mechanistic explanation for that non-linearity resides in the presence of obligatory thermoregulation and allometric growth. While the size of the exponent is debated, the outcome is uniformly less than unity. Thus, increments in body size are accompanied by disproportionately smaller elevations in basal metabolic rate per unit mass. In other words, larger animals, due to their thermal inertia (Gordon, 2012a; Taylor and Notley, 2018), require progressively less metabolically produced heat to sustain normothermia in temperate conditions. Similarly, time-dependent heat losses from the centres of similarly shaped, heated objects of uniform composition will be non-linear, and slower in both heavier inanimate objects (French and Klopsch, 1926) and animals (Gordon, 2012a; Taylor and Notley, 2018).

When cold challenged, mammalian shivering and non-shivering thermogenesis are elevated. To evaluate the impact of that effect on animals of varying mass (0.025 g [sparrow] through to 10 kg [dog]), Heath et al. (1971) analysed the metabolic costs of defending the body temperatures of five homoeothermic species. They derived the metabolic effect of a body temperature reduction, and expressed that as a ratio of the metabolic response induced by a decrease in ambient temperature. The resulting quotients were higher for the larger animals. That is, those animals possessed a greater thermal inertia, so ambient cooling had a much smaller impact on body-tissue cooling. When those data were expressed relative to body mass, the relationship followed a power function ($mass^{0.57}$; Heath et al., 1971). Therefore, the non-linear relationship between metabolic rate and body mass applies to both normothermic and hypothermic states.

We shall now consider the impact of morphological differences on the cutaneous vascular responses to heat and cold stress, and changes in the distribution of blood from the deeper tissues to the limbs. Whilst less is known about the heterothermic nature of rodent limbs, and how that might affect thermal homoeostasis, it is well known that the furless tails of mice and rats provide a critical avenue for modulating heat loss, with tail blood flow abruptly increasing at ambient temperatures approximating the lower critical temperature (Rand et al., 1965; Young and Dawson, 1982; Gordon, 1990; 1993).

Human hands and feet can function in a manner resembling the ears of elephants (Phillips and Heath, 1992) and toucan bills (Tattersall et al., 2009); they are physiological radiators, as well as having insulative and evaporative capabilities (Taylor et al., 2014a). In the heat, cutaneous vasodilatation is extensive, and can reach 7–8 L min^{-1} in humans (Rowell et al., 1970). Similar responses have been observed in baboons, with pronounced changes found in the limbs and tail, and particularly in their most distal segments (Hales et al., 1979). The same occurs in humans (Caldwell et al., 2014). In cooler states, limb blood flow is reduced (Caldwell et al., 2016), with significant counter-current heat exchanges between the arteries and veins of the limbs helping to conserve body heat in mammals (Scholander and Krog, 1957; Weinbaum et al., 1984). During more extreme cold, hand and foot blood flows are reduced to levels below the local metabolic requirement (Abramson, 1965), resulting in a physiological amputation to ensure overall survival (Forster et al., 1946; Caldwell et al., 2014; Taylor et al., 2014a), but often at the expense of the peripheral tissues (Golden et al., 2013). Those mechanisms are not easily extrapolated to rodents.

Phillips and Heath (1995) extended our understanding of the interaction of body size with those cutaneous vascular responses using infrared imaging. They analysed the impact of body size on the surface temperatures of 29 mammalian species (20 g [mouse] to 4000 kg [elephant]). Surface temperatures determine ambient heat exchanges, and are influenced by cutaneous blood flow, piloerection and variations in the exposed (effective) surface area. Estimates of the reliance upon cutaneous vasomotor activity (the vasomotor index) to dissipate heat were derived from basal metabolic rate, effective surface area, and the difference between the basal deep-body and the lower critical temperatures (Phillips and Heath, 1995). That vasomotor index also revealed a morphological dependency (Fig. 5), as it scaled positively and non-linearly with variations in the mass of each species. Thus, larger species, and presumably also larger individuals within each species, are better able to modulate heat loss through peripheral mechanisms; cutaneous blood flow, piloerection or varying their effective surface areas. On the other hand, smaller individuals were forced to rely more on heat production to offset transcutaneous losses; they are the "*metabolic specialists*" (Phillips and Heath, 1995; P. 288). This is not to imply that rodents do not utilise peripheral vasomotor control over heat loss. Instead, it puts that role into perspective.

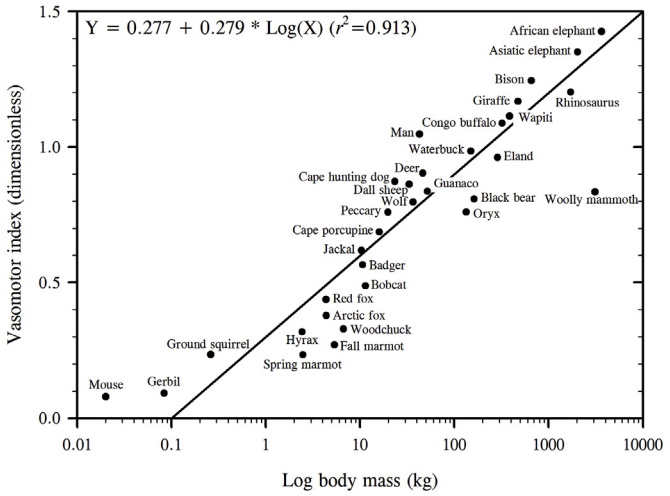


Fig. 5. The morphological dependency of cutaneous vasomotor activity (vasomotor index) on body mass in terrestrial mammals. The vasomotor index was calculated from basal metabolic rate, the effective surface area of each animal and the temperature difference between the normothermic deep-body and the lower critical temperatures. Modified from Phillips and Heath (1995) with permission of ©Elsevier (all rights reserved).

What happens when metabolic heat production displaces body temperatures into regions slightly warmer than preferred? Passive heat-loss pathways immediately start to dissipate excess thermal energy. If the thermal forcing function is gradual, then (passive) transcutaneous heat losses may obviate the need to activate autonomic regulatory mechanisms, particularly for individuals with a larger specific surface area. However, if the forcing function is slightly more powerful, physiological defences will be activated. If thermal stability is successfully defended, then the elevated metabolic rate is said to have been physiologically compensated (Belding and Hatch, 1955).

During such thermal compensation, both rodents and humans rely on cutaneous vasodilatation and evaporative cooling to minimise heat storage, with the latter being resource wasteful in the longer term, and potentially life threatening, although it is very effective for humans. The engineering efficiency of natural selection leads one to the, not necessarily novel, prediction of an autonomic recruitment progression in humans, commencing with vasodilatation and progressing through to sweating, but only if required. The conceptual novelty of this reality comes from the possibility that the progression is slower, or even incomplete, in people with larger specific surface areas. Consequently, there exist first-principles bases upon which one would expect to observe more than one thermoeffector threshold, with a possible cascade of progressively more powerful heat-loss pathways being activated as physiological strain increases (Jessen and Ludwig, 1971; Satinoff, 1978; Kanosue et al., 2010; Romanovsky, 2018). It is also possible that the recruitment and progression through those autonomic mechanisms is morphologically dependent.

That proposition was recently re-examined in two human experiments, although linkages between the vasomotor and sudomotor responses and morphological configuration have long been known (Wyndham et al., 1964; Docherty et al., 1986). In the first study (Notley et al., 2016), an homogeneous sample of males (N = 36), selected across a wide range of body sizes (specific surface area range: 232.3–292.7 $cm^2\,kg^{-1}$), was investigated in temperate conditions (28 °C, water vapour pressure 1.36 kPa) during steady-state rest (20 min) and exercise (45 min cycling). Those conditions were physiologically compensable. Participant selection was such that, regardless of body mass (range: 56.3–94.2 kg), all were habitually and similarly active, and all had similar levels of adiposity. In addition, matched, clamped and area-specific metabolic heat-production rates were used (light: ~135 $W\,m^{-2}$; moderate: ~200 $W\,m^{-2}$), resulting in equivalent heat-loss requirements and mean body temperature changes being elicited across all participants. That experiment confirmed the morphological dependency of thermoeffector reliance, with cutaneous vasomotor modulation of heat loss being more effective in smaller individuals (larger specific surface area). Conversely, cutaneous vasodilatation was less effective in the larger subjects, forcing a progression to, and a greater dependence on, sweating and evaporative cooling.

That observation represents the other side of the coin described by Phillips and Heath (1995; Fig. 5). That is, larger individuals (species) can more easily prevent unwanted heat loss via peripheral mechanisms that take advantage of anatomical (fur) and physiologically variable insulation (cutaneous vascular compensation), but it is more difficult to lose excess heat unless they can recruit evaporative cooling mechanisms. Fortunately, humans are endowed with a huge capacity for evaporative heat loss, and that ability enabled our hominid ancestors to hunt (persistence hunting; Bramble and Lieberman, 2004) and forage during the heat of the day in the African savannahs.

In another experiment (Notley et al., 2017), hormonally standardised women (N = 24) were investigated, using the same selection criteria and identical methods, with their results analysed with those of the males from the first project (N = 60). Now, regardless of gender, heat loss via cutaneous vasomotor modulation was again more effective in the smaller individuals, with larger subjects relying more on evaporative cooling. Indeed, after accounting for morphological differences across subjects, gender explained < 5% of the variability in the thermoeffector responses, which were largely morphologically determined.

Those outcomes are important, since whilst men and women differ in so many ways, from a thermoregulatory perspective, we can have confidence that the recruitment of heat-loss effectors is determined by similar mechanisms, with morphological configuration having a direct, but gender-independent, influence on the extent that different individuals rely upon those thermoeffectors. Moreover, it follows that, within physiologically compensable states, humans recruit only the effectors necessary to satisfy their immediate regulatory requirements, with a reliance upon passive heat-loss pathways preceding autonomic recruitment, and with sudomotor activation occurring only if vasodilatation is unable to keep pace with heat production. Thus, evidence exists for the presence of a thermoeffector recruitment cascade. Since the need to recruit those effectors is largely morphologically determined, then it is reasonable to conclude that attempts to explain thermoeffector control, without also examining body size, may yield incomplete, and possibly misleading experimental outcomes.

2.2. *Which afferent signals are responsible for thermoeffector activation?*

"*There is no single temperature which could be called the 'controlled temperature'*" (Brück et al., 1970: P. 170). Nevertheless, primacy of the hypothalamic thermoreceptors was claimed for determining thermoeffector activation (Benzinger et al., 1963; Burton, 1963; Nakayama et al., 1963; Hammel et al., 1963), with dominance further implied through the widely adopted convention of reporting deep-body temperature thresholds for those effectors. Such approaches might seem dismissive of the extensive neural networks linking the extra-hypothalamic central and peripheral receptors to the central nervous system, almost as if they were vestigial structures.

Why would natural selection have retained such vast interconnections if they were not functional? Certainly, there is convergence of those peripheral signals *en route* to the hypothalamus and somatosensory cortex (Wit and Wang, 1968; Hellon, 1969), but they do reach those destinations (Egan et al., 2005; Nakamura and Morrison, 2008, 2010). Therefore, they must form part of the thermally regulated body mass (Snellen, 1966; Brown and Brengelmann, 1970; Hensel, 1973; Satinoff, 1974; Simon, 1974; Jessen, 2011) that, through negative feedback to the hypothalamus, determines the thermoeffector thresholds, and continually modulates that activity (Robinson, 1949; Savage and Brenglemann, 1996; Farrell et al., 2013, 2015). Some have

described thermoafferent flow from the periphery as being of an exclusively feedforward nature (*e.g.*, Savage and Brenglemann, 1996; Romanovsky, 2007; Kanosue et al., 2010). Whilst that is the correct term when referring to structures in which there is no physiological modulation of local temperatures, or that are used to discriminate between innocuous and potentially harmful thermal stimuli, it may (unintentionally) imply that the associated autonomic responses, and the resultant peripheral tissue temperature changes, are not of a thermoregulatory origin.

To avoid possible confusion, 'feedforward' will be reserved for describing efferent signals generated within the central nervous system that, independently of existing regulatory mechanisms, travel via sympathetic pathways (corollary discharge) to activate effector organs and structures in preparation for a higher level of activation ('central command': Krogh and Lindhard, 1913; Eldridge et al., 1981; Vissing and Hjortsø, 1996; Shibasaki et al., 2003, 2005). For example, at the commencement of exercise, parallel messages are sent to the skeletal muscles (motor commands) and to the organs that support their heightened metabolic requirement (feedforward).

Mammalian thermoregulatory systems have multiple sources of thermal feedback that collectively provide feedback concerning the thermal state of the entire body (mean body temperature: Bligh, 1998; Morrison and Nakamura, 2011). Thus, "*the concept of a particular controlled variable (e.g., hypothalamic temperature) is untenable*" (Bligh, 1976: P. 939). Instead, like all sensory mechanisms, there is continual feedback to the central nervous system, most of which goes without eliciting a response, unless there is some minimal change in the thermal *status quo*. When that occurs, the relative importance, as well as the interplay, of the various thermosensitive regions is dictated by the magnitude, rate and location, of those temperature changes (Hensel, 1973; Simon et al., 1986, 1998; Boulant, 2011; Pierau, 2011).

The term 'mean body temperature' is used to reflect the combined peripheral and deep-body thermosensory feedback, as well as the enthalpy of the body, although it is improbable that both components can be adequately reflected within a single value. The latter is most realistically estimated via whole-body calorimetry, the absence of which makes it very difficult to estimate mean body temperature (Bazett, 1949; Taylor et al., 2014b). Thermometric derivations are approximations (at best) derived from weighted combinations of deep-body and mean skin temperatures, with changes in the mixing coefficients used to reflect variations in the distribution of blood between the deep-body and cutaneous tissues when moving away from thermoneutrality (*e.g.*, Hardy and DuBois, 1938; Vallerand et al., 1992a, 1992b). That two-compartment approach is based on the assumption of somewhat uniform deep-body temperatures, along with the parabolic thermal gradient observed when moving towards the thermally less uniform skin surface (Burton, 1935; see Taylor et al. [2014b] for a detailed discussion).

With regard to whole-body thermosensory feedback, it is recognised that local thermal energy content is transduced into neuronal signals that arise from the deep-body and peripheral tissues. An approximation of that afferent information may be obtained from the mean body temperature, for it is assumed that those central and peripheral signals participate in both our sensory awareness and autonomic thermoregulation. Thermal modelling has also been used to approximate probable thermoafferent flow into the central thermoregulatory networks (Werner et al., 1989). Whilst the compartmental weighting coefficients for this combined information varies across thermal conditions (as noted above), they should be adapted to reflect differences in thermoreceptor density and regional thermosensitivity, when valid empirical evidence exists.

Whilst attempts have been made to evaluate differences in regional cutaneous thermosensitivity that might be used (in humans) to derive a mean skin temperature that better reflects thermoafferent flow (Nadel et al., 1973; Crawshaw et al., 1975; Libert et al., 1984; Patterson et al., 1998; Cotter and Taylor, 2005; Burdon et al., 2017), only one group used thermal clamping to negate the confounding influences of thermal feedback from the non-treated skin regions (Patterson et al., 1998; Cotter and Taylor, 2005; Burdon et al., 2017). Those experiments involved localised heating and cooling in the presence of deep-body and mean skin temperature clamps, and revealed that variations in the cortical representations of different body segments (the somatosensory homunculus) did not match either thermal sensations or autonomically mediated sweating or cutaneous blood flow, at least within the mild thermal domain. Thus, there is, as yet, no convincing human evidence to support replacing an area-weighted summation of local skin temperatures with cutaneous thermosensitivity coefficients.

2.3. One threshold or a thermoeffector recruitment cascade?

Mammalian homoeothermy has resulted from a unique combination of tachymetabolism, a dependence of metabolic rate on body size, appropriate behavioural responses to combat excessive heat gains or losses, and the possession of capabilities to autonomically modify heat production, cutaneous insulation and heat loss (Bligh, 1998). Mammals also have thermal sensors located throughout their bodies, which that can influence the functional states of several different thermoeffectors. Mammals also possess a multitude of neural pathways, at least at the receptor and effector levels (Jessen, 2011; Pierau, 2011; Blessing et al., 2016), but do those pathways feed into, and leave from, a common central controller? Evidence consistent with that possibility would be the observation of a common activation switch (threshold) for all thermoeffectors, or perhaps for each effector pair.

However, it has long been acknowledged that the thresholds for the heat-loss and heat-production effectors are not identical (Burton and Bazett, 1936; DuBois, 1939; Brück et al., 1970; Jessen and Ludwig, 1971). It was once even thought that vasodilatation was triggered by a humoral agent(s) released from active sweat glands (Fox and Hilton, 1958). Nevertheless, experimental data did not always support the existence of discrete thresholds (Benzinger et al., 1963; Cabanac and Massonnet, 1977), presumably due to measurement resolution limitations. However, the regulation of body temperature around a single threshold would be "*energetically costly, and perhaps physiologically unnecessary, since sweating and shivering need not be initiated as soon as a displacement … is sensed*" (Mekjavic and Eiken, 2006: P. 2071). Thus, the natural selection of such control was unlikely, and this is exemplified within the waxing and waning of rodent deep-body temperatures (Fig. 3).

Jessen and Ludwig (1971) provided perhaps the first physiological demonstration (anaesthetised dogs, $N = 2$) for the separation of the heat-production and heat-loss thresholds, with a definite zone of separation (hypothalamic temperature range < 1 °C). It is noted that anaesthesia widens the zone of thermoneutrality, as do some hypothalamic ablations (Keller and McClaskey, 1964), but widening should not occur if those effectors were recruited at a common temperature (point). Conversely, Cabanac and Massonnet (1977), using sequential heating (38.8 °C) and cooling (28 °C) in water baths to clamp skin temperatures (humans, $N = 6$), reported identical deep-body (oesophageal) temperature thresholds for heat production (37.34 °C) and heat loss (37.32° and 37.38 °C), and concluded that those activation points were superimposed. That is, they could not identify a zone in which neither shivering nor sweating was present (a "*dead band*") in humans. Nonetheless, they suggested that "*vasoconstriction was complete, before the onset of shivering*" (P. 587), although their Table 1 did not necessarily support that interpretation; the respective effector thresholds were 37.30 °C and 37.34 °C. With measurement resolution to the second decimal place being doubtful, one is tempted to attribute those differences to statistically significant, but physiologically inconsequential observations. Since two different water temperatures were used, then two different skin-temperature clamps were applied. In such circumstances, given the impact of skin temperature on thermoregulation, it becomes difficult to interpret those deep-body temperature

thresholds.

Discrepancies between the observations described by Jessen and Ludwig (1971) and Cabanac and Massonnet (1977) prompted Mekjavić and Bligh (1989) to replicate the latter experimental treatments, to which they added exercise (humans, $N = 7$). Whilst sudomotor thresholds were evident, shivering thresholds could not be detected. Therefore, Mekjavić et al. (1991) repeated the experiment (humans, $N = 9$), but now with participants exercising in water (28 °C) until steady-state sweating was established, then resting until shivering was clearly present (passive cooling). In that study, the thermal clamping of skin temperature persisted throughout each trial. During progressive cooling, the deep-body (oesophageal) temperature thresholds for thermogenesis (36.95 °C) and sudomotor deactivation (37.42 °C) were identified, with a clear separation (range 0.03–0.71 °C [recalculated from their Table 2]). Those authors described that neutral region as a "*null zone*". Unfortunately, only Cabanac and Massonnet (1977) had attempted to evaluate the cutaneous vascular response, so a further investigation was warranted.

2.3.1. Discrete thermoeffector thresholds

The most recent human evaluation of thermoeffector thresholds involved all three effectors (Caldwell et al., 2011, 2015; Taylor et al., 2019). In those experiments, critical temperatures for the cutaneous vasomotor (finger, forearm, calf) and whole-body thermogenesis, as well as those for the secretion of both precursor (primary) and discharged sweat (finger, forearm, forehead), were identified in resting, normothermic individuals ($N = 8$) during separate passive (forced) cooling and heating trials. Those trials were performed following whole-body immersion in thermoneutral water (two normothermic, control trials), warm water (pre-heating followed by passive cooling) and cool water (pre-cooling with passive heating). Heat losses and gains were achieved by manipulating the temperature of water circulating through a purpose-built, water-perfusion suit, as well as the air temperature. Under those conditions, both the skin and deep-body temperatures were modified, with data from the normothermic trials enabling the identification of two distinct thermoregulatory zones referenced to mean body temperature (temperature-specific, weighted combinations of oesophageal and mean skin temperatures).

In the first instance, the vasomotor zone was identified between the initiation of pronounced cutaneous vasoconstriction and vasodilatation (Fig. 6), and defined by distinct lower and upper critical temperatures derived during the control trials. That region has also been called the thermoneutral zone (Hardy and Soderstrom, 1938; Mekjavić et al., 1991; Bligh, 2006; Mekjavic and Eiken, 2006; Werner et al., 2008), although Mekjavic and Eiken (2006) appeared to base their theoretical definition on the attainment of maximal vasomotor activity. Since the cutaneous vasculature is continually active throughout the normothermic range, particularly in the hands and feet (Bazett, 1949; Taylor et al., 2014a), and since the points of maximal constriction and dilatation often remain unknown due to the dependence of cutaneous vascular conductance on a unique combination of deep-body, mean skin and local tissue temperatures (Caldwell et al., 2014, 2016), then perhaps those definitions were imprecise. Accordingly, using a definition based on the initiation of non-basal vasomotor activity (overt constriction or dilatation), the vasomotor zones for three different body segments, derived from simultaneous measurements using two different techniques, spanned a mean body temperature range of 3.7 °C (standard error of the mean [±] 0.1 °C; Fig. 6; Taylor et al., 2019). Bligh (1976) had originally suggested that "*no such threshold operates on the pathway to PVMT* [peripheral vasomotor tone]" (P. 938), but he did not retain that view (Bligh, 1998).

Secondly, the region bordered by the onset of whole-body shivering and the production of precursor sweat was derived for three body segments (Fig. 6; Taylor et al., 2019). This is the inter-threshold zone (Brück et al., 1970; Mekjavic and Eiken, 2006). To increase the precision of the upper threshold detection, precursor sweat measurements were used. That index more closely reflects the time at which cholinergic activation occurs, since high rates of electrolyte and (obligatory) water reabsorption within the distal sweat duct can prevent the appearance of discharged sweat (Sato, 1977; Machado-Moreira et al., 2015).

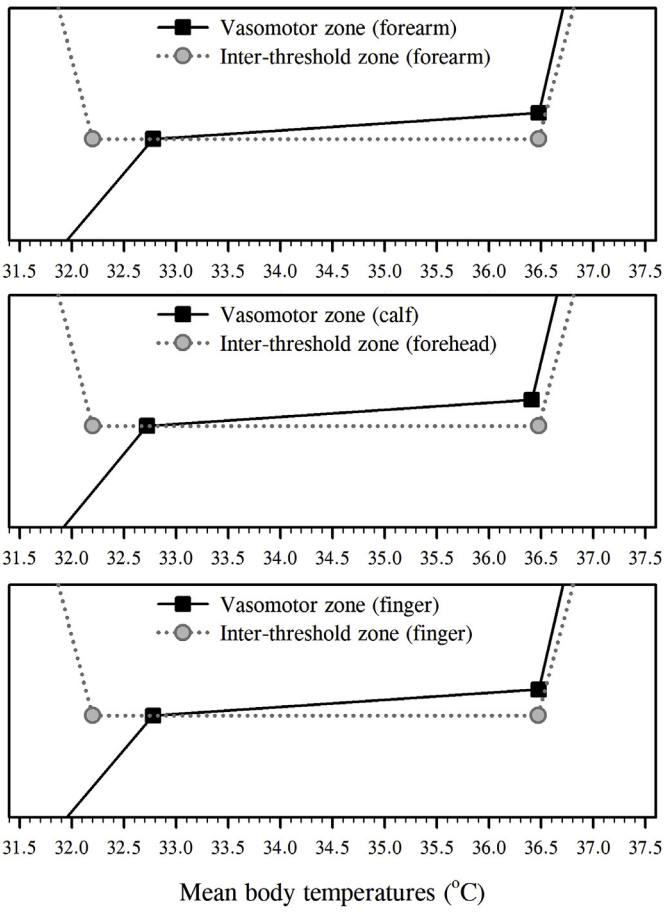


Fig. 6. The vasomotor (thermoneutral) and inter-threshold zones of resting (supine) adults during separate trials of passive cooling and heating (data extracted from Taylor et al., 2019). The vasomotor zones were derived from the mean body temperature thresholds for pronounced vasoconstriction and vasodilatation, with those points determined from changes in vascular conductance, simultaneously measured from three body segments (forearm [laser-Doppler flowmetry], calf and finger [venous-occlusion plethysmography]). The slope on each vasomotor zone is a qualitative reminder that the cutaneous vasculature is not quiescent, even under thermoneutral conditions. The inter-threshold zones were defined by the thresholds for shivering thermogenesis (increased whole-body oxygen consumption) and the production of precursor (primary) sweat, and simultaneously measured from the forearm, forehead and finger (skin conductance).

On average, those inter-threshold zones covered a mean body temperature range of 4.3 °C (± 0.1 °C; Fig. 6; Taylor et al., 2019). Thus, the inter-threshold zone was 0.54 °C (± 0.11 °C) larger than the vasomotor zone. Furthermore, the critical temperature for the onset of shivering was 0.53 °C lower than the mean cutaneous vasoconstriction threshold, with each of the regional differences being significant ($P < 0.05$). The average critical temperature for precursor sweat secretion was < 0.1 °C higher than the average vasodilatation threshold, with none of the individual, between-effector threshold differences being significant ($P > 0.05$). For comparative purposes with the "*null zone*" observations of Mekjavić et al. (1991), the lower and upper critical (oesophageal) temperatures were 36.41 °C and 36.81 °C (Taylor et al., 2019). Whilst the absolute critical temperatures differed, presumably due to water immersion producing both uniform and clamped

skin temperatures (28 °C; Mekjavić et al., 1991), the oesophageal temperature differences between the lower and upper critical temperatures that defined the inter-threshold zones were very similar (0.40° versus 0.47 °C [Mekjavić et al., 1991]).

That experiment provided a definitive demonstration that the vasomotor and inter-threshold zones were not equivalent, either in magnitude or their critical body temperatures (Taylor et al., 2019). Therefore, those zones do not describe the same phenomenon, which was implied in Fig. 2. Instead, they are functionally independent regions of autonomic regulation. Moreover, there exist separate lower and upper critical temperatures (thresholds) for cutaneous vasomotor, thermogenic and sudomotor activation. Whilst the separation of the thresholds for vasodilatation and sweating is perhaps trivial under resting, thermoneutral conditions (Fig. 6), those thresholds were found to move independently when the same individuals were pre-cooled prior to the passive heating treatment (next section; Taylor et al., 2019). Taken collectively, those outcomes lend support to the possibility that each of these thermoeffectors has its own discrete central controller, and we return to this point when reviewing animal experiments.

2.3.1.1. Independent changes in thermoeffector thresholds. In a further illustration of the possibility of independent control centres, Taylor et al. (2019) demonstrated that, when the same heating treatment was administered following pre-experimental cooling (water immersion), the upper critical temperatures for the vasomotor and sudomotor effectors were modified (Fig. 7). While the thresholds for vasodilatation in each of three body segments were reduced (average change −0.37 °C), five of the six sudomotor thresholds (three body segments) were elevated (average change 0.19 °C). Hellstrøm and Hammel (1967) similarly reported an upward displacement of the panting threshold in unanaesthetised dogs following pre-cooling. Given the comprehensive nature of the former project, it would not be unreasonable to suggest those divergent threshold displacements were consistent with each group of thermoeffectors being independently controlled, either functionally or anatomically, and we further consider that possibility in Section 2.5.

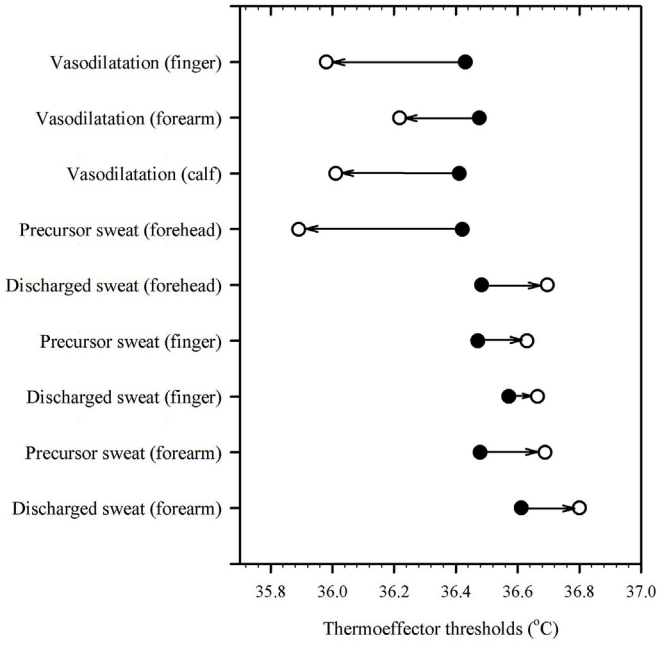


Fig. 7. Comparisons of the upper thresholds (critical mean body temperatures) for cutaneous vasodilatation and sudomotor activation (humans). Data were extracted from Taylor et al. (2019), in which thermoeffector function was simultaneously measured from different body segments during the passive heating of participants ($N = 8$) in both normothermic (solid symbols) and pre-cooled states (open symbols). Arrows show the direction of each threshold change following thermal pre-conditioning.

The downward displacement of the vasomotor thresholds should not be interpreted to signify that the reduced (pre-cooled) mean body temperature was being defended. Only the points of effector activation were determined, and not the response intensities (sensitivities or gains). It is speculated that less powerful effector responses would occur, following their earlier onset, resulting in a more gradual dissipation of heat.

However, one obvious anomaly was apparent (Taylor et al., 2019); the reduction of the precursor sweat threshold measured at the forehead (−0.53 °C), while each of the other five critical (sudomotor) temperatures was elevated (Fig. 7). That divergence at the forehead should not be ascribed to experimental error, for it was seen in seven of the eight subjects. Indeed, it highlights the need for caution when endeavouring to interpret local sudomotor responses within a whole-body context, as others have noted (Patterson et al., 2000; Taylor and Machado-Moreira, 2013; Notley et al., 2017), particularly if sweat rates are measured from only one site, and most particularly if that site is the forehead. For example, had we used only discharged indices, which were similarly reliable across participants, the anomaly would not have been apparent, possibly leading to erroneous interpretations regarding the neurological significance of that threshold shift. Instead, that within-site threshold difference most likely resulted from the time taken for precursor sweat production to exceed its ductal reabsorption (Sato, 1977; Taylor and Machado-Moreira, 2013), and, for that reason, the discharged sweat data of the forehead can be disregarded.

What then are the neurological implications of that precursor sudomotor anomaly? One possibility is that the facial sweat glands have a separate central controller. That is unlikely, given the evidence of oscillation synchronisation between discharged sweat from the face and the other body regions (Ogawa and Bullard, 1972; Taylor and Machado-Moreira, 2013). Alternatively, the possibility exists that, downstream of the hypothalamus, neurones travelling to the facial sweat glands might receive excitatory and inhibitory influences that differ from the rest of the body, and might act to independently modulate thermoefferent flow (Taylor et al., 2019).

2.3.1.2. Methodological considerations: humans. There exists a range of naturally occurring thermal and non-thermal circumstances that can modify the thermoeffector thresholds (*e.g.*, circadian variations [Stephenson et al., 1984; Aoki et al., 2001], exercise [Hammel, 1972; Haight and Keatinge, 1973], menstrual cycling [Hessemer and Brück, 1985]). In addition, various pharmacological (Chinyanga, 1991; Sessler, 2000) and experimental manipulations (Cabanac and Massonnet, 1977; Mekjavić et al., 1991; Taylor et al., 2019) can be used to explore those thresholds. Notwithstanding those methodological variations, the treatments used must be suitable to the experimental objective, and if that is to better understand mechanistic physiology, it is essential to avoid the impact of artefactual thermal and non-thermal influences on those mechanisms, and, where possible, to replicate naturally occurring thermal stresses that may have driven natural selection.

The first group of non-thermal considerations must include interactions with other regulatory systems with which thermoregulation shares effectors. For instance, changes in hydration state and mean arterial pressure can independently modulate cutaneous vasomotor and sudomotor functions, and must therefore be controlled. Naturally occurring, and pharmacologically influenced, variations in body temperature should also be minimised. This means that circadian and menstrual variations need to be standardised, and febrile states, as well as many pharmacological preparations, must be avoided.

The second group of non-thermal influences pertains to altered states of arousal, which include exercise. In rodents, such non-thermal stresses have a profound impact on thermoregulation (Section 2.3.1.3). For humans, it is well established that both psychogenic stress and

exercise can independently modify cutaneous vasomotor and sudomotor responses, with exercise acting through centrally mediated sympathetic feedforward (Krogh and Lindhard, 1913; Eldridge et al., 1981; Vissing and Hjortsø, 1996; Shibasaki et al., 2003, 2005). For example, when a psychogenic stress is applied to resting, normothermic individuals, there occurs an almost immediate constriction of the cutaneous vasculature (Darrow, 1929; Ackner, 1956; Delius et al., 1972). Furthermore, when resting subjects watch visual stimuli recorded by an exercising person, they experience significant, albeit physiologically small, cardiovascular changes that would normally accompany that exercise (Brown et al., 2013). When actually exercising, the cutaneous vasculature is further modified. For instance, at the commencement of dynamic exercise, a generalised cutaneous vasoconstriction occurs (Blair et al., 1961; Bevegård and Shepherd, 1966). Moreover, cutaneous vascular conductance is significantly reduced when static exercise is performed during whole-body heating (Shibasaki et al., 2005).

With regard to sudomotor function, psychogenic stress can independently elicit eccrine sweating (Darrow, 1937; Kuno, 1956; Kennard, 1963; Ogawa, 1975; Iwase et al., 1997). Indeed, Machado-Moreira and Taylor (2012a, 2012b) demonstrated such secretion to be a whole-body phenomenon that occurs with or without thermal priming of the sweat glands. Furthermore, Machado-Moreira et al. (2012) conclusively established, using a systemic cholinergic blockade and whole-body thermal clamping, that psychogenic and exercise-induced sweating were activated via sympathetic (cholinergic) pathways. Most recently, that group reported that the same sweat glands were activated during the separate application of psychogenic and thermal stimuli within resting individuals (Schwarck et al., 2019). Collectively, those observations indicate that psychogenic stimuli interact with the sudomotor neural pathway in an excitatory manner, either at the hypothalamus or downstream, with the possibility that both thermogenic and psychogenic efferent flows travel along the same sympathetic neurones to arrive at the same eccrine sweat glands.

Given the right combination of conditions (sudomotor priming), sweat secretion can start at, or within a few seconds of commencing dynamic exercise (van Beaumont and Bullard, 1963). Such a phase delay is too short for heat generated within the muscles to be transported centrally, so the resultant sweating must be of a neural origin. Two mechanistic possibilities exist; feedforward (central command: Vissing et al., 1991; Shibasaki et al., 2003, 2006) or intramuscular thermoreceptor feedback (Robinson et al., 1965; Jessen et al., 1983; Todd et al., 2014). When exercise is performed with an existing thermal load, the sudomotor intensity increases as the thermal load rises (Kondo et al., 2002). That response appears not to be influenced by the size of the activated muscle mass, but seems more dependent upon the intensity of the exercise (Gordon et al., 2016). Regardless of the mechanism, that non-thermal influence will modify sweating independently of thermoregulatory control, and should generally be avoided in experiments designed to explore those control mechanisms.

Assuming the effective removal of non-thermal influences, then we next need to consider how heating and cooling stimuli might be applied. In naturally occurring states, heating occurs via exogenous and endogenous avenues, while cooling only occurs following exposure to lower ambient temperatures, or through contact with cooler objects. Accordingly, it is reasonable to assume that evolution accompanied those experiences, and that humans are better suited to defending body temperature when exposed to those states. If exercise is avoided, then passive (forced), externally applied heating and cooling might best replicate natural thermal stresses, and it is suggested that such treatments might be considered as the criterion experimental methods.

If that is an acceptable interpretation, then it is perhaps incumbent upon investigators using different methods to first demonstrate that those methods yield the same data as those produced via passive thermal treatments (Mekjavić et al., 1991; Taylor et al., 2019). To illustrate this, consider the following series of experiments: Lopez et al. (1994), Ozaki et al. (1994) and Lopez et al. (1995). In those experiments, participants were firstly warmed (passive) and then exposed to passive cooling via the intravenous infusion of cold saline (3–4 °C). In the first two studies, mean skin temperature was kept constant (36 °C), while in the last, an exercise stimulus followed cooling. In those circumstances, there was a reversal of the thermal gradient normally encountered during cooling. That is, instead of thermal energy moving from the deeper to the peripheral tissues, it moved from the heated skin towards the core. Whilst we do not wish to challenge the outcomes of that research, in the absence of a methodological validation against a criterion method, the interpretation of those thermoeffector thresholds becomes rather difficult.

2.3.1.3. Methodological considerations for rodent thermoregulation: its impact on inter-specific data extrapolation. Whilst the initial objective of this review was to contrast and compare thermoeffector thresholds between humans and laboratory rodents, such an endeavour is fraught with uncertainty and inaccuracies. With regard to the limitations for extrapolating data from rodents to humans, several points require careful consideration. Firstly, human thermoregulatory data are collected from willing, unstressed volunteers who are generally in a physiological steady state within a laboratory. On the other hand, it is reasonable to assume that most rodent data were collected from animals subjected to unknown levels of psychogenic stress. The exceptions include experiments where animals were monitored in undisturbed and unrestrained conditions, utilising radiotelemetry or comparable methods.

For rodents, significant psychological stress accompanies restraint, the tethering of a cable or wire to the animal, placement in an open field or a novel environment, or just the presence of people in the vicinity of the animal. Those stresses are sufficient to induce significant alterations in thermoregulatory function (Nagasaka et al., 1979; Briese and Cabanac, 1991; Cabanac and Briese, 1992; Gordon, 1993, Gordon, 2012b), making it very difficult to compare the thermophysiological responses of rodents and humans.

Fortunately, the advent of radiotelemetry revolutionised the study of thermoregulation in animals. Commercially available systems provide researchers with the means to monitor deep-body and skin temperatures, brown adipose tissue temperatures, shivering and other physiological processes in undisturbed and unstressed animals. Moreover, those animals remain in their home-cage environment, and are oblivious to the data collection procedures. Regarding deep-body temperature, past methods of repeatedly inserting a colonic probe to measure the temperature of a mouse or rat has long been recognised as stressful, inducing changes in both body temperature and thermoeffector function (reactive errors) that can persist for hours after the initial measurement (Gordon, 1993, Gordon, 2012b). Radiotelemetric monitoring now provides very accurate assessments of the limits of normothermia in unrestrained and unstressed rodents (Fig. 3). Indeed, mice have become the predominant test species in biomedical research (Maloney et al., 2014). In view of the lability of their thermoregulatory system (Gordon, 2009), radiotelemetric monitoring provides researchers with the best means of detecting transient and long-term changes in deep-body temperatures during pharmaceutical treatments and other experimental manipulations.

There is an enormous database concerning the thermoeffector function and temperature regulation of rodents using various restraint methods. However, when restrained, rats are unable to use evaporative cooling by grooming with saliva, and they also exhibit a reduced ability to activate shivering during cold stress (Shimada and Stitt, 1983; Gordon, 1993). Indeed, under a standard room temperature (22 °C), rats placed in restraint typically become hyperthermic, whereas mice will often become hypothermic (Aydin et al., 2011; Gordon, 1993, Gordon, 2012b). Clearly, ambient conditions that are compatible with the thermoneutrality of unrestrained rodents, no longer remain so when animals of that body size (thermal inertia) are restrained.

Aydin et al. (2011) assessed the impact of physical restraint on the

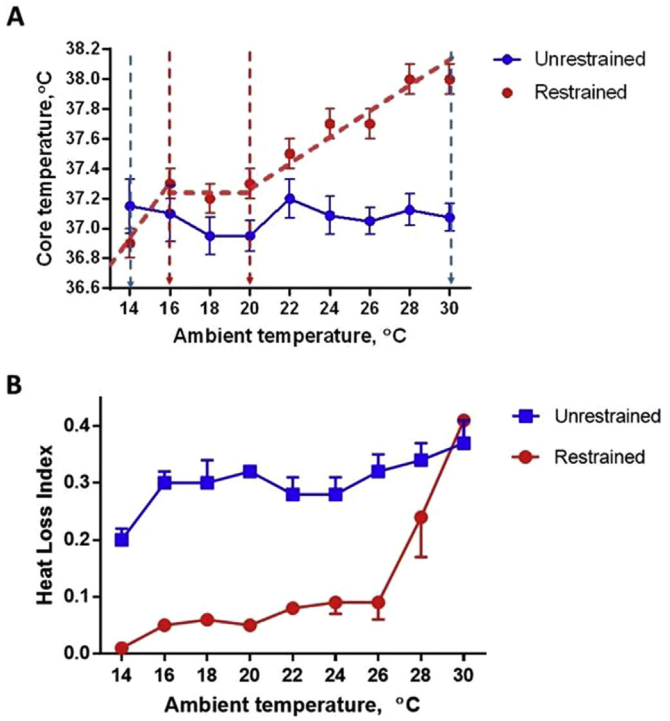


Fig. 8. The impact of physical restraint on the limits of normothermia (Fig. 8A) and the heat-loss index of the tail (Fig. 8B) of the male brown (Norwegian) rat. Dashed red, vertical lines indicate the limits of normothermia during restraint; dashed blue, vertical lines indicate the limits of normothermia in unrestrained conditions. Under this range of temperatures, the limits of normothermia were not exceeded in the unrestrained rat (see Fig. 4). Modified from Aydin et al. (2011) with permission of the authors and The Physiological Society (London).

limits of normothermia in brown (Norwegian) rats that were well adapted to the restraint procedure. Under unrestrained conditions, deep-body temperature was maintained within 36.9–37.2 °C over an ambient temperature range of 14–30 °C (Fig. 8A). Heat loss from the tail showed a marked drop as ambient temperature decreased from 16° to 14 °C, reflecting cutaneous vasoconstriction. There was a gradual rise in heat loss as ambient temperature increased above 26 °C (Fig. 8B), consistent with an increase in tail blood flow. On the other hand, physical restraint of those same animals led to a marked reduction in the limits of normothermia. The rats were now unable to successfully regulate body temperature at ambient temperatures either below 16 °C, or above 20 °C (Fig. 8A).

One obvious impact of that restraint was reduced heat loss from the tail. Even though the deep-body temperature of the restrained rats showed a steady elevation as ambient temperature rose from 20° to 30 °C, tail heat losses remained very low, and only showed an abrupt increase when ambient temperature was above 26 °C. Increased sympathetic tone accompanies restraint-induced stress. Since that change generally results in cutaneous vasoconstriction, the rat's ability to modulate tail blood flow to meet the demands of altered ambient temperatures is limited. The take home point is that, if the limits of normothermia are reduced to just a 4 °C ambient temperature range for rats adapted to restraint, then attempting to assess the critical ambient and body temperatures for eliciting either thermogenic or thermolytic responses will be limited when one relies on data collected using restrained-rodent models. Furthermore, trying to extrapolate observations from rodents to humans will also be limited, and this applies to all protocols that invoke any form of psychogenic stress.

The older observations from restrained rats typically reveal an ambient temperature of 28 °C as the threshold for eliciting an abrupt increase in tail blood flow, as controlled by arterial sphincters at the base of the tail (Rand et al., 1965; Gordon, 1990; 1993). Responses from

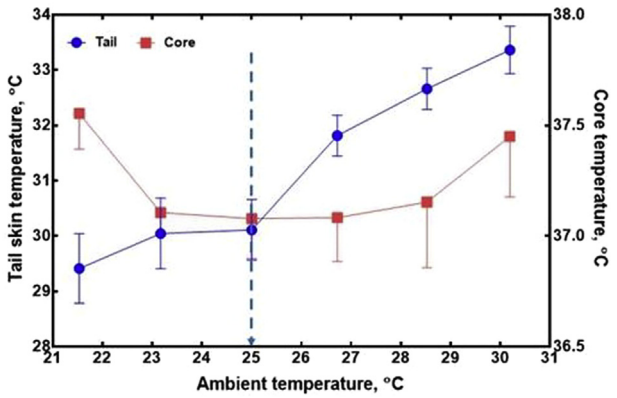


Fig. 9. The time course of deep-body and tail skin temperatures monitored using radiotelemetry in male, Sprague-Dawley rats subjected to a step-wise elevation in ambient temperature. Note the abrupt rise in tail skin temperature denoted by the vertical, dashed blue line as ambient temperature increased above 25 °C. Modified from Gordon et al. (2002) with permission of ©Elsevier (all rights reserved).

unrestrained rats (Fig. 8) indicate that an active increase in tail blood flow occurs at an ambient temperature of 26 °C. In another study of tail skin temperature in unrestrained (Sprague-Dawley) rats, it was clear that a similar abrupt rise in tail skin temperature occurred as ambient temperature rose above 25 °C (Fig. 9; Gordon et al., 2002). The application of infrared thermography, as well as other stress-free methods for measuring body temperatures and thermoeffector responses in undisturbed animals, will provide more accurate methods for comparing both the effector thresholds and the zones of mammalian thermoregulation.

2.3.1.4. Methodological considerations for thermoregulation in mice: torpor. There are at least 171 species of mammals capable of drastically reducing their metabolic rate and body temperature during periods of cold exposure, or during either food or water deprivation (Ruf and Geiser, 2015). This heterothermic response is typically divided between species that exhibit either torpor, as characterised by a transient hypothermic response lasting less than 24 h, or hibernation, where periods of hypothermia persist for days to weeks. We will focus on torpor in laboratory mice. This is a critical issue, because researchers unaware to this unique thermoregulatory response are likely to collect data or tissue samples, or perhaps perform experiments, on animals that have only recently recovered from a prolonged bout of hypothermia, whilst they were housed in standard laboratory settings.

Unlike laboratory rats, mice are one of the many species of small mammals that, when faced with even relatively brief periods of food deprivation, such as an overnight fast, will allow their deep-body (core) temperature and metabolic rate to fall precipitously, and then remain suppressed for hours (for reviews, see: Swoap, 2008; Ruf and Geiser, 2015). In recent years, the application of miniaturised telemetry systems in mice subjected to periods of caloric restriction has led to remarkable advances in our understanding of the thermoregulatory mechanisms of torpor (Swoap, 2008; Swoap and Gutilla, 2009; Vicent et al., 2017; van der Vinne et al., 2018). Fasting-induced torpor typically occurs during the latter part of the night, when mice would normally being foraging for food. When access to food is blocked for as little as 6 h, mice undergo a marked reduction in metabolism, heart rate and deep-body temperature (Fig. 10). At a standard room temperature of ~22 °C, the deep-body temperature of fasted mice can drop to just a few degrees above ambient temperature (*i.e.*, a drop of over 10 °C). Simultaneously, the heart rate will decrease from 500 to < 200 beats.min^{-1} (Swoap and Gutilla, 2009; Gordon, 2012b). This hypothermic bradycardia reflects the initiation of a physiologically advantageous bradymetabolic response, which acts to preserve energy

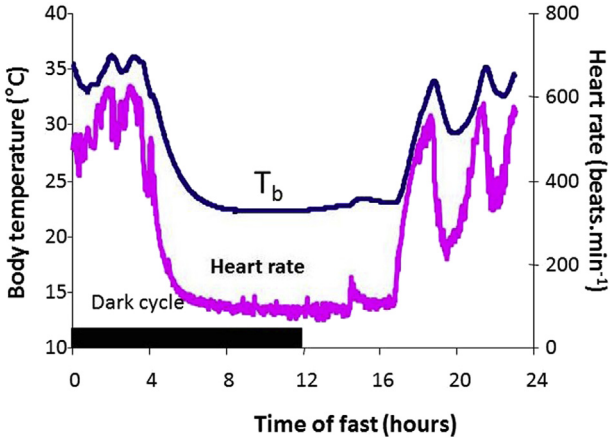


Fig. 10. The time-course of the deep-body temperature and heart rate of a female mouse (C57BL/6) subjected to a 24-h fast. Note the marked drops in deep-body temperature and heart rate during dark cycle following 6 h of fasting, and the spontaneous recovery during the light phase. Modified from Swoap and Gutilla (2009). Also see Gordon, 2012b for discussion).

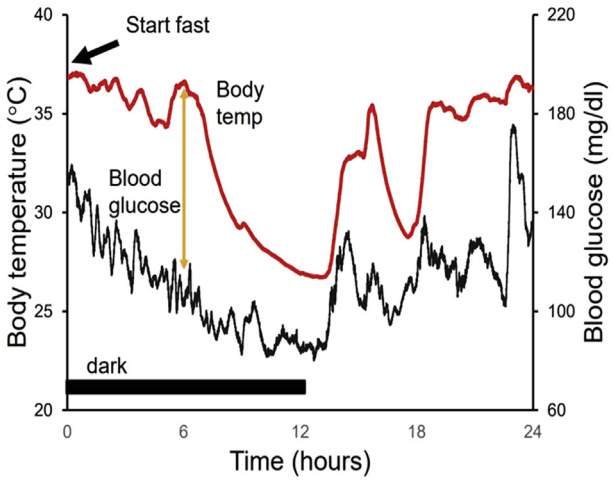


Fig. 11. The time-course of blood glucose concentration and deep-body temperature changes of a female mouse (C57BL/6) subjected to a 24-h fast. Arrow shows time point where there was a marked drop in deep-body temperature during the fast, as blood glucose gradually decreased. Spontaneous blood glucose and temperature recoveries occurred while the mouse remained food deprived. Graph courtesy of Dr. S.J. Swoap. For details of study, see Lo Martire et al. (2018).

reserves during caloric restriction. However, if access to food persists, the mouse will spontaneously recover from torpor, typically during the latter half of the daylight phase (Fig. 10).

That mice may undergo torpor following just 6 h of food deprivation, highlights the obligation of researchers to be fully aware of its physiological impact. For instance, where a pre-experimental period of fasting is required for metabolic assessments, investigators using the mouse model must be aware that the control period itself may actually modify the variable of experimental interest; the resulting bradymetabolism is a reactive error. Whilst overnight food restriction routinely precedes measurements of metabolic rate, so that the thermogenic and digestive impacts of food do not confound data collection, the affect of that experimental standardisation varies across species. The impact for humans is negligible. For mice, however, a blood sample drawn in the morning, following an all-night fast (Fig. 10; 12–16 h of fasting), will coincide with the period of bradymetabolism, hypothermia and bradycardia, yet researchers may remain unaware of the profound nocturnal, physiological responses accompanying that pre-experimental fast.

Utilising a biotelemetry transmitter that provided continuous measures of blood glucose, deep-body temperature and motor activity, one group (Lo Martire et al., 2018) has shown how the fast-induced drop in blood glucose concentration is a key factor in the activation of the torpor response in mice (Fig. 11). In this example, the mouse was fasted at the start of the dark phase. Blood glucose concentration decreased gradually, whilst deep-body temperature was initially defended at ~36.5 °C (0–6 h). After just 6 h of fasting, blood glucose decreased from 140 to 100 mg dL^{-1}, and there was now a marked drop in deep-body temperature that persisted throughout the dark period. Blood glucose continued to decrease, but its reduction was now more gradual compared to the drop in deep-body temperature. Approximately 1 h into the light phase, but with fasting continued, there were spontaneous increases in both blood glucose concentration and deep-body temperature, followed by another transient drop (13–14 h), and then full recovery of body temperature (beyond 18 h). Nonetheless, marked variations in blood glucose persisted through to the end of the light phase. The authors also noted that, in addition to drop in blood glucose, bouts of hyperactivity during the fasting period appeared to be critical in eliciting the torpor response (Lo Martire et al., 2018).

As emphasised elsewhere in this review, advancements in miniaturised telemetry systems for mice and rats have led to a re-evaluation of our understanding and appreciation of the unique thermophysiological mechanisms of rodents, and especially mice. The role of blood glucose concentration and motor activity in the mediation of the torpor response of mice should have broad implications in a variety of biomedical research disciplines.

2.4. Zones of mammalian thermoregulation

To our knowledge, the first descriptions of the zones of human thermoregulation were contemporaneously provided by Giaja (1938; Fig. 1) and Hardy and Soderstrom (1938). The latter described just three zones: a cold zone, in which there was no autonomic control over heat loss, causing body cooling to resemble that of inanimate objects, a vasomotor (or comfort) zone, wherein heat exchanges were modulated via variations in cutaneous vasomotor activity, and a zone of vasomotor and evaporative regulation, in which vascular and sudomotor activities regulated body temperature. Those three regions were subsequently, and respectively, redefined as the zone of increased metabolic rate, the vasomotor (thermoneutral) zone and the zone of evaporative regulation (Hardy, 1961).

From preceding sections, it is clear that a single thermoregulatory switch (threshold) for all human thermoeffectors does not exist. Instead, two regulatory zones are apparent (Fig. 6), as defined by four independent critical temperatures (thresholds). Of course, beyond those thresholds, zones of sudomotor and thermogenic temperature regulation also exist (Fig. 12: zones three and five), and beyond those regions, one finds zones of thermoregulatory failure (Fig. 12: zones four and six), but they are not the emphasis of this communication. Instead, our focus is directed to states bounded by those lower and upper thresholds, as shown in a contemporary schema of human thermoregulation (Fig. 12: zones one and two).

The cutaneous vasomotor zone (zone one) is delimited by the thresholds for pronounced vasoconstriction and vasodilatation, whilst the inter-threshold zone is defined by the shivering and sweating thresholds (zone two). The absolute temperatures for each of those thresholds are different (Fig. 6). Therefore, the historical use of one lower and one upper critical temperature (Fig. 2 and Commission for Thermal Physiology, 2001) is another simplification that may be incorrectly interpreted as describing the simultaneous activation of each thermoeffector pair. Although a singular value for those activation points was not necessarily intended to signify their simultaneous activation, that possibility has now been removed.

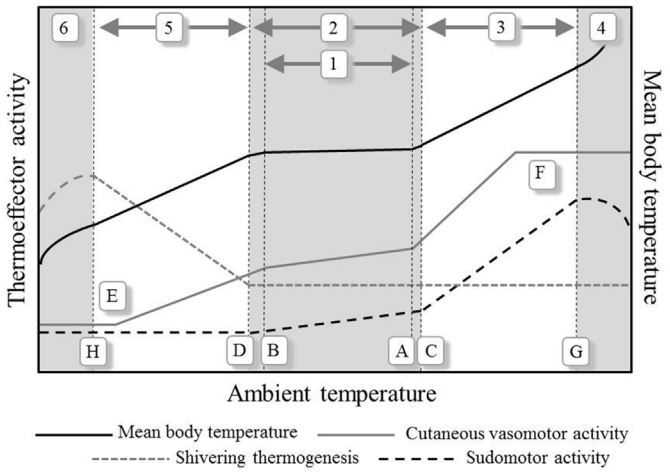


Fig. 12. A contemporary perspective of the human thermoregulatory zones (modified from Werner et al. [2008] and used with permission of ©Elsevier). The vasomotor (thermoneutral) zone (1) lies between the mean body temperature thresholds for the onset of cutaneous vasodilatation (A: upper critical, vasomotor temperature) and vasoconstriction (B: lower critical, vasomotor temperature). The inter-threshold zone (2) is defined by the thresholds for the activation of sweating (C: upper critical, sudomotor temperature) and shivering (D: lower critical, thermogenic temperature). Those thresholds signify entry into regions of sudomotor (3) and thermogenic (5) temperature regulation. Plateaux E and F show maximal vasoconstriction and vasodilatation (respectively), whilst peak rates of sweating (G) and shivering (H) define boundaries beyond which thermoregulatory failure eventually ensues (zones 4 and 6, respectively).

Fig. 12 has a human orientation. However, we know that the width of the inter-threshold zone in mammals is phylogenetically influenced, with Riek and Geiser (2013) comparing 93 mammalian species. They defined the inter-threshold zone using only deep-body critical temperatures (the "*range of normothermia*": Gordon, 2005). For marsupials, there was a strong correlation between body mass and the inter-threshold zone width ($r^2 = 0.78$). For placental mammals, however, that relationship was only moderate ($r^2 = 0.36$), although there was a clear body-mass dependency of the lower critical temperatures across all species (Riek and Geiser, 2013). That dependency would obtain for humans, but, due to the absence of fur and the presence of eccrine sweat glands, the upper critical temperatures are unlikely to be comparable. Indeed, when based only on oesophageal temperatures, the width of the human inter-threshold zone seems to be $< 0.5\,^{\circ}C$ (Mekjavić et al., 1991; Taylor et al., 2019).

It is important to recall that those critical temperatures do not define points at which thermoreceptor feedback starts, or points from which thermoefferent flow commences. Both sets of neural messages are ever-present. In the former case, feedback during thermoneutral states does not elicit a significant change in efferent traffic. However, even in those states, there is continual (subliminal) thermoefferent flow (Ogawa and Bullard, 1972; Elizondo, 1973), but those messages do not activate the effectors. During thermoneutrality, there is a continual modulation of cutaneous vascular conductance (Jessen and Ludwig, 1971). Indeed, perfusion of the hands and feet is rarely stable (Grant and Pearson, 1938; Blair et al., 1961; Taylor et al., 2014a), and quite variable among individuals. Those variations are of a thermoregulatory nature, and this is reflected by the gradient for cutaneous vasomotor activity (non-evaporative heat loss) between points A and B of Fig. 12. Therefore, thermoneutrality is an individualised physiological phenomenon that is not merely dictated by the ambient conditions or passive heat exchanges, but should be defined on the basis of minimal cutaneous vasomotion.

As noted above, mammalian evolution occurred over aeons, commencing with the possible acquisition of cutaneous vascular control. That mechanism existed possibly 200 million years before the appearance of endotherms, although it was perhaps only with localised control in the ectotherms (Morgareidge and White, 1969), rather than the central control mechanisms that now exist in mammals (O'Leary et al., 1985; Johnson et al., 2014). Whether or not those mechanisms were inherited, or arose independently, when mammals acquired their thermogenic responses to cold-sensitive receptor activation, is open to speculation. Nevertheless, it took another 100 million years for eccrine sweaters to appear (Best and Kamilar, 2018). That timescale begs the question: was each thermoeffector, and its neural pathway, simply tacked onto existing pathways, or did each effector evolve with an independent control mechanism?

Since *homo sapiens* evolved only ~250,000 years ago, following unusually rapid (< 100 years; Gowlett, 2001) and large temperature changes (very cold to tropical) within the African continental climate (Balter, 2002; Grigg et al., 2004), then it is easy to imagine those individuals may originally have relied upon peripheral receptors and neural pathways that might minimise the risk of hypothermia, possibly inherited from heterothermic (poikilothermic) species (Simon, 2000). Not surprisingly, the skin contains a density of cold-sensitive receptors which is several-fold greater than the warm-sensitive receptor density (Hensel, 1952). Conversely, being a tachymetabolic species that found itself in a tropical climate, with ambient temperatures close to, or greater than, body temperature, as well as being a species that relied upon endurance-based hunting and evasion strategies (Ruben, 1995; Bramble and Lieberman, 2004; Lieberman, 2015), one would expect to find warm-sensitive thermoreceptors dominating the deep-body regions of humans. Whilst warm:cold sensor ratios of 3:1 are reported for the hypothalamus and spinal cord of some mammals (Kanosue et al., 1998; Simon et al., 1998), we can only speculate that the same distribution obtains for humans.

Against this background, we shall now explore the hypothesis that mammals not only possess multiple thermoreceptive fields, several different thermoeffectors and multiple neural pathways, but that they also have several central, yet functionally independent, controllers of thermoeffector function.

2.5. Are there multiple central controllers?

The pre-eminence of the hypothalamus (Ott, 1884; Richet, 1884; Isenschmid and Schnitzler, 1914), and in particular its preoptic-anterior and posterior regions (Barbour, 1921; Magoun et al., 1938; Hemingway et al., 1940; Ranson, 1940), in the regulation of mammalian body temperature is well established (Boulant, 2011; Nakamura, 2011). However, there is less clarity with regard to whether all thermoeffectors are controlled by the one central nervous system controller, by separate heat-retention and heat-dissipation controllers, or by independent central controllers for each effector. The current authors support the hypothesis that mammalian thermoregulatory systems have several independent, yet interacting effector controllers; a view perhaps first proposed by Satinoff (1974, 1978).

Thus far, evidence has been presented concerning the evolutionary acquisition of the mammalian thermoeffectors. Given that evolution favours the selection of beneficial natural variations and mutations, which occur randomly, then it may be difficult to accept the possibility that processes that led to the presence of several different thermoeffectors, might also have resulted in each effector having the same central controller (Satinoff, 1978). An alternative possibility is that evolution resulted in regulatory optimisation, with mammals possessing several controllers, as well as the capacity not just to activate each controller in proportion to the magnitude of the thermal strain, but for their independent and cascading recruitment in situations of greater strain (Jessen and Ludwig, 1971; Satinoff, 1978; Kanosue et al., 2010; Notley et al., 2017; Romanovsky, 2018; Taylor et al., 2019). Since it is unlikely that opportunities to test the probability of that evolutionary outcome will eventuate, we are left with evaluating existing empirical

evidence that might favour that possibility.

The first step involves separating the behavioural from the autonomic thermal responses. Even though they form complementary aspects of the same homoeostatic system, we know those responses are directed by separate central nervous centres (Lipton, 1968; Satinoff and Rutstein, 1970; Satinoff, 1974; Craig et al., 1994; Craig, 2002), although it is beyond the scope of this manuscript to expand into behavioural thermoregulation. Nevertheless, it is important to differentiate between the protective, reflex behaviours driven by dynamic feedforward from the cutaneous thermoreceptors during sudden, potentially damaging, changes in skin temperature, and the deliberate behaviours that follow gradual changes in heat storage (interoception: Sherrington, 1900; Konietzny and Hensel, 1979; Strigo and Craig, 2016). The former are responses to thermal sensations, while the latter fall into the psychophysical category of alliesthesial responses; in this instance, variations in thermal comfort (Cabanac et al., 1972; Attia and Engel, 1981; Farrell et al., 2011).

The autonomic domain also relies upon those thermoafferent signals, but now in the form of sensory feedback that provides information concerning the effectiveness of physiological responses activated in the defence of mean body temperature. Over time, there has been a gradual accumulation of evidence consistent with the possibility that each thermoeffector has its own control centre, perhaps with shared afferent pathways, but with independent central and excitatory, and even inhibitory, networks.

One of the first groups to test that hypothesis was Gilbert and Blatteis (1978). They used bilateral incisions of the preoptic-anterior hypothalamus of rats, demonstrating that, whilst the cutaneous vasomotor response to cold-air exposure (5 °C) was obliterated, the thermogenic capabilities remained largely unaffected. Since the hypothalamus is temperature sensitive (Nakayama et al., 1961; Boulant, 1981, 2011), then the use of external cooling meant that, while hypothalamic temperature would eventually decline, the initial responses were stimulated by peripheral, cold-sensitive thermoreceptors. Furthermore, those microcuts had a negligible impact on cutaneous vasodilatation when the animals were externally heated (33 °C). Those observations led to perhaps the first conclusion that different control centres existed, not just for the two heat-conservation thermoeffectors, but also for cutaneous vasoconstriction and vasodilatation. That research gave rise to progressively more complex investigations of those possibilities, as more advanced experimental techniques became available.

Most of those techniques cannot be used in humans, forcing reliance on lessons learned from animal models, so student readers need to be aware of differences in the neural control of the cutaneous vasculature across mammalian species, of differences in the modes of thermogenesis (non-shivering [brown adipose tissue] and shivering) and of the variations in evaporative heat-loss (panting, saliva spreading and eccrine sweating). For instance, in humans, the blood vessels of the skin can actively constrict, passively dilate via a release of that constrictor tone and also actively dilate. That last function is not present in every skin region, and it is controlled by a separate efferent pathway (Johnson et al., 2014). Rabbits and rats appear not to have a capacity for active vasodilatation (O'Leary et al., 1985; Anderson et al., 2006), although that appears not to have been unequivocally resolved (Ootsuka and Tanaka, 2015).

For consistency with the evolutionary timescale, the thermoregulatory control of the cutaneous vasculature will be covered first, with more detailed elaborations provided elsewhere (Dampney, 1994; McAllen et al., 2010; Ootsuka and Tanaka, 2015; Blessing et al., 2016). Thermoafferent flow from deep-body and peripheral temperature sensors converges *en route* to the preoptic-anterior hypothalamus (Hellon, 1969; Nagashima et al., 2000; Nakamura and Morrison, 2008, 2010). Using a series of hypothalamic microcuts (rats), Kanosue et al. (1994a) investigated the downstream vasomotor network involved in thermoregulation, revealing that the descending vasomotor pathways crossed the midline below the hypothalamus. More recently, those thermoefferent signals have been shown to travel to the rostral medullary raphé, where both excitatory and inhibitory neurones innervate, and control, the cutaneous vascular beds (rodents and rabbits: Blessing et al., 1999; Rathner and McAllen, 1999; Korsak and Gilbey, 2004; Tanaka et al., 2011).

Further support for the existence of at least one central vasomotor controller (cutaneous vasoconstriction) that operates independently of the centre controlling thermogenesis in rats, was provided by Ootsuka and McAllen (2006). The lower critical temperatures for cutaneous vasoconstriction have also been shown, by that same group, to differ between the glabrous (hairless; tail) and non-glabrous (hairy; back) skin of the rat (Tanaka et al., 2007). Those authors interpreted that observation to imply the existence of different central neural paths; an hypothesis further supported when neural pathways were tracked between the preoptic-anterior hypothalamus and the rostral medullary raphé (Tanaka et al., 2011). Most recently, the same interpretation was applied to observations in humans (Figs. 6 and 7; Taylor et al., 2019).

It is presumed that a similar combination of convergent peripheral and deep-body afferent signals is responsible for the activation of thermogenesis in mammals, with the former dominating (Morrison, 2011), due to their greater density within the peripheral tissues (Hensel, 1952, 1973). Again, there is a heavy reliance upon evidence obtained from rodents, which primarily utilise a non-shivering, heat-production mechanism (Himms-Hagen, 1984; Janský, 1995; Cannon and Nedergaard, 2004). On the other hand, cold-induced heat production in humans is primarily dependent upon, but not limited to (Nedergaard et al., 2007), skeletal-muscle shivering (Hemingway, 1963; Hohtola, 2004; Haman and Blondin, 2017).

Activation of the warm-sensitive thermoreceptors of the hypothalamus exerts an inhibitory influence on shivering in rats (Zhang et al., 1995), with that control being via a different central network, and presumably involving a different central controller from that which modulates cutaneous vasomotion (Kanosue et al., 1994a, 1994b). Indeed, shivering efferents emanate independently from the right and left sides of the preoptic-anterior hypothalamus (rats: Kanosue et al., 1994a). Thus, the available neurological evidence supports the presence of independent control centres and efferent pathways for both vasomotion and thermogenesis, with the integrated observations of Taylor et al. (2019) providing human evidence consistent with those observations.

The most recently acquired heat-loss effector is the secretion of eccrine sweat (Best and Kamilar, 2018). Whilst the neural pathways for sudomotor control in humans, as well as those for initiating saliva production (autonomic) and spreading (behavioural) in rodents, remain unknown (Morrison and Nakamura, 2011), recent technological advances have permitted increased insight into those mechanisms. Indeed, the first neuroimaging evidence for the participation of the preoptic-anterior hypothalamus in human thermoregulation, and the control of eccrine sweating, was provided by Farrell et al. (2014). That group found that neural activity within the dorsal cingulate cortex, the anterior insula and the midbrain correlated with preoptic neural activity during passive, whole-body heating that resulted in thermal sweating. They had earlier demonstrated nuclei within the brainstem that were associated with sweat secretion (Farrell et al., 2013). Thus, evidence is accumulating that has convinced some of the existence of separate central controllers for each thermoeffector (Kanosue et al., 1998; Nagashima et al., 2000; McAllen et al., 2010).

When viewed collectively, observations from the preceding sections, and their interpretations, are consistent with the presence of multiple thermoreceptive fields that, at least within rodents and humans, relay sensory feedback to discrete central controllers, which, via separate neural pathways, then modulate the function of several different thermoeffectors (Satinoff, 1978; Romanovsky, 2014, 2018; Taylor et al., 2019). How might those possibilities be integrated within existing theoretical models of mammalian thermoregulation?

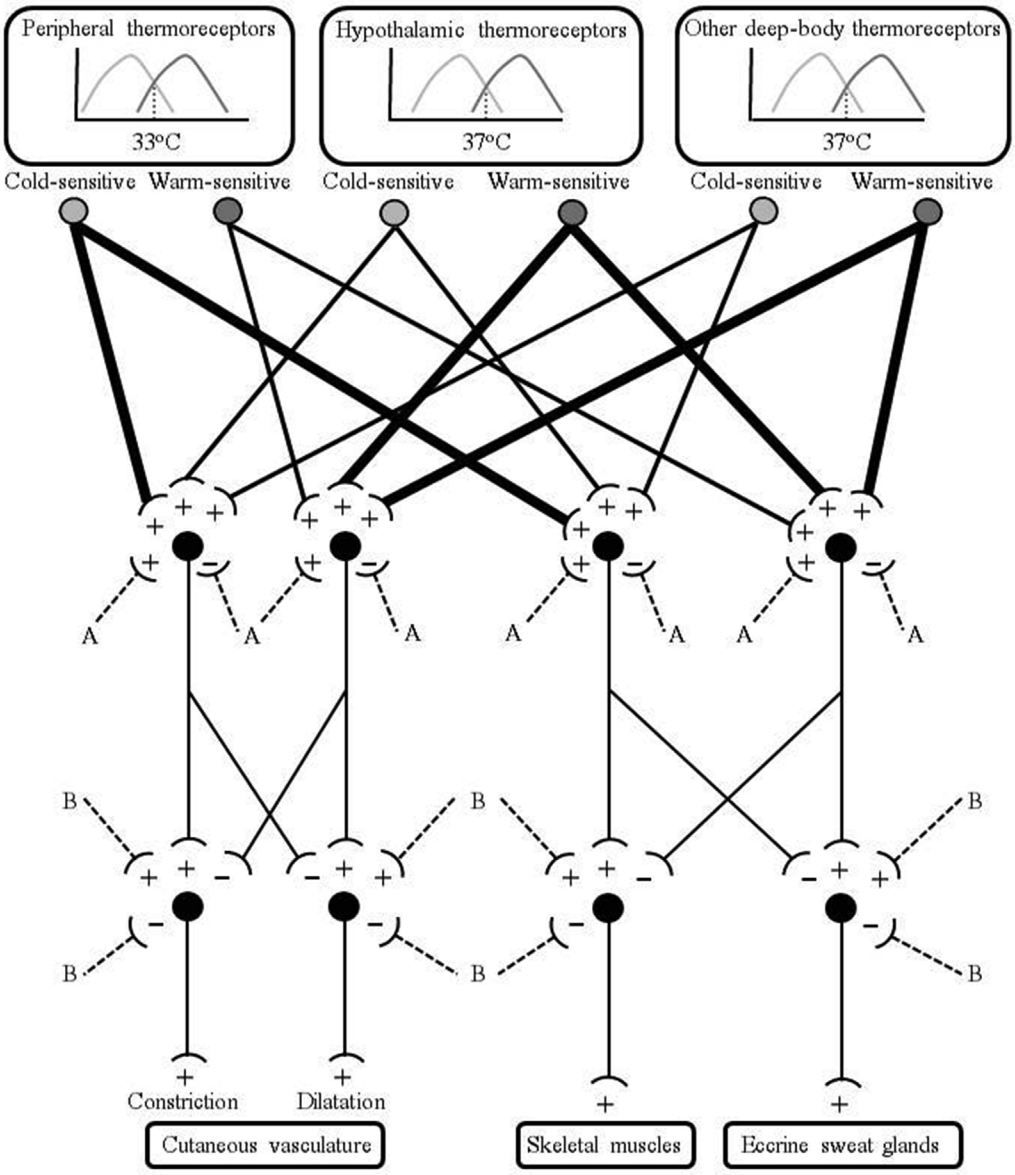


Fig. 13. An hypothetical update of the neuronal model of mammalian thermoregulation proposed by Bligh (1972, 1976, 1998), adapted for human thermoregulation, and including recent neuronal and whole-body experimental evidence for the existence of functionally discrete central controllers for each thermoeffector.

2.6. Revisiting theoretical neuronal models

A variety of theoretical models exist to describe and explain the underlying mechanisms of mammalian thermoregulation (*e.g.*, Hardy, 1961, 1965; Wissler, 1961, 1964, 2018; Hammel, 1965, 1968; Wyndham and Atkins, 1968; Bligh, 1972, 1976, 1998; Mitchell et al., 1970, 1972; Werner, 1980, 2010; Boulant, 1981; Mekjavic and Morrison, 1985). It is neither our intention, nor necessarily within our capacities, to critique those variations (instead, see: Bligh, 1998; Kanosue et al., 2010; Werner, 2010; Havenith and Fiala, 2016; Wissler, 2018). However, many of those models contain common elements (*e.g.*, reciprocal cross inhibition: Boulant, 1981; Bligh, 1998), and this has led some to use those concepts to explain thermal and non-thermal interactions within human thermoregulation (Mekjavic and Eiken, 2006). Herein, we follow that lead.

Before embarking on that exercise, a further embellishment of the Bligh (1972, 1976, 1998) neuronal model is offered (Fig. 13), based upon the evolutionary, physiological and neurological evidence presented above. At the top of Fig. 13, hypothetical intersections of the sensory feedback from cold- and warm-sensitive thermoreceptors are shown for the peripheral, hypothalamic and extra-hypothalamic (other deep-body) tissues. Those localised intersections are believed to occur when feedback from those local (counteracting) receptors is equal and opposite (Bazett, 1927, 1949; Vendrik, 1959; Mitchell et al., 1970). However, as outlined in Section 2.1.1, those points are neither reference points nor are they identical to the thermoregulatory balance (operating) points. The afferent signals that arise from those thermoreceptive fields are shown with differences in neuronal thickness, which are intended to reflect local variations in cold- and warm-sensitive receptor densities.

The principal change in that schematic, relative to the final iteration of Bligh (1998), is within the central controllers (hypothalamus). Each thermoeffector is now shown with separate neuronal control. For the cutaneous vasculature (left side), there are separate heat-conservation (constriction) and heat-loss pathways (dilatation). There is one heat-production path to the skeletal muscles (centre), and one heat-loss path to the sweat glands (right side). Reciprocal cross-inhibitory neurones are shown between the heat-loss paths, and the corresponding heat-

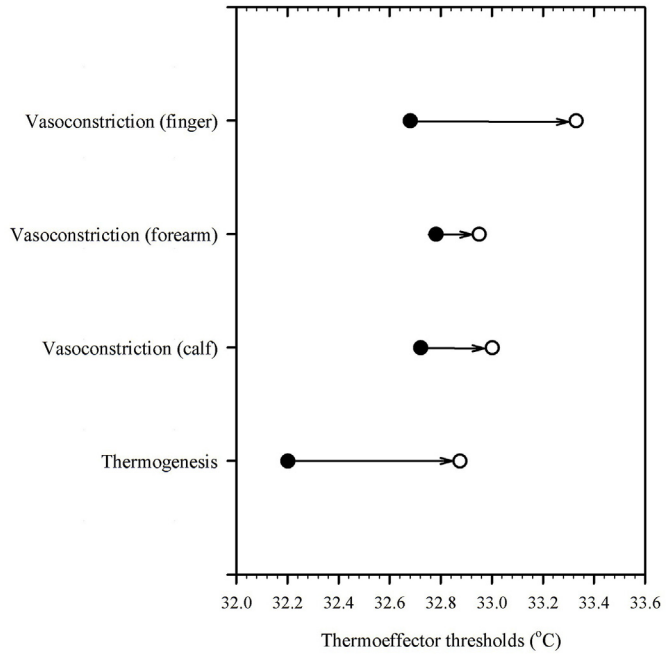


Fig. 14. Comparisons of the lower thresholds (critical mean body temperatures) for cutaneous vasoconstriction and whole-body thermogenesis in humans (data extracted from Taylor et al., 2019). Thermoeffector responses were simultaneously measured from different body segments during passive cooling ($N = 8$) in both normothermic (solid symbols) and pre-heated states (open symbols). Arrows indicate the direction of each threshold change following thermal preconditioning.

conservation and heat-production pathways. Finally, at positions A and B, both excitatory and inhibitory neurones are shown adjacent to the cell bodies. Those neurones may be activated by changes other than, but necessarily exclusive of, thermoregulation, and their existence has been established in rodents (Zhang et al., 1997; Blessing et al., 1999; Rathner and McAllen, 1999).

Using this neuronal model, we revisit the observations of Taylor et al. (2019), this time looking at displacements of the thermoeffector thresholds following both pre-experimental, whole-body cooling and heating. Let us firstly consider the impact of pre-experimental heating on the lower critical temperatures (Fig. 14), for it is conceptually easier to understand. Pre-heating elevated the mean body temperatures of all participants. If the absolute thresholds for cutaneous vasoconstriction and thermogenesis remained stable, then the activation of those thermoeffectors would have been delayed. Indeed, there was no regulatory urgency to either conserve or produce heat following pre-heating. However, the opposite was observed, with the thresholds for cutaneous vasoconstriction at the finger, forearm and calf, as well as whole-body thermogenesis, being shifted to the right, and to significantly higher mean body temperatures (Fig. 14).

According to the neuronal model above (Fig. 13), the critical temperatures for vasoconstriction can be elevated if pre-heating created an excitatory influence that acted on the interneurones within the vasoconstrictor pathway, either upstream (position A) or downstream (position B) of the reciprocal cross-inhibitory neurones. The same neuronal explanation, but now of an excitatory nature, could account for the upward displacement of the shivering threshold. Thus, it appears as if those control mechanisms were responding to temperature changes rather than to the attainment of some absolute temperature. However, whilst the general *loci* of those possible neural influences might be theoretically identifiable, the cause and origin of those influences remain uncertain.

Following pre-experimental cooling, the upper critical temperatures for the onset of cutaneous vasodilatation at each of three different body segments (finger, forearm and calf) were reduced (Fig. 7). That too is evidence of a sensitivity to a change in mean body temperature. From Fig. 13, one may explain that outcome if an inhibitory influence acted upon the vasodilator pathway either before (position A) or after (position B) the cross-inhibitory neurones.

Conversely, thresholds for five of the six sudomotor indices were simultaneously elevated. The divergent response for forehead precursor sweating was discussed above (Section 2.3.1.1). For the sudomotor threshold displacements observed at the finger and forearm (Fig. 7), there are both thermodynamic and neuronal explanations. If one accepts that reductions in the critical temperatures for vasodilatation were real, and there is no evidence to the contrary, then heat loss during passive heating would commence earlier following pre-cooling, and would perhaps be more effective, thereby allowing for a delayed initiation of evaporative cooling (an effector recruitment cascade). Alternatively, that same outcome could eventuate if pre-cooling created an excitatory influence on the interneurones within the sudomotor path either upstream (position A) or downstream (position B) of the reciprocal cross-inhibitory neurones.

3. Conclusions

A theme of this communication has been comparative mammalian thermoregulation, with an emphasis upon the extrapolation of thermoeffector responses between rodents and humans. Between those species, the thermoeffector thresholds are somewhat comparable, provided that investigators have removed the impact of external stress and altered arousal states. Natural variations in the deep-body temperatures of mice, rats and humans are relatively similar, although significant oscillations are seen in rodents, whereas the metabolic heat production differs by at least an order of magnitude between mice and men. This means that each species uses different thermoregulatory strategies to maintain thermal homoeostasis under a variety of environmental conditions. Nevertheless, for humans, the critical body temperatures for thermoeffector activation represent neither unitary nor fixed points. Instead, they are unique and adjustable thresholds. Those outcomes are interpreted to signify the presence of functionally independent central controllers for the vasomotor and sudomotor responses, and possibly also for thermogenesis. That conclusion is consistent with the phylogenetic acquisition of those effectors, and also with neurological evidence obtained from rodents and other experimental species. Moreover, there is increasing evidence for the existence of a cascading recruitment of the passive and autonomically mediated mechanisms for the regulation of mean body temperature, with that progression being morphologically dependent. It is concluded that mammals not only possess multiple thermoreceptive fields and thermoeffectors with unique neural pathways, but they also have discrete central controllers for those thermoeffectors.

Conflicts of interest

There are no conflicts of interest.

Acknowledgments

The research and associated scholastic activities summarised within this manuscript were supported, in part, by grants from the Australian Research Council, the Defence Science and Technology Group (Australia). Invaluable contributions came from dedicated and enthusiastic friends, students and colleagues: Catriona Burdon, Joanne Caldwell, Herbert Groeller, Christiano Machado-Moreira, Sean Notley, Gregory Peoples, Steve Swoap, Elizabeth Taylor and Anne van den Heuvel.

References

Abramson, D.I., 1965. Pathophysiology of arteriovenous shunts in the extremities. J. Cardiovasc. Surg. 5 (Suppl. l), 217–230.

Abreu-Vieira, G., Xiao, C., Gavrilova, O., Reitman, M.L., 2015. Integration of body temperature the analysis of energy expenditure in the mouse. Molecular Metabolism 4, 461–470.

Ackner, B., 1956. Emotions and the peripheral vasomotor system: a review of previous work. J. Psychosom. Res. 1, 3–20.

Allen, J.A., 1877. The influence of physical conditions in the genesis of species. Radical Review 1, 108–140.

Anderson, C.R., Bergner, A., Murphy, S.M., 2006. How many types of cholinergic sympathetic neuron are there in the rat stellate ganglion? Neuroscience 140, 567–576.

Andjus, P.R., Stojilkovic, S.S., Cvijic, G., 2016. Ivan Djaja (Jean Giaja) and the Belgrade School of physiology. Physiol. Res. 60, S1–S13.

Aoki, K., Stephens, D.P., Johnson, J.M., 2001. Diurnal variation in cutaneous vasodilator and vasoconstrictor systems during heat stress. Am. J. Physiol. 281, R591–R595.

Attia, M., Engel, P., 1981. Thermal alliesthesial response in man is independent of skin location stimulated. Physiol. Behav. 27, 439–444.

Aydin, C., Grace, C.E., Gordon, C.J., 2011. Effect of physical restraint on the limits of thermoregulation in telemetered rats. Exp. Physiol. 96, 1218–1227.

Balter, M., 2002. Why get smart? Science 295, 1225.

Barbour, H.G., 1921. The heat-regulating mechanism of the body. Physiol. Rev. 1, 295–326.

Bazett, H.C., 1927. Physiological responses to heat. Physiol. Rev. 7, 531–599.

Bazett, H.C., 1949. The regulation of body temperatures. In: Newburgh, L.H. (Ed.), Physiology of Heat Regulation and the Science of Clothing. W.B. Saunders, Philadelphia, pp. 109–192.

Belding, H.S., Hatch, T.F., 1955. Index for evaluating heat stress in terms of resulting physiological strain. Heating/Piping/Air Cond. 27, 129–136.

Benzinger, T.H., Kitzinger, C., Pratt, A.W., 1963. The human thermostat. In: In: Hardy, J.D. (Ed.), Temperature - its Measurement and Control in Science and Industry, vol. 3. Reinhold Publishing Corp, New York, pp. 637–665 Part 3.

Bergmann, C., 1847. Ueber die verhältnisse der wärmeökonomie der tiere zu ihrer grösse. Göttinger Studien 3, 595–708.

Bernard, C., 1879. Leçons sur les phénomènes de la vie communs aux animaux et aux végétaux. J.-B. Baillière et Fils, Paris.

Best, A., Kamilar, J.M., 2018. The evolution of eccrine sweat glands in human and non-human primates. J. Hum. Evol. 117, 33–43.

Bevegård, B.S., Shepherd, J.T., 1966. Reaction in man of resistance and capacity vessels in forearm and hand to leg exercise. J. Appl. Physiol. 21, 123–132.

Blair, D.A., Glover, W.E., Roddie, I.C., 1961. Vasomotor responses in the human arm during leg exercise. Circ. Res. 9, 264–274.

Blessing, W., McAllen, R., McKinley, M., 2016. Control of the cutaneous circulation by the central nervous system. Comprehensive Physiology 6, 1161–1197.

Blessing, W.W., Yu, Y.H., Nalivaiko, E., 1999. Raphe pallidus and parapyramidal neurons regulate ear pinna vascular conductance in the rabbit. Neurosci. Lett. 270, 33–36.

Bligh, J., 1972. Neuronal models of mammalian temperature regulation. In: Bligh, J., Moore, R.E. (Eds.), Essays on Temperature Regulation. North-Holland Publishing Company, Amsterdam, pp. 105–120.

Bligh, J., 1973. Temperature Regulation in Mammals and Other Vertebrates. Frontiers of Biology, vol. 30 North-Holland Publishing Company, Amsterdam.

Bligh, J., 1976. Is mammalian thermoregulation based on a setpoint mechanism or a dynamic balance mechanism? A consideration based on neuronal evidence and neuronal models. Isr. J. Med. Sci. 12, 934–941.

Bligh, J., 1987. Human cold exposure and the circumstances of hypothermia. In: Mekjavic, I.B., Banister, E.W., Morrison, J.B. (Eds.), Environmental Ergonomics. Taylor & Francis, London, pp. 3–21.

Bligh, J., 1998. Mammalian homeothermy: an integrative thesis. J. Therm. Biol. 23, 143–258.

Bligh, J., 2006. A theoretical consideration of the means whereby the mammalian core temperature is defended at a null zone. J. Appl. Physiol. 100, 1332–1337.

Boulant, J.A., 1981. Hypothalamic mechanisms in thermoregulation. Fed. Proc. 40, 2843–2850.

Boulant, J.A., 2006. Neuronal basis of Hammel's model for set-point thermoregulation. J. Appl. Physiol. 100, 1347–1354.

Boulant, J.A., 2011. Hypothalamic neurons regulating body temperature. In: Comprehensive Physiology 2011, Supplement 14: Handbook of Physiology, Environmental Physiology, pp. 105–126 First published in print 1996.

Bowes, H.M., Burdon, C.A., Taylor, N.A.S., 2015. The scaling of human basal metabolic rate in adult males. Proc. Aust. Physiol. Soc. 46, 54P.

Bramble, D.M., Lieberman, D.E., 2004. Endurance running and the evolution of Homo. Nature 432, 345–352.

Briese, E., Cabanac, M., 1991. Stress hyperthermia: physiological arguments that it is a fever. Physiol. Behav. 49, 1153–1157.

Brody, S., 1945. Bioenergetics and Growth - with Special Reference to the Efficiency Complex in Domestic Animals. Reinhold Publishing Corp., New York.

Brown, A.C., Brengelmann, G.L., 1970. The interaction of peripheral and central inputs in the temperature regulation system. In: Hardy, J.D., Gagge, A.P., Stolwijk, J.A.J. (Eds.), Physiological and Behavioral Temperature Regulation. C.C. Thomas, Springfield, Illinois, pp. 684–702.

Brown, R., Kemp, U., Macefield, V., 2013. Increases in muscle sympathetic nerve activity, heart rate, respiration, and skin blood flow during passive viewing of exercise. Front. Neurosci. 7, 102.

Brück, K., Wünnenberg, W., Gallmeier, H., Ziehm, B., 1970. Shift of threshold temperature for shivering and heat polypnea as a mode of thermal adaptation. Pflügers Archiv 321, 159–172.

Burdon, C.A., Tagami, K., Park, J., Caldwell, J.N., Taylor, N.A.S., 2017. Indirect hand and forearm vasomotion: regional variations in cutaneous thermosensitivity during normothermia and mild hyperthermia. J. Therm. Biol. 65, 95–104.

Burton, A.C., 1935. Human calorimetry: II. The average temperature of the tissues of the body. J. Nutr. 9, 261–280.

Burton, A.C., 1941. The operating characteristics of the human thermoregulatory mechanism. In: American Institute of Physics. Temperature - its Measurement and Control in Science and Industry, vol. 1. Reinhold Publishing Corp, New York, pp. 522–528.

Burton, A.C., 1963. The pattern of response to cold in animals and the evolution of homeothermy. In: In: Hardy, J.D. (Ed.), Temperature - its Measurement and Control in Science and Industry, vol. 3. Reinhold Publishing Corp, New York, pp. 363–371 Part 3.

Burton, A.C., Bazett, H.C., 1936. A study of the average temperature of the tissues, of the exchanges of heat and vasomotor responses in man by means of a bath calorimeter. Am. J. Physiol. 117, 36–54.

Cabanac, M., 1972. Thermoregulatory behavior. In: Bligh, J., Moore, R.E. (Eds.), Essays on Temperature Regulation. North-Holland Publishing Company, Amsterdam, pp. 19–36.

Cabanac, M., 2006. Adjustable set point: to honor Harold T. Hammel. J. Appl. Physiol. 100, 1338–1346.

Cabanac, A., Briese, E., 1992. Handling elevates the colonic temperature of mice. Physiol. Behav. 51, 95–98.

Cabanac, M., Massonnet, B., 1977. Thermoregulatory responses as a function of core temperature in humans. J. Physiol. 265, 587–596.

Cabanac, M., Massonnet, B., Belaiche, R., 1972. Preferred skin temperature as a function of internal and mean skin temperature. J. Appl. Physiol. 33, 699–703.

Caldwell, J.N., Matsuda-Nakamura, M., Taylor, N.A.S., 2014. Three-dimensional interactions of mean body and local skin temperatures in the control of hand and foot blood flows. Eur. J. Appl. Physiol. 114, 1679–1689.

Caldwell, J.N., Matsuda-Nakamura, M., Taylor, N.A.S., 2016. Interactions of mean body and local skin temperatures in the modulation of human forearm and calf blood flows: a three-dimensional description. Eur. J. Appl. Physiol. 116, 343–352.

Caldwell, J.N., Nykvist, Å., Powers, N., Notley, S.R., Lee, D.S., Peoples, G.E., Taylor, N.A.S., 2011. An investigation of forearm vasomotor and sudomotor thresholds during passive heating, following whole-body cooling. In: Kounalakis, S.N., Koskolou, M. (Eds.), Proceedings of the Fourteenth International Conference on Environmental Ergonomics. Nafplio, Greece, pp. 132–135 July 10th-15th, 2011.

Caldwell, J.N., Nykvist, Å., Powers, N., Notley, S.R., Taylor, N.A.S., 2015. The impact of thermal pre-conditioning on cutaneous vasomotor and shivering thresholds. Extreme Physiol. Med. 4 (Suppl. 1), A117.

Cannon, W.B., 1929. Organisation for physiological homeostasis. Physiol. Rev. 9, 399–431.

Cannon, B., Nedergaard, J., 2004. Brown adipose tissue: function and physiological significance. Physiol. Rev. 84, 277–359.

Carroll, R.L., 1970. The ancestry of reptiles. Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci. 257, 267–308.

Chinyanga, H.M., 1991. Temperature regulation and anesthesia. In: Schönbaum, E., Lomax, P. (Eds.), Thermoregulation: Pathology, Pharmacology and Therapy. Pergamon Press Inc., New York, pp. 347–361.

Clarke, A., Rothery, P., Isaac, N.J.B., 2010. Scaling of basal metabolic rate with body mass and temperature in mammals. J. Anim. Ecol. 79, 610–619.

Clarkson, C., Jacobs, Z., Marwick, B., Fullagar, R., Wallis, L., Smith, M., Roberts, R.G., Hayes, E., Lowe, K., Carah, Z., Florin, S.A., McNeil1, J., Cox, D., Arnold, L.J., Hua, Q., Huntley, J., Brand, H.E.A., Manne, T., Fairbairn, A., Shulmeister, J., Lyle, L., Salinas, M., Page, M., Connell, K., Park, G., Norman, K., Murphy, T., Pardoe, C., 2017. Human occupation of northern Australia by 65,000 years ago. Nature 547, 306–310.

Clauser, C.E., McConville, J.T., Young, J.W., 1969. Weight, volume, and center of mass of segments of the human body. Aerospace Medical research Laboratory, Aerospace Medical division, air force systems command, U.S.A.

Commission for Thermal Physiology, 2001. Glossary of terms for thermal physiology. Jpn. J. Physiol. 51, 245–280.

Cooper, K.E., 1972. The body temperature “set-point” in fever. In: Bligh, J., Moore, R.E. (Eds.), Essays on Temperature Regulation. North-Holland Publishing Company, Amsterdam, pp. 149–162.

Cotter, J.D., Taylor, N.A.S., 2005. The distribution of cutaneous sudomotor and alliesthesial thermosensitivity in mildly heat-stressed humans: an open-loop approach. J. Physiol. 565, 335–345.

Cowles, R.B., Bogert, C.M., 1944. A preliminary study of the thermal requirements of desert reptiles. Bull. Am. Mus. Nat. Hist. 83, 261–296.

Craig, A.D., 2002. How do you feel? Interoception: the sense of the physiological condition of the body. Nat. Rev. Neurosci. 3, 655–666.

Craig, A.D., Bushnell, M.C., Zhang, E.T., Blomqvist, A., 1994. A thalamic nucleus specific for pain and temperature sensation. Nature 372, 770–773.

Crawshaw, L., Grahn, D., Wollmuth, L., Simpson, L., 1985. Central nervous regulation of body temperature in vertebrates: comparative aspects. Pharmacol. Ther. 30, 19–30.

Crawshaw, L.I., Nadel, E.R., Stolwijk, J.A.J., Stamford, B.A., 1975. Effect of local cooling on sweating rate and cold sensation. Pflügers Archiv 354, 19–27.

Dampney, R.A., 1994. Functional organization of central pathways regulating the cardiovascular system. Physiol. Rev. 74, 323–364.

Darrow, C.W., 1929. The galvanic skin-reflex and finger volume changes. Am. J. Physiol. 88, 219–229.

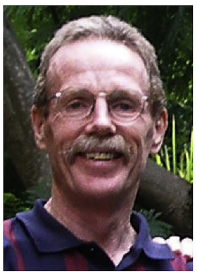
Darrow, C.W., 1937. Neural mechanisms controlling the palmar galvanic skin reflex and palmar sweating. Arch. Neurol. Psychiatr. 37, 641–663.

Delius, W., Hagbarth, K.E., Hongell, A., Wallin, B.G., 1972. Manoeuvres affecting sympathetic outflow in human skin nerves. Acta Physiol. Scand. 84, 177–186.
Docherty, D., Eckerson, J.D., Hayward, J.S., 1986. Physique and thermoregulation in prepubertal males during exercise in a warm, humid environment. Am. J. Phys. Anthropol. 70, 19–23.
DuBois, E.F., 1939. Heat loss from the human body. Bull. N. Y. Acad. Med. 15, 143–173.
Dzialowski, E.M., O'Connor, M.P., 1999. Utility of blood flow to the appendages in physiological control of heat exchange in reptiles. J. Therm. Biol. 24, 21–32.
Egan, G.F., Johnson, J., Farrell, M., McAllen, R., Zamarripa, F., McKinley, M.J., Lancaster, J., Denton, D., Fox, P.T., 2005. Cortical, thalamic, and hypothalamic responses to cooling and warming the skin in awake humans: A positron-emission tomography study. In: Proceedings of the National Academy of Sciences of the United States of America, vol. 102. pp. 5262–5267.
Eldridge, F.L., Millhorn, D.E., Waldrop, T.G., 1981. Exercise hyperpnea and locomotion: parallel activation from the hypothalamus. Science 211, 844–846.
Elizondo, R.S., 1973. Local control of eccrine sweat gland function. Fed. Proc. 32, 1583–1587.
Farmer, C.G., 2015. The evolution of unidirectional pulmonary airflow. Physiology 30, 260–272.
Farrell, M.J., Johnson, J., McAllen, R., Zamarripa, F., Denton, D.A., Fox, P.T., Egan, G.F., 2011. Brain activation associated with ratings of the hedonic component of thermal sensation during whole-body warming and cooling. J. Therm. Biol. 36, 57–63.
Farrell, M.J., Trevaks, D., McAllen, R.M., 2014. Preoptic activation and connectivity during thermal sweating in humans. Temperature 1, 135–141.
Farrell, M.J., Trevaks, D., Taylor, N.A.S., McAllen, R.M., 2013. Brain stem representation of thermal and psychogenic sweating in humans. Am. J. Physiol. 304, R810–R817.
Farrell, M.J., Trevaks, D., Taylor, N.A.S., McAllen, R.M., 2015. Regional brain responses associated with thermogenic and psychogenic sweating events in humans. J. Neurophysiol. 114, 2578–2587.
Forster, R.E., Ferris, B.G., Day, R., 1946. The relationship between total heat exchange and blood flow in the hand at various ambient temperatures. Am. J. Physiol. 146, 600–609.
Fox, R.H., Hilton, S.M., 1958. Bradykinin formation in human skin as a factor in heat vasodilatation. J. Physiol. 142, 219–232.
French, H.J., Klopsch, O.Z., 1926. Some Characteristics of Quenching Curves, vol. 313. Technologic Papers of the Bureau of Standards, pp. 365–385 20.
Gelineo, S., 1964. Organ systems in adaptation: the temperature regulating system. In: Dill, D.B., Adolph, E.F. (Eds.), Handbook of Physiology. Section 4. Adaptation to the Environment. American Physiological Society, Washington, D.C, pp. 229–282.
Giaja, J., 1938. Homéothermie et thermorégulation I - L'homothermie. Hermann & Cie, Paris.
Gilbert, T.M., Blatteis, C.M., 1978. Hypothalamic thermoregulatory pathways in the rat. J. Appl. Physiol. 43, 770–777.
Golden, F.StC., Francis, T.J.R., Gallimore, D., Pethybridge, R., 2013. Lessons from history: morbidity of cold injury in the Royal Marines during the Falklands conflict of 1982. Extreme Physiol. Med. 2, 23.
Gordon, C.J., 1990. Thermal biology of the laboratory rat. Physiol. Behav. 47, 963–991.
Gordon, C.J., 1993. Temperature Regulation in Laboratory Rodents. Cambridge University Press, New York.
Gordon, C.J., 1994. 24-hour control of body temperature in the rat: I. Integration of behavioral and autonomic effectors. Am. J. Physiol. 267, R71–R77.
Gordon, C.J., 2001. The therapeutic potential of regulated hypothermia. Emerg. Med. J. 18, 81–89.
Gordon, C.J., 2005. Temperature and Toxicology: an Integrative, Comparative, and Environmental Approach. CRC Press, Boca Raton.
Gordon, C.J., 2009. Quantifying the instability of core temperature in rodents. J. Therm. Biol. 34, 213–219.
Gordon, C.J., 2012a. The mouse: an "average" homeotherm. J. Therm. Biol. 37, 286–290.
Gordon, C.J., 2012b. Thermal physiology of laboratory mice: defining the limits of thermoneutrality. J. Therm. Biol. 37, 654–685.
Gordon, C.J., 2017. The mouse thermoregulatory system: its impact on translating biomedical data to humans. Physiol. Behav. 179, 55–66.
Gordon, C.J., Caldwell, J.N., Taylor, N.A.S., 2016. Non-thermal modulation of sudomotor function during static exercise and the impact of intensity and muscle-mass recruitment. Temperature 3, 1–10.
Gordon, C.J., Puckett, E., Padnos, B., 2002. Rat tail skin temperature monitored non-invasively by radiotelemetry: characterization by examination of vasomotor responses to thermomodulatory agents. J. Pharmacol. Toxicol. Methods 47, 107–114.
Gowlett, J.A.J., 2001. Out in the cold. Nature 413, 33–34.
Grant, R.T., Pearson, R.S.B., 1938. The blood circulation in the human limb; observations on the differences between the proximal and distal parts and remarks on the regulation of body temperature. Clin. Sci. 3, 119–173.
Grigg, G.C., Beard, L.A., Augee, M.L., 2004. The evolution of endothermy and its diversity in mammals and birds. Physiol. Biochem. Zool. 77, 982–997.
Hafez, E.S.E., 1964. Behavioral thermoregulation in mammals and birds. Int. J. Biometeorol. 7, 231–240.
Haight, J.S.J., Keatinge, W.R., 1973. Elevation in set point for body temperature regulation after prolonged exercise. J. Physiol. 229, 77–85.
Hainsworth, F.R., Stricker, E.M., 1971. Evaporative cooling in the rat: differences between salivary glands as thermoregulatory effectors. Can. J. Physiol. Pharmacol. 49, 573–580.
Hales, J.R.S., Rowell, L.B., King, R.B., 1979. Regional distribution of blood flow in awake heat-stressed baboons. Am. J. Physiol. 237, H705–H712.
Haman, F., Blondin, D.P., 2017. Shivering thermogenesis in humans: origin, contribution and metabolic requirement. Temperature 4, 217–226.
Hammel, H.T., 1965. Neurons and temperature regulation. In: Yamamoto, W.S., Brobeck, J.R. (Eds.), Physiological Control and Regulations. W.B. Saunders, Philadelphia, pp. 71–97.
Hammel, H.T., 1968. Regulation of internal body temperature. Annu. Rev. Physiol. 30, 641–710.
Hammel, H.T., 1972. The set-point in temperature regulation: analogy or reality. In: Bligh, J., Moore, R.E. (Eds.), Essays on Temperature Regulation. North-Holland Publishing Company, Amsterdam, pp. 121–137.
Hammel, H.T., Jackson, D.C., Stolwijk, J.A.J., Hardy, J.D., Stromme, S.B., 1963. Temperature regulation by hypothalamic proportional control with an adjustable set-point. J. Appl. Physiol. 18, 1146–1154.
Hankenson, F.C., Marx, J.O., Gordon, C.J., David, J.M., 2019. Effects of rodent thermoregulation on animal models in the research environment. Comp. Med. 68, 425–438.
Hardy, J.D., 1961. Physiology of temperature regulation. Physiol. Rev. 41, 521–606.
Hardy, J.D., 1965. The "set-point" concept in physiological temperature regulation. In: Yamamoto, W.S., Brobeck, J.R. (Eds.), Physiological Control and Regulations. W.B. Saunders, Philadelphia, pp. 98–116.
Hardy, J.D., DuBois, E.F., 1938. The technic of measuring radiation and convection. J. Nutr. 15, 461–475.
Hardy, J.D., Soderstrom, G.F., 1938. Heat loss from the nude body and peripheral blood flow at temperatures of 22°C. to 33°C. J. Nutr. 16, 493–510.
Havenith, G., Fiala, D., 2016. Thermal indices and thermophysiological modeling for heat stress. Comprehensive Physiology 6, 255–302.
Heath, J.E., Williams, B.A., Mills, S.H., 1971. Interactions of hypothalamic thermosensitivity and body size in vertebrates. Int. J. Biometeorol. 15, 254–257.
Hellon, R.F., 1969. Environmental temperature and firing rate of hypothalamic neurons. Experientia 25, 610.
Hellstrøm, B., Hammel, H.T., 1967. Some characteristics of temperature regulation in the unanesthetized dog. Am. J. Physiol. 213, 547–556.
Hemingway, A., 1963. Shivering. Physiol. Rev. 43, 397–422.
Hemingway, A., Rasmussen, T., Wikoff, H., Rasmussen, A.T., 1940. Effects of heating hypothalamus of dogs by diathermy. J. Neurophysiol. 3, 329–338.
Hensel, H., 1952. Physiologie der thermoreception. Ergeb. Physiol. Biol. Chem. Exp. Pharmakol. 47, 166–368.
Hensel, H., 1973. Neural processes in thermoregulation. Physiol. Rev. 53, 948–1017.
Hessemer, V., Brück, K., 1985. Influence of menstrual cycle on shivering, skin blood flow, and sweating responses measured at night. J. Appl. Physiol. 59, 1902–1910.
Himms-Hagen, J., 1984. Nonshivering thermogenesis. Brain Res. Bull. 12, 151–160.
Hohtola, E., 2004. Shivering thermogenesis in birds and mammals. In: Barnes, B.M., Carey, H.V. (Eds.), Life in the Cold: Evolution, Mechanisms, Adaptation, and Application. Twelfth International Hibernation Symposium, pp. 241–252.
Isenschmid, R., Schnitzler, W., 1914. Beitrag zur Lokalisation des der Wärmeregulation vorstehenden Zentral-apparates im Zwischenhirn. Archiv für experimentelle Pathologie und Pharmakologie 76, 202–223.
Iwase, S., Ikeda, T., Kitazawa, H., Hakusui, S., Sugenoya, J., Mano, T., 1997. Altered response in cutaneous sympathetic outflow to mental and thermal stimuli in primary palmoplantar hyperhidrosis. J. Auton. Nerv. Syst. 64, 65–73.
Janský, L., 1995. Humoral thermogenesis and its role in maintaining energy balance. Physiol. Rev. 75, 237–259.
Jastroch, M., Withers, K.W., Taudien, S., Frappell, P.B., Helwig, M., Fromme, T., Hirschberg, V., Heldmaier, G., McAllan, B.M., Firth, B.T., Burmester, T., Platzer, M., Klingenspor, M., 2008. Marsupial uncoupling protein 1 sheds light on the evolution of mammalian nonshivering thermogenesis. Physiol. Genom. 32, 161–169.
Jenkinson, D.M., 1973. Comparative physiology of sweating. Br. J. Dermatol. 88, 397–406.
Jessen, C., 2011. Interaction of body temperatures in control of thermoregulatory effector mechanisms. In: Comprehensive Physiology, Supplement 14: Handbook of Physiology, Environmental Physiology, pp. 127–138 First published in print 1996.
Jessen, C., Feistkorn, G., Nagel, A., 1983. Temperature sensitivity of skeletal muscle in the conscious goat. J. Appl. Physiol. 54, 880–886.
Jessen, C., Ludwig, O., 1971. Spinal cord and hypothalamus as core sensors of temperature in the conscious dog. II. Addition of signals. Pflügers Archiv 324, 205–216.
Johnson, J.M., Minson, C.T., Kellogg, D.L., 2014. Cutaneous vasodilator and vasoconstrictor mechanisms in temperature regulation. Comprehensive Physiology 4, 33–89.
Kanosue, K., Crawshaw, L., Nagashima, K., Yoda, T., 2010. Concepts to utilize in describing thermoregulation and neurophysiological evidence for how the system works. Eur. J. Appl. Physiol. 19, 5–11.
Kanosue, K., Hosonso, T., Zhang, Y.-H., Chen, X.M., 1998. Neuronal networks controlling thermoregulatory effectors. In: In: Sharma, H.S., Westman, J. (Eds.), Progress in Brain Research ume 115. Elsevier, Amsterdam, pp. 50–62.
Kanosue, K., Yanase-Fujiwara, M., Hosono, T., 1994a. Hypothalamic network for thermoregulatory vasomotor control. Am. J. Physiol. 267, R283–R288.
Kanosue, K., Zhang, Y.H., Yanase-Fujiwara, M., Hosono, T., 1994b. Hypothalamic network for thermoregulatory shivering. Am. J. Physiol. 267, R275–R282.
Keller, A.D., McClaskey, E.B., 1964. Localization, by the brain slicing method, of the level or levels of the cephalic brainstem upon which effective heat dissipation is dependent. Am. J. Phys. Med. 43, 181–213.
Kennard, D.W., 1963. The nervous regulation of the sweating apparatus of the human skin, and emotive sweating in thermal sweating areas. J. Physiol. 165, 457–467.
Kinahan, A.A., Inge-moller, R., Bateman, P.W., Kotze, A., Scantlebury, M., 2007. Body temperature daily rhythm adaptations in African savanna elephants (*Loxodonta africana*). Physiol. Behav. 92, 560–565.
Kleiber, M., 1932. Body size and metabolism. Hilgardia 6, 315–353.
Kondo, N., Horikawa, N., Aoki, K., Shibasaki, M., Inoue, Y., Nishiyasu, T., Crandall, C.G., 2002. Sweating responses to a sustained static exercise is dependent on thermal load in humans. Acta Physiol. Scand. 175, 289–295.
Konietzny, F., Hensel, H., 1979. The neural basis of the sensory quality of warmth. In:

Kenshalo, D.R. (Ed.), Sensory Functions of the Skin of Humans. Springer, New York, pp. 241–259.
Korsak, A., Gilbey, M.P., 2004. Rostral ventromedial medulla and the control of cutaneous vasoconstrictor activity following i.c.v. prostaglandin E_1. Neuroscience 124, 709–717.
Krogh, A., Lindhard, L., 1913. The regulation of respiration and circulation during the initial stages of muscular work. J. Physiol. 47, 112–136.
Kuno, Y., 1956. Human Perspiration. C.C. Thomas, Springfield, Illinois.
LaJoy, M.H., 1954. Industrial Automatic Controls. Longmans, London.
Libert, J.P., Candas, V., Sagot, J.C., Meyer, J.P., Vogt, J.J., Ogawa, T., 1984. Contribution of skin thermal sensitivities of large body areas to sweating response. Jpn. J. Physiol. 34, 75–88.
Lieberman, D.E., 2015. Human locomotion and heat loss: an evolutionary perspective. Comprehensive Physiology 5, 99–117.
Lin, M.T., Chen, Y.-F., Liu, G.-G., Chang, T.-C., 1979. Studies on thermoregulation in the rat. Proc. Natl. Sci. Counc. Repub. China 3, 46–52.
Lipton, J.M., 1968. Effects of preoptic lesions on heat-escape responding and colonic temperature in the rat. Physiol. Behav. 3, 165–169.
Lo Martire, V., Valli, A., Bingaman, M.J., Zoccoli, G., Silvani, A., Swoap, S.J., 2018. Changes in blood glucose as a function of body temperature in laboratory mice: implications for daily torpor. Am. J. Physiol. 315, E662–E670.
Lopez, M., Sessler, D.I., Walter, K., Emerick, T., Ayyalapu, A., 1995. Reduced sweating threshold during exercise-induced hyperthermia. Pflügers Archiv 430, 606–611.
Lopez, M., Sessler, D.I., Walter, K., Emerick, T., Ozaki, M., 1994. Rate and gender dependence of the sweating, vasoconstriction, and shivering thresholds in humans. Anesthesiology 80, 780–788.
Machado-Moreira, C.A., Barry, R.J., Vosselman, M.J., Ruest, R.M., Taylor, N.A.S., 2015. Temporal and thermal variations in site-specific thermoregulatory sudomotor thresholds: precursor versus discharged sweat production. Psychophysiology 52, 117–123.
Machado-Moreira, C.A., McLennan, P.L., Lillioja, S., van Dijk, W., Caldwell, J.N., Taylor, N.A.S., 2012. The cholinergic blockade of both thermally and non-thermally induced human eccrine sweating. Exp. Physiol. 97, 930–942.
Machado-Moreira, C.A., Taylor, N.A.S., 2012a. Sudomotor responses from glabrous and non-glabrous skin during cognitive and painful stimulations following passive heating. Acta Physiol. 204, 571–581.
Machado-Moreira, C.A., Taylor, N.A.S., 2012b. Psychological sweating from glabrous and non-glabrous skin surfaces under thermoneutral conditions. Psychophysiology 49, 369–374.
Magoun, H.W., Harrison, F., Brobeck, J.R., Ranson, S.W., 1938. Activation of local heat loss mechanisms by local heating of the brain. J. Neurophysiol. 1, 101–114.
Maloney, S.K., Fuller, A., Mitchell, D., Gordon, C.J., Overton, M., 2014. Translating research from animal models: does it matter that our rodents are cold? Physiology 29, 413–420.
Malvin, G.M., Wood, S.C., 1992. Behavioral hypothermia and survival of hypoxic protozoans Paramecium caudatum. Science 255, 1423–1425.
McAllen, R.M., Tanaka, M., Ootsuka, Y., McKinley, M.J., 2010. Multiple thermoregulatory effectors with independent central controls. Eur. J. Appl. Physiol. 109, 27–33.
Mekjavić, I.B., Bligh, J., 1989. Core temperature thresholds for sweating. Can. J. Physiol. Pharmacol. 67, 1038–1044.
Mekjavic, I.B., Eiken, O., 2006. Contribution of thermal and nonthermal factors to the regulation of body temperature in humans. J. Appl. Physiol. 100, 2065–2072.
Mekjavic, I.B., Morrison, J.B., 1985. A model of shivering thermogenesis based on the neurophysiology of thermoreception. IEEE (Inst. Electr. Electron. Eng.) Trans. Biomed. Eng. 32, 407–417.
Mekjavić, I.B., Sundberg, C.J., Linnarsson, D., 1991. Core temperature “null zone”. J. Appl. Physiol. 71, 1289–1295.
Mekjavic, I.B., Tipton, M.J., Eiken, O., 2003. Thermal considerations in diving. In: Brubakk, A.O., Neumann, T.S. (Eds.), Bennett and Elliott's Physiology and Medicine of Diving, 5th ed. Saunders, Edinburgh, pp. 115–152.
Mitchell, D., Atkins, A.R., Wyndham, C.H., 1972. Mathematical and physical models of thermoregulation. In: Bligh, J., Moore, R.E. (Eds.), Essays on Temperature Regulation. North-Holland Publishing Company, Amsterdam, pp. 37–54.
Mitchell, D., Snellen, J.W., Atkins, A.R., 1970. Thermoregulation during fever: change of set-point or change of gain. Pflügers Archiv 321, 293–302.
Morgareidge, K.R., White, F.N., 1969. Cutaneous vascular changes during heating and cooling in the Galapagos marine iguana. Nature 223, 587–591.
Morrison, S.F., 2011. Central neural pathways for thermoregulatory cold defense. J. Appl. Physiol. 110, 1137–1149.
Morrison, S.F., Nakamura, K., 2011. Central neural pathways for thermoregulation. Front. Biosci. 16, 74–104.
Nadel, E.R., Mitchell, J.W., Stolwijk, J.A.J., 1973. Differential thermal sensitivity in the human skin. Pflügers Archiv 340, 71–76.
Nagasaka, T., Hirata, K., Sugano, Y., Shibata, H., 1979. Heat balance during physical restraint in rats. Jpn. J. Physiol. 29, 383–392.
Nagashima, K., Nakai, S., Tanaka, M., Kanosue, K., 2000. Neuronal circuitries involved in thermoregulation. Auton. Neurosci. 85, 18–25.
Nakamura, K., 2011. Central circuitries for body temperature regulation and fever. Am. J. Physiol. 301, R1207–R1228.
Nakamura, K., Morrison, S.F., 2008. A thermosensory pathway that controls body temperature. Nat. Neurosci. 11, 62–71.
Nakamura, K., Morrison, S.F., 2010. A thermosensory pathway mediating heat-defense responses. Proc. Nat. Acad. Sci. U.S.A. 107, 8848–8853.
Nakayama, T., Eisenman, J.S., Hardy, J.D., 1961. Single unit activity of anterior hypothalamus during local heating. Science 134, 560–561.
Nakayama, T., Hammel, H.T., Hardy, J.D., Eisenman, J.S., 1963. Thermal stimulation of electrical activity of single units of the preoptic region. Am. J. Physiol. 204, 1122–1126.
Nedergaard, J., Bengtsson, T., Cannon, B., 2007. Unexpected evidence for active brown adipose tissue in adult humans. Am. J. Physiol. 293, E444–E452.
Nelson, D.O., Heath, J.E., Prosser, C.L., 1984. Evolution of temperature regulatory mechanisms. Am. Zool. 24, 791–807.
Notley, S.R., Park, J., Tagami, K., Ohnishi, N., Taylor, N.A.S., 2016. Morphological dependency of cutaneous blood flow and sweating during compensable heat stress when heat-loss requirements are matched across participants. J. Appl. Physiol. 121, 25–35.
Notley, S.R., Park, J., Tagami, K., Ohnishi, N., Taylor, N.A.S., 2017. Variations in body morphology explain sex differences in thermoeffector function during compensable heat stress. Exp. Physiol. 102, 545–562.
Nowack, J., Giroud, S., Arnold, W., Ruf, T., 2017. Muscle non-shivering thermogenesis and its role in the evolution of endothermy. Front. Physiol. 8, 889.
Ogawa, T., 1975. Thermal influence on palmar sweating and mental influence on generalized sweating in man. Jpn. J. Physiol. 25, 525–536.
Ogawa, T., Bullard, R.W., 1972. Characteristics of subthreshold sudomotor neural impulses. J. Appl. Physiol. 33, 300–305.
O'Leary, D.S., Johnson, J.M., Taylor, W.F., 1985. Mode of neural control mediating rat tail vasodilation during heating. J. Appl. Physiol. 59, 1533–1538.
Ootsuka, Y., McAllen, R.M., 2006. Comparison between two rat sympathetic pathways activated in cold defense. Am. J. Physiol. 291, R589–R595.
Ootsuka, Y., Tanaka, M., 2015. Control of cutaneous blood flow by central nervous system. Temperature 2, 392–405.
Ott, I., 1884. The relation of the nervous system to the temperature of the body. J. Nerv. Ment. Dis. 11, 141–152.
Ozaki, M., Kurz, A., Sessler, D.I., Lenhardt, R., Schroeder, M., Moayeri, A., Noyes, K.M., Rotheneder, E., 1994. Thermoregulatory thresholds during epidural and spinal anesthesia. Anesthesiology 81, 282–288.
Partridge, L.D., 1982. The good enough calculi of evolving control systems: evolution is not engineering. Am. J. Physiol. 242, R173–R177.
Patterson, M.J., Cotter, J.D., Taylor, N.A.S., 1998. Human sudomotor responses to heating and cooling upper body skin surfaces: differential cutaneous thermal sensitivity. Acta Physiol. Scand. 163, 289–296.
Patterson, M.J., Galloway, S.D.R., Nimmo, M.A., 2000. Variations in regional sweat composition in normal human males. Exp. Physiol. 85, 869–875.
Phillips, M.J., Bennett, T.H., Lee, M.S., 2009. Molecules, morphology, and ecology indicate a recent, amphibious ancestry for echidnas. Proc. Nat. Acad. Sci. U.S.A. 106, 17089–17094.
Phillips, P.K., Heath, J.E., 1992. Heat exchange by the pinna of the African elephant (*Loxodonta africana*). Comparative Biochemistry and Physiology. Comp. Physiol. 101, 693–699.
Phillips, P.K., Heath, J.E., 1995. Dependency of surface temperature regulation on body size in terrestrial mammals. J. Therm. Biol. 20, 281–289.
Pierau, F.-K., 2011. Peripheral Thermosensors. Comprehensive Physiology 2011, Supplement 14: Handbook of Physiology, Environmental Physiology. pp. 85–104 First published in print 1996.
Plagenhoef, S., Evans, F.G., Abdelnour, T., 1983. Anatomical data for analyzing human motion. Res. Q. Exerc. Sport 54, 169–178.
Prosser, C.L., 1964. Perspectives of adaptation: theoretical aspects. In: Dill, D.B., Adolph, E.F. (Eds.), Handbook of Physiology. Section 4. Adaptation to the Environment. American Physiological Society, Washington, D.C, pp. 11–25.
Rand, R.P., Burton, A.C., Ing, T., 1965. The tail of the rat, in temperature regulation and acclimatization. Can. J. Physiol. Pharmacol. 43, 257–267.
Ranson, S.W., 1940. Regulation of Body Temperature, vol. 20. Research Publications - Association for Research in Nervous and Mental Disease, pp. 342–399.
Rathner, J.A., McAllen, R.M., 1999. Differential control of sympathetic drive to the rat tail artery and kidney by medullary premotor cell groups. Brain Res. 834, 196–199.
Richet, C., 1884. La fièvre traumatique nerveuse et l’influence des lésions du cerveau sur la température générale. Comptes Rendus de la Société de Biologie 1, 189–195.
Riek, A., Geiser, F., 2013. Allometry of thermal variables in mammals: consequences of body size and phylogeny. Biol. Rev. Camb. Philos. Soc. 88, 564–572.
Robertshaw, D., 2006. Mechanisms for the control of respiratory evaporative heat loss in panting animals. J. Appl. Physiol. 101, 664–668.
Robinson, S., 1949. Tropics. In: Newburgh, L.H. (Ed.), Physiology of Heat Regulation and the Science of Clothing. W.B. Saunders, Philadelphia, pp. 338–350.
Robinson, S., Meyer, F.R., Newton, J.L., Ts’ao, C.H., Holgersen, L.O., 1965. Relations between sweating, cutaneous blood flow, and body temperature in work. J. Appl. Physiol. 20, 575–582.
Romanovsky, A.A., 2007. Thermoregulation: some concepts have changed. Functional architecture of the thermoregulatory system. Am. J. Physiol. 292, R37–R46.
Romanovsky, A.A., 2014. Skin temperature: its role in thermoregulation. Acta Physiol. 210, 498–507.
Romanovsky, A.A., 2018. The thermoregulation system and how it works. Handb. Clin. Neurol. 156, 3–43.
Rowell, L.B., Brengelmann, G.L., Blackmon, J.R., Murray, J.A., 1970. Redistribution of blood flow during sustained high skin temperature in resting man. J. Appl. Physiol. 28, 415–420.
Royal Society, 1975. Quantities, Units and Symbols: a Report. Royal Society, London.
Ruben, J., 1995. The evolution of endothermy in mammals and birds: from physiology to fossils. Annu. Rev. Physiol. 57, 69–95.
Rubner, M., 1883. Über den einfluss der körpergrösse auf Stoff- und kraftwechsel. Zeitschrift fur Biologie 19, 535–562.
Ruf, T., Geiser, F., 2015. Daily torpor and hibernation in birds and mammals. Biol. Rev. Camb. Philos. Soc. 90, 891–926.

Satinoff, E., 1974. Neural integration of thermoregulatory responses. In: DiCara, L.V. (Ed.), Limbic and Autonomic Nervous Systems Research. Plenum Press, New York, pp. 41–83.
Satinoff, E., 1978. Neural organization and evolution of thermal regulation in mammals. Science 201, 16–22.
Satinoff, E., Rutstein, J., 1970. Behavioral thermoregulation in rats with anterior hypothalamic lesions. J. Comp. Physiol. Psychol. 71, 77–82.
Sato, K., 1977. The physiology, pharmacology, and biochemistry of the eccrine sweat gland. Rev. Physiol. Biochem. Pharmacol. 79, 51–131.
Savage, M.V., Brenglemann, G.L., 1996. Control of skin blood flow in the neutral zone of human body temperature regulation. J. Appl. Physiol. 80, 1249–1257.
Schmidt-Nielsen, K., 1984. Scaling: Why Is Animal Size So Important. Cambridge University Press, U.K.
Scholander, P.F., Krog, J., 1957. Countercurrent heat exchange and vascular bundles in sloths. J. Appl. Physiol. 10, 405–411.
Schwarck, J.B., Burdon, C.A., Taylor, E.A., Peoples, G.E., Machado-Moreira, C.A., Taylor, N.A.S., 2019. Thermogenic and psychogenic sweating in humans: identifying eccrine glandular recruitment patterns from glabrous and non-glabrous skin surfaces. J. Therm. Biol. 82, 242–251.
Seebacher, F., Franklin, C.E., 2005. Physiological mechanisms of thermoregulation in reptiles: a review. J. Comp. Physiol. B 175, 533–541.
Sessler, D.I., 2000. Perioperative heat balance. Anesthesiology 92, 578–596.
Sherrington, C.S., 1900. Cutaneous sensations. In: Schäfer, E.A. (Ed.), Text-book of Physiology. Volume Two. Young J. Pentland, Edinburgh, pp. 920–1001.
Shibasaki, M., Secher, N.H., Johnson, J.M., Crandall, C.G., 2005. Central command and the cutaneous vascular response to isometric exercise in heated humans. J. Physiol. 565, 667–673.
Shibasaki, M., Secher, N.H., Selmer, C., Kondo, N., Crandall, C.G., 2003. Central command is capable of modulating sweating from non-glabrous human skin. J. Physiol. 553, 999–1004.
Shibasaki, M., Wilson, T.E., Crandall, C.G., 2006. Neural control and mechanisms of eccrine sweating during heat stress and exercise. J. Appl. Physiol. 100, 1692–1701.
Shimada, S.G., Stitt, J.T., 1983. Inhibition of shivering during restraint hypothermia. Can. J. Physiol. Pharmacol. 61, 977–982.
Simon, E., 1974. Temperature regulation: the spinal cord as a site of extrahypothalamic thermoregulatory functions. Rev. Physiol. Biochem. Pharmacol. 71, 1–76.
Simon, E., 2000. The enigma of deep-body thermosensory specificity. Int. J. Biometeorol. 44, 105–120.
Simon, E., Pierau, F.-K., Taylor, D.M., 1986. Central and peripheral thermal control of effectors in homeothermic temperature regulation. Physiol. Rev. 66, 235–300.
Simon, E., Schmid, H.A., Pehl, U., 1998. Spinal neuronal thermosensitivity in vivo and in vitro in relation to hypothalamic neuronal thermosensitivity. In: In: Sharma, H.S., Westman, J. (Eds.), Progress in Brain Research, vol. 115. Elsevier, Amsterdam, pp. 25–47.
Smith, E.N., 1979. Behavioral and physiological thermoregulation of crocodilians. Am. Zool. 19, 239–247.
Snellen, J.W., 1966. Mean body temperature and the control of thermal sweating. Acta Physiol. Pharmacol. Neerl. 14, 99–174.
Snellen, J.W., 1972. Set point and exercise. In: Bligh, J., Moore, R.E. (Eds.), Essays on Temperature Regulation. North-Holland Publishing Company, Amsterdam, pp. 139–148.
Stanier, M.W., Mount, L.E., Bligh, J., 1984. Energy balance and temperature regulation. In: Cambridge Texts in Physiological Sciences, vol. 4 Cambridge University Press, Cambridge.
Stephenson, L.A., Wenger, C.B., O'Donovan, B.H., Nadel, E.R., 1984. Circadian rhythm in sweating and cutaneous blood flow. Am. J. Physiol. 246, R321–R324.
Stolwijk, J.A.J., Hardy, J.D., 2011. Control of Body Temperature. Comprehensive Physiology. Supplement 26: Handbook of Physiology, Reactions to Environmental Agents. pp. 45–68 First published in print 1977.
Strigo, I.A., Craig, A.D., 2016. Interoception, homeostatic emotions and sympathovagal balance. Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci. 371 20160010.
Sullivan, C.M., 1954. Temperature reception and responses in fish. J. Fish. Res. Board Can. 11, 153–170.
Swoap, S.J., 2008. The pharmacology and molecular mechanisms underlying temperature regulation and torpor. Biochem. Pharmacol. 76, 817–824.
Swoap, S.J., Gutilla, M.J., 2009. Cardiovascular changes during daily torpor in the laboratory mouse. Am. J. Physiol. 297, R769–R774.
Tanaka, M., McKinley, M.J., McAllen, R.M., 2011. Preoptic-raphé connections for thermoregulatory vasomotor control. J. Neurosci. 31, 5078–5088.
Tanaka, M., Ootsuka, Y., McKinley, M.J., McAllen, R.M., 2007. Independent vasomotor control of rat tail and proximal hairy skin. J. Physiol. 582, 421–433.
Tanner, J.M., 1949. Fallacy of per-weight and per-surface area standards, and their relation to spurious correlation. J. Appl. Physiol. 2, 1–15.
Tattersall, G.J., Andrade, D.V., Abe, A.S., 2009. Heat exchange from the toucan bill reveals a controllable vascular thermal radiator. Science 325, 468–472.
Tattersall, G.J., Cadena, V., Skinner, M.C., 2006. Respiratory cooling and thermoregulatory coupling in reptiles. Respir. Physiol. Neurobiol. 154, 302–318.
Taylor, N.A.S., 2015. Overwhelming physiological regulation through personal protection. J. Strength Cond. Res. 29, S111–S118.
Taylor, N.A.S., Kondo, N., Kenney, W.L., 2008a. The physiology of acute heat exposure, with implications for human performance in the heat. In: Taylor, N.A.S., Groeller, H. (Eds.), Physiological Bases of Human Performance during Work and Exercise. Churchill Livingstone Elsevier, Edinburgh, pp. 341–358.
Taylor, N.A.S., Machado-Moreira, C.A., 2013. Regional variations in transepidermal water loss, eccrine sweat gland density, sweat secretion rates and electrolyte composition in resting and exercising humans. Extreme Physiol. Med. 2, 4.
Taylor, N.A.S., Machado-Moreira, C.A., van den Heuvel, A.M.J., Caldwell, J.N., 2014a. Hands and feet: physiological insulators, radiators and evaporators. Eur. J. Appl. Physiol. 114, 2037–2060.
Taylor, N.A.S., Mekjavic, I.B., Tipton, M.J., 2008b. The physiology of acute cold exposure, with particular reference to human performance in the cold. In: Taylor, N.A.S., Groeller, H. (Eds.), Physiological Bases of Human Performance during Work and Exercise. Churchill Livingstone Elsevier, Edinburgh, pp. 359–377.
Taylor, N.A.S., Notley, S.R., 2018. Morphological and physiological considerations for the modelling of human heat loss. In: In: Shrivastava, D. (Ed.), Theory and Applications of Heat Transfer in Humans, vol. 2. John Wiley & Sons, Hoboken, New Jersey, pp. 463–499.
Taylor, N.A.S., Nykvist, Å., Powers, N., Caldwell, J.N., 2019. Thermoeffector threshold plasticity: the impact of thermal pre-conditioning on sudomotor, cutaneous vasomotor and thermogenic thresholds. J. Therm. Biol. 83, 37–46.
Taylor, N.A.S., Tipton, M.J., Kenny, G.P., 2014b. Considerations for the measurement of core, skin and mean body temperatures. J. Therm. Biol. 46, 72–101.
Templeton, J.R., 1970. Reptiles. In: In: Wittow, G.C. (Ed.), Comparative Physiology of Thermoregulation, vol. I. Academic Press, New York, pp. 167–223.
Tikuisis, P., Meunier, P., Jubenville, C.E., 2001. Human body surface area: measurement and prediction using three dimensional body scans. Eur. J. Appl. Physiol. 85, 264–271.
Todd, G., Gordon, C.J., Groeller, H., Taylor, N.A.S., 2014. Does intramuscular thermal feedback modulate eccrine sweating in exercising humans? Acta Physiol. 212, 86–96.
Vallerand, A.L., Savourey, G., Bittel, J.H.M., 1992a. Determination of heat debt in the cold: partitional calorimetry vs. conventional methods. J. Appl. Physiol. 72, 1380–1385.
Vallerand, A.L., Savourey, G., Hanniquet, A.-M., Bittel, J.H.M., 1992b. How should body heat storage be determined in humans: by thermometry or calorimetry? Eur. J. Appl. Physiol. 65, 286–294.
van Beaumont, W., Bullard, R.W., 1963. Sweating: its rapid responses to muscular work. Science 141, 643–646.
van der Vinne, V., Bingaman, M.J., Weaver, D.R., Swoap, S.J., 2018. Clocks and meals keep mice from being cool. J. Exp. Biol. 221, jeb179812.
Vendrik, A.J.H., 1959. The regulation of body temperature in man. Ned. Tijdschr. Geneeskd. 103, 240–244.
Vicent, M.A., Borre, E.D., Swoap, S.J., 2017. Central activation of the A_1 adenosine receptor in fed mice recapitulates only some of the attributes of daily torpor. J. Comp. Physiol. B 187, 835–845.
Vissing, S.F., Hjortsø, E.M., 1996. Central motor command activates sympathetic outflow to the cutaneous circulation in humans. J. Physiol. 492, 931–939.
Vissing, S.F., Scherrer, U., Victor, R.G., 1991. Stimulation of skin sympathetic nerve discharge by central command. Differential control of sympathetic outflow to skin and skeletal muscle during static exercise. Circ. Res. 69, 228–238.
von Euler, C., Söderberg, U., 1958. Co-ordinated changes in temperature thresholds for thermoregulatory reflexes. Acta Physiol. Scand. 42, 112–129.
Weinbaum, S., Jiji, L.M., Lemons, D.E., 1984. Theory and experiment for the effect of vascular microstructure on surface tissue heat transfer - Part I: anatomical foundation and model conceptualization. J. Biomech. Eng. 106, 321–330.
Werner, J., 1980. The concept of regulation for human body temperature. J. Therm. Biol. 5, 75–82.
Werner, J., 2010. System properties, feedback control and effector coordination of human temperature regulation. Eur. J. Appl. Physiol. 19, 13–25.
Werner, J., Buse, M., Foegen, A., 1989. Lumped versus distributed thermoregulatory control: results from a three-dimensional dynamic model. Biol. Cybern. 62, 63–73.
Werner, J., Mekjavic, I.B., Taylor, N.A.S., 2008. Concepts in physiological regulation: a thermoregulatory perspective. In: Taylor, N.A.S., Groeller, H. (Eds.), Physiological Bases of Human Performance during Work and Exercise. Churchill Livingstone Elsevier, Edinburgh, pp. 325–340.
White, C.R., Kearney, M.R., 2014. Metabolic scaling in animals: methods, empirical results, and theoretical explanations. Comprehensive Physiology 4, 231–256.
White, C.R., Seymour, R.S., 2003. Mammalian basal metabolic rate is proportional to body mass$^{2/3}$. Proc. Nat. Acad. Sci. U.S.A. 100, 4046–4049.
Wissler, E.H., 1961. Steady-state temperature distribution in man. J. Appl. Physiol. 16, 734–740.
Wissler, E.H., 1964. A mathematical model of the human thermal system. Bull. Math. Biophys. 26, 147–166.
Wissler, E.H., 2018. Human Temperature Control: a Quantitative Approach. Springer-Verlag, Berlin.
Wit, A., Wang, S.C., 1968. Temperature-sensitive neurons in preoptic-anterior hypothalamic region: effects of increasing ambient temperature. Am. J. Physiol. 215, 1151–1159.
Worthing, A.G., 1941. Is temperature a basic concept? In: American Institute of Physics. Temperature: its Measurement and Control in Science and Industry. Reinhold Publishing Corporation, New York, pp. 41–44.
Wyndham, C.H., Atkins, A.R., 1968. A physiological scheme and mathematical model of temperature regulation in man. Pflügers Archiv 303, 14–30.
Wyndham, C.H., McPherson, R.K., Munro, A., 1964. Reactions to heat of aborigines and Caucasians. J. Appl. Physiol. 19, 1055–1058.
Yang, Y., Gordon, C.J., 1996. Ambient temperature limits and stability of temperature regulation in telemetered male and female rats. J. Therm. Biol. 21, 353–363.
Young, A.A., Dawson, N.J., 1982. Evidence for on-off control of heat dissipation from the tail of the rat. Can. J. Physiol. Pharmacol. 60, 392–398.
Yu, C.-Y., Lin, C.-H., Yang, Y.-H., 2010. Human body surface area database and estimation formula. Burns 36, 616–629.
Zhang, Y.H., Hosono, T., Yanase-Fujiwara, M., Chen, X.M., Kanosue, K., 1997. Effect of midbrain stimulations on thermoregulatory vasomotor responses in rats. J. Physiol.

503, 177–186.
Zhang, Y.,H., Yanase-Fujiwara, M., Hosono, T., Kanosue, K., 1995. Warm and cold signals from the preoptic area: which contribute more to the control of shivering in rats? J. Physiol. 485, 195–202.



Nigel A.S. Taylor: Nigel has over thirty years of research experience in human stress physiology, with emphases on environmental physiology, and in particular, human temperature regulation. He is a graduate of the following institutions: University of Queensland (Australia), University of London (U.K.) and Simon Fraser University (Canada). He completed post-doctoral studies at the Naval Medical Research Institute (U.S.A.), and held an academic position at the University of Otago (New Zealand) before returning to Australia in 1991 (University of Wollongong). He retired from administrivia, but not from life or science, in 2018.

Christopher J. Gordon: Chris Gordon has spent the past four decades studying the behavioural and autonomic mechanisms of thermoregulation in experimental animals and humans. Dr. Gordon received a B.S. in biology and M.S. in Zoology from the University of Idaho in 1977 and a Ph.D. in Physiology from the University of Illinois, Champaign-Urbana in 1980. His doctoral research focused on the neural mechanisms of the thermoregulation in rabbits. In 1980 he was hired as Research Physiologist by the U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, to study the thermoregulatory effects of microwaves and radiofrequency (RF) radiation. His research addressed how RF radiation affected the behavioural and autonomic mechanisms of thermoregulation and the stability of core temperature in a variety of mammalian species. He later began to focus his research on the thermoregulatory effects of neurotoxicants and environmental pollutants on the thermoregulatory system of experimental animals and humans. The thermoregulatory effects of RF radiation that that is experienced during a Magnetic Resonance Imaging procedure is also a field of interest. He retired from the US EPA in 2018.