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# RECENT ADVANCES IN THERMOREGULATION

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**ABBREVIATED TITLE:** Thermoregulation update

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## **ABSTRACT**

Thermoregulation is the maintenance of a relatively constant core body temperature. Humans normally maintain a body temperature at 37°C and maintenance of this relatively high temperature is critical to human survival. So important is it that control of thermoregulation is often the principal example cited when teaching physiological homeostasis. A basic understanding of the processes underpinning temperature regulation is necessary for all undergraduate students studying biology and biology-related disciplines and a thorough understanding is necessary for those students in clinical training. Our aim in this review is to broadly present the thermoregulatory process taking into account current advances in this area. Firstly, we summarize the basic concepts of thermoregulation, and subsequently assess the physiological responses to heat and cold stress including: vasodilation and vasoconstriction, sweating, non-shivering thermogenesis, piloerection, shivering and altered behavior. Current research is presented concerning the body's detection of thermal challenge peripheral and central thermoregulatory control mechanisms, including brown adipose tissue in adult humans, temperature transduction by the relatively recently discovered TRP channels, and finally we present an updated understanding of the neuroanatomical circuitry supporting thermoregulation.

## Introduction

An understanding of body temperature regulation is necessary to learn the basic concept of homeostasis and for a wide variety of physiological and clinical applications. It is covered in most elementary physiology courses, but often with a degree of superficiality and dogma, due to time and content constraints. As research in this area has progressed over the last few decades, major advances in our understanding have been made, particularly in the central circuitry involved in thermoregulatory control and in the peripheral sensory mechanisms of temperature transduction. These advances have not necessarily filtered through to general textbooks that form the cornerstone of many medical-related and basic science courses (see 26). Here we describe the processes of thermoregulation, taking these recent advances into account so that those involved in teaching thermoregulation provide a more up-to-date representation.

Normal core body temperature is around 37°C and controlled within a narrow range (33.2-38.2°C) and narrowing further when disregarding oral measurements in favour of rectal, tympanic or axillary measurements (68). There are normal fluctuations that occur throughout the day (circadian rhythm), throughout a month (menstrual cycle) and throughout a life-time (aging). Abnormal core temperature deviations of even a couple of degrees will challenge the body's thermoregulatory mechanisms and swings in temperature outside the normal range can prove fatal. For example, beyond a body temperature of 42°C cytotoxicity occurs with protein denaturation and impaired DNA synthesis (38), resulting in end organ failure and neuronal impairment. If body temperature drops below 27°C (severe hypothermia) the associated neuromuscular, cardiovascular, haematological and respiratory changes can equally prove fatal (40). Despite the need for tight regulation of core temperature humans can survive in the most inhospitable of places and can challenge their thermoregulatory capacity in the most extreme ways. Humans participate in the Marathon Des Sables (a 251 km endurance running challenge in the Sahara desert, a place where day time temperatures can reach 50°C) and ice diving where water temperatures may only be a few degrees above freezing. How is it possible that they can do this and survive?

To ensure optimal physiological function and survival, humans must be able to preserve core body temperature (within the head, thorax and abdomen) in the face of environmental temperature challenges. Thus, heat gain to the body must equal heat loss.

As humans are endothermic homeotherms, we produce our own body heat and can regulate our body temperature. Our high core temperature is achieved principally through heat production as a result of metabolism. Heat transfer always occurs down a thermal gradient (from hot to cold)

through the processes of radiation, conduction and /or convection. As humans are often the hottest objects in a given environment, the normal direction of heat transfer is from the body to the surroundings. However, as core temperature rises heat loss through evaporation becomes the primary mechanism of heat dissipation.

The heat balance equation addresses the internal and external factors that contribute to thermal balance and therefore maintenance of core temperature:

Heat Storage = metabolism - work - evaporation  $\pm$  radiation  $\pm$  conduction  $\pm$  convection

where:

- Metabolism refers to the chemical reactions occurring within the body that produce heat. During exercise the working muscle liberates large amounts of heat.
- Work is the external work done.
- Evaporation is the heat loss to environment as water vaporized from the respiratory passages and the skin surface. Total sweat vaporized from skin depends on three factors:
  - i. surface area exposed to environment
  - ii. temperature & relative humidity of ambient air
  - iii. convective air currents around the body
- Radiation is the electromagnetic radiation (heat) transferred to bodies not in contact, including the ultraviolet light radiation from the sun which penetrates through to the surface of the earth and the infrared radiation from the body.
- Conduction is the movement of heat to/from the body directly to objects in contact with the body. Usually the amount of heat exchanged in this way is minimal.
- Convection is the transfer of heat to a moving gas or liquid. When a body is warm the air molecules that make contact with the body will be warmed, reducing their density which causes the molecules to rise and be replaced with cooler air. Convective heat exchange is increased by movement of the body in air or water or movement of air or water across the skin.

When the heat storage is zero, the body is thermally balanced. In humans, normal thermoregulation involves a dynamic balance between heat production/gain and heat loss, thereby minimalizing any heat exchange with the environment. Thus, a constant core temperature is maintained.

## Temperature regulation

When discussing body temperature we usually refer to the central core and peripheral shell temperatures. The core temperature reflects the temperature within the 'deep' body tissues, organs that have a high level of basal metabolism (such as the brain, heart and liver). The shell temperature is influenced by blood flow to the skin, which is raised with a high core temperature, and environmental temperature. It is usually measured at the skin of hands and feet. The surface area to mass ratio of these sites is high (for example, the surface area to mass ratio of each hand is 4–5 times greater than that of the body (72) and it is known that surface-area-to-mass ratio is important to the transfer of thermal energy. With a high surface-area-to-mass ratio the hand will chill faster than the torso which has a lower surface area to mass ratio. Notwithstanding this, the shell temperature is an important indicator of the heat exchange requirements of the body. Shell temperature is usually around 4°C lower than core temperature. In a warm environment the difference in temperature between the core and shell decreases as skin blood flow is increased and skin temperature approaches ambient temperature (see skin blood vessels section). As humans, we are generally warmer than the ambient temperature and so the general flow of heat is from the shell to the environment. During cold stress skin blood flow is reduced leading to a decrease in shell temperature and conservation of heat to the core. Temperature gradients between core and skin can be a useful non-specific monitor of thermal status. For example, there is an increased gradient between core and peripheral temperature in shock states and the gradient is useful in distinguishing between cardiovascular or respiratory causes of dyspnea (16).

The hypothalamus is the co-ordinating, or central integration center for thermoregulation. Evidence suggests that it is the pre-optic anterior hypothalamus that is the most important region for autonomic temperature control (57). The input to the hypothalamus comes from peripheral as well as central thermoreceptors. Recent experimental work from a number of laboratories has provided neural substrates for thermoregulatory control and is discussed in more detail later. Both peripheral and central thermoreceptors have two subtypes – those responding to cold and those responding to warmth. The peripheral thermoreceptors are located in the skin where the cold receptors are more abundant than the warm. Warm central thermoreceptors, located in the hypothalamus, spinal cord, viscera and great veins, are more numerous than cold. The impact of central thermoreceptor activation is most significant in terms of core temperature and it seems the activation of warm thermoreceptors causes inhibition of cold receptors (28). Table 1 below summarises the physiological and behavioral responses to the activation of these thermal receptors.

**Table 1**

<b>Body Temperature Stimulus</b>	<b>Sensors</b>	<b>Control Center</b>	<b>Effectors</b>	<b>Responses</b>
Increase	Peripheral & central thermoreceptors	Hypothalamus	<ol style="list-style-type: none"><li>1. Skin blood vessels</li><li>2. Sweat glands</li><li>3. Endocrine tissue</li><li>4. Behavior</li></ol>	<ol style="list-style-type: none"><li>1. Arteriolar and arterio-venous anastomoses (AVA) vasodilation</li><li>2. Sweating</li><li>3. Decreased metabolic rate (adrenal and thyroid glands)</li><li>4. Reduced activity, stretched body position and loss of appetite</li></ol>
Decrease	Peripheral & central thermoreceptors	Hypothalamus	<ol style="list-style-type: none"><li>1. Skin blood vessels</li><li>2. Arrector pili muscles</li><li>3. Skeletal muscles</li><li>4. Endocrine tissue</li><li>5. Behavior</li><li>6. Brown adipose tissue (BAT)</li></ol>	<ol style="list-style-type: none"><li>1. Arteriolar and AVA vasoconstriction</li><li>2. Piloerection and air trapping</li><li>3. Shivering thermogenesis</li><li>4. Increased metabolic rate (adrenal and thyroid glands), BAT</li><li>5. Increased activity, huddled body position, increased appetite</li><li>6. Non-shivering thermogenesis</li></ol>

## Effector organ response to an increase in body temperature

### Skin blood vessels

The skin plays a substantive role in the thermoregulatory process. In response to increased or decreased ambient or internal temperatures, skin blood flow is modified accordingly through sympathetic vasodilation and vasoconstriction mechanisms, respectively. Heat is dissipated from the body when blood is brought in close proximity to the skin's surface. This is achieved through vasodilation of skin blood vessels.

The mechanisms of thermal control for the cutaneous circulation have been thoroughly reviewed recently (29, 30, 31). The autonomic nervous system plays a major role in control of blood flow to the skin (15). Hair-bearing skin (non-glabrous skin) is innervated by both noradrenergic vasoconstrictor and cholinergic vasodilator nerves whereas non-hair-bearing skin (glabrous skin), present on the palms, soles and lips is innervated solely by vasoconstrictor nerve fibres.

In normothermia there is a baseline level of vasoconstrictive tone. In glabrous skin the principal response to heat is to increase cutaneous blood flow through passive vasodilation of blood vessels through sympathetic nervous activity withdrawal (25, 32). The presence of numerous arteriovenous anastomosis (AVAs) in glabrous skin can lead to large changes in blood flow to these regions, for example, in the heat AVAs open and blood flows directly from artery to vein bypassing the high resistance arterioles and the capillary loops (Fig. 1). **Put in Fig 1 here**

In non-glabrous skin, if the convective heat loss resulting from relaxation of vasoconstrictor tone is insufficient to cool the core then a further increase in skin blood flow can occur by active vasodilatation (31), thus increasing convective heat loss further. This active vasodilation is, at least in part, in response to the release of acetylcholine and other co-transmitters from sympathetic cholinergic nerves, and can increase cutaneous blood flow from  $300 \text{ ml}\cdot\text{min}^{-1}$  up to or exceeding  $8 \text{ L}\cdot\text{min}^{-1}$  (31). Various hypotheses that have been proposed with regard to the mechanisms involved in cutaneous active vasodilation (31). Very little is known for certain about the control processes; however the following has been proposed:

- 1) acetylcholine is the most important chemical for initialising active vasodilator responses to body heating but co-transmitter(s) appear to be principally responsible for the overall response. Candidates include vasoactive intestinal peptide, substance P, histamine, prostaglandins and TRPV-1 receptor activation



- 2) the cholinergic nerves that govern sweating may be the same as those that control active vasodilation. This hypothesis originates from the fact that active vasodilation and sweating seem to occur concurrently.
- 3) there seems to be a role for nitric oxide in active vasodilation as the response is attenuated by nitric oxide synthase inhibition.

## **Sweat glands**

Sweat production and subsequent evaporation is the principal mode of heat loss in humans when ambient temperature rises, as well as during exercise. In fact, evaporative cooling is the only mechanism of heat loss once ambient temperature exceeds body temperature. Exposure to a hot environment, or exercise, elevates core and skin temperatures, both of which contribute to the increased sweat rate. The threshold for sweating normally exceeds the threshold for vasoconstriction by approximately 0.2°C. However, it is known that sweating begins within seconds of the onset of exercise (74), before any measureable changes in internal temperature. This is thought to be mediated by a combination of inputs from central command and the exercise pressor reflex (61).

Sweat is released by eccrine glands which are distributed in large numbers (1.6-4 million) over the entire surface of the body, with regional distributions in density. Sweating is mediated by activation of sympathetic cholinergic fibres (62). Evaporation of sweat allows heat to be transferred to the environment as water vapour from respiratory passages and the skin surface. The major limiting factor in a human's ability to maintain body temperature in the face of a thermal challenge is the availability of water for sweat production. High volumes of sweat can be produced if a person becomes heat acclimatized, 2-3 litres per hour (2), compared to 1 litre per hour in non-acclimatized individuals (3). Heat acclimatization enhances the sweating mechanism and has previously been associated with a redistribution of sweat secretion towards the limbs (28). This could potentially be desirable as limbs have a relatively large surface area to mass ratio. An elevation in sweating and evaporation at these sites could therefore enhance thermal homeostasis. However, more recent evidence suggests that a redistribution of sweating from the trunk to the limbs does not occur (55, 71).

With heat acclimatization there is a lower body temperature threshold for sweating, and sweat gland sensitivity and capacity improves, so for a given core temperature the sweat rate increases (8, 17, 37, 56, 58). An increased sweat rate alters the composition of sweat and is particularly associated with depletion of plasma sodium and chloride concentrations. However, acclimatization

has been shown to attenuate this reduction. This is likely to be related to the increased renin and aldosterone levels that have been found in acclimatized individuals producing a lower sweat sodium concentration (49).

## **Behavioral adaptations**

Physiological thermoregulatory mechanisms have a finite capacity. Behavioral thermoregulation does not, therefore, changes in human behaviour can be extremely effective in response to a change in body temperature. Behavioral thermoregulation means that we can consciously and intentionally alter the heat exchange that takes place with our environments. For example, we can seek shelter from extreme heat by turning on the heating, grabbing a sweater, staying in the shade, consume ice-cold drinks etc. (for review see 22).

## **Exercise in heat**

Humans usually encounter thermal stress through adverse weather conditions, but thermal stress can result from the body's overproduction of heat (e.g. during exercise, fever). Exercise of itself will increase body temperature. This may be, in part, due to an initial cutaneous vasoconstriction, along with vasoconstriction in other non-active muscle vascular beds (splanchnic, renal, etc), that results in more of the cardiac output being available to active skeletal muscle (6, 33). Thus, exercising in the heat represents a particular challenge as heat loss is more difficult to maintain. It is associated with early fatigue and decrements in exercise capacity (23) and performance (70). If accompanied by a high relative humidity, the situation is exacerbated. This is principally due to the fact that less sweat can be evaporated from the skin's surface in humid environments (the sweating response to heat acclimatization is described above).

The development of fatigue during exercise in the heat is not associated with a single factor, but rather involves the interaction of many physiologic processes (52). At high exercise intensities or during prolonged exercise in the heat, heart rate increases and stroke volume reduces in parallel with a rise in core temperature. In addition cutaneous blood flow plateaus at a core temperature of approximately 38C (24). Therefore, beyond this core temperature the ability of the athlete to dissipate heat is reduced. A circulatory conflict is observed between the skin and the skeletal muscle, which contributes to fatigue. This situation is made all the worse if accompanied by substantial sweat loss and dehydration.

Training or repeated bouts of exercise have been shown to improve exercise performance (39) through various physiologic adaptations the most important of these are changes that facilitate increased peripheral blood flow while maintaining arterial blood pressure. Endurance training and heat acclimatization have been shown to improve vasodilatory ability (5, 7).

There are alterations in energy metabolism when exercising in the heat. Fatigue occurs earlier and is associated with glycogen depletion (21), while carbohydrate supplementation has been shown to improve exercise capacity in the heat (11). Exercise in the heat is associated with alterations in central nervous system function and motor drive, leading to central fatigue (27,51). Training and heat acclimatization are invaluable to athletes who exercise in warm environments. Knodo and co-workers (35) describe five phenotypic adaptations to heat: reduced heart rate at a fixed workload, expanded plasma volume, lower core temperature at an equivalent workload (thus increasing time to fatigue), superior salt reabsorption from sweat and an elevated sweat rate. All of these adaptations contribute to increased exercise performance in the heat.

## **Effector organ response to a decrease in body temperature**

### **Skin blood vessels**

When vasoconstriction occurs as a response to cold, then blood is shunted away from the skin surface through the deeper veins and heat is thus conserved and a widening of the gradient between core and peripheral temperature is observed. In response to cold, sympathetic vasoconstrictor nerves act primarily on  $\alpha$ -noradrenergic receptors to cause blood vessel smooth muscle contraction and vasoconstriction. Other sympathetically released co-transmitters also contribute to this vasoconstriction, such as ATP and neuropeptide Y (see 9; 10), the latter of which has been shown to contribute significantly to cutaneous vascular tone vasoconstrictor responses to human body cooling (64, 66).

### **Brown Adipose Tissue (BAT)**

BAT is specialised for the process of non-shivering thermogenesis where oxidative metabolism is uncoupled from ATP production and in the process energy is expended. This tissue is thermogenic by increasing the metabolic rate. BAT was, until recently, thought to be only important in small mammals and neonates. However, evidence for the activation of BAT in adult humans in response to cold has recently emerged (48, 59, 76), and a role for BAT in thermoregulation for adults as well

as neonates has become established (75). There is some debate as to whether this tissue that behaves like BAT, actually is true BAT, or is the so-called 'beige adipose tissue' which can develop from white fat cells in response to cold or  $\beta_3$ -adrenergic agonists (77, 80).

BAT's potential metabolic role has been recognised to the extent that it is considered as a potential site for drugs aimed at altering energy expenditure (73). BAT could potentially be a therapeutic site for treatment of obesity. Sympathetic nervous system activity, in response to inputs from peripheral and central thermoreceptors, can stimulate BAT thermogenesis. Catecholamines acting on  $\beta_3$ -adrenergic receptors can activate an uncoupling protein on the inner mitochondrial membrane. This uncoupling protein, thermogenin, allows  $H^+$  to cross the mitochondrial membrane without ATP production. It is known that sympathetic nervous system activity is increased in the cold and non-shivering thermogenesis increases likewise (34). In addition, BAT thermogenesis can be modulated by a number of non-thermal factors including hypoxia, infection, hypoglycaemia and psychological stress (42).

### **Piloerection (Goosebumps)**

The arrector pili muscle is a small band of smooth muscle that connects the hair follicle to the connective tissue of the basement membrane in non-glabrous skin. It is innervated by the autonomic nervous system. In response to increased sympathetic nerve discharge the arrector pili muscles at the base of tiny hairs in the skin contract and cause the hairs to become upright, trapping air and thus increasing the insulating layer of air around the body and minimizing heat loss. This is known as piloerection. As the muscle contracts the epidermis buckles creating 'goose bumps'. Piloerection is a known reaction to cold and also strong emotional stimuli. Piloerection is used as an index of autonomic sympathetic activity and is thought to be mediated by  $\alpha_1$ -adrenergic receptors (1). As humans possess relatively little hair and are often clothed, heat conservation through piloerection is usually regarded as insignificant and rudimentary. However, piloerection may become more important in conjunction with shivering potentially enhancing the effectiveness of the shivering response (54).

### **Shivering**

When exposed to mild cold, humans will conserve heat through mechanisms such as vasoconstriction and piloerection, which are energetically inexpensive and by changes in behavior.

If these adjustments are insufficient to maintain temperature shivering occurs. The onset of shivering has been used as an indicator that maximal vasoconstriction has already been achieved (19). It is initiated by the hypothalamic preoptic area but mediated by the somatic motor cortex in response to signals from cold receptors in the skin in particular; therefore, the normal stimulus for shivering is the skin temperature rather than the core temperature. Shivering threshold is normally described as the core temperature at which shivering is triggered. This is usually related to a given skin temperature.

Shivering is involuntary, rapid, oscillating contractions of skeletal muscle. ATP is hydrolyzed but no work is done through the contraction and so the energy produced is released as heat. In adults shivering, at its peak, can elicit heat production equivalent to five times the basal metabolic rate (20), however in neonates there is a notable absence of shivering due to the immaturity of their skeletal muscles, and non-shivering thermogenesis is the most important means by which heat is generated (67).

### **Behavioral adaptations to cold**

Behavioral thermoregulation seems to be particularly important in situations where the body is exposed to extreme cold, where vasoconstriction and shivering have a limited effect. Recent research suggests that behavioral control is influenced by many different areas of the brain—medulla oblongata, pons, midbrain, somatosensory cortex, amygdala, thermoregulatory centers in the hypothalamus as well as the pre-frontal cortex (for review see 22).

### **Transduction of temperature**

Major advances in the transduction processes in peripheral thermal sensation have been made since the discovery of the transient receptor potential (TRP) family of ion channels in the last decade and a half. TRPs are a superfamily of proteins that can be expressed in cell membranes and in membranes of internal structures (see 81). Many are polymodal in their activation, all resulting in cation influx. Nine are established as being sensitive to temperature and their roles have been extensively reviewed (12, 60). The classic notion of activation of a thermoreceptive neuron might describe a rather vague idea of receptor stimulation resulting from a change in intracellular metabolic chemical reactions in proportion to temperature (26). Yet this may also

describe specific sub-populations of temperature receptors that discriminate cold noxious, cold, warm and hot noxious stimuli with overlap between the stimulatory temperatures (see fig 2). Individual TRP channels have now been identified that may sub-serve these specific temperature discrimination roles. Each has a relatively narrow band of temperature activation, yet overlapping of these sensitivities allows for a wide range of temperature discrimination. TRPV1 and TRPV2 channels were amongst the first to be identified with temperature sensitivity (13, 14). They are activated by temperatures higher than 43°C and 52°C, respectively and may mediate noxious hot sensation. TRPV4 and TRPV3 are activated by temperatures above 25°C and 31°C, likely mediating innocuous warm sensation (63, 78). TRPM8 is increasingly activated as temperature drops below 27°C and is likely to mediate innocuous cold sensation (36). TRPA1 channels are activated at temperatures below 17°C and may contribute to noxious cold sensation, although this role is more controversial, as are the roles of TRPM2, M4 and M5 (12, 60). The role of these TRP channels can now be effectively mapped on to textbook figures produced prior to the knowledge of TRP channels, describing discharge frequencies at different temperatures of neurons from these temperature receptors (see Fig. 2). However, this must be viewed cautiously at present as few studies have identified these channels as the transduction mechanisms on primary thermosensitive afferents (46, 60, 65). Nevertheless, for many (thousands of) years we have been aware of chemical agonist stimulation of these channels. We may be familiar with the cooling sensation of menthol (TRPM8 agonist) as we chew our gum, or the warming/burning sensation we experience when eating food spiced with chilli (capsaicin, TRPV1 agonist).

Figure 2 here

It is likely that TRP channels are involved in thermal sensation. They may contribute by direct activation of sensory fibres; for example, TRPM8 channels are expressed in primary somatosensory neurons (4). They may also indirectly stimulate primary sensory fibres; for example, TRPV3 and V4 are expressed in abundance in skin keratinocytes which may secrete diffusible factors that stimulate sensory fibres (81). The molecular mechanisms responsible for temperature transduction in the brain, particularly the hypothalamus, are largely unknown, although involvement of TRP channels has not been found to date (see 47). With regard to neurons in the preoptic hypothalamus (POA), it has been proposed that spontaneous activity in their membranes represents pacemaker activity capable of generating spontaneous action potentials, and their temperature sensitivity reflects the temperature sensitivity of these membrane currents (79, 83). It has been proposed that thermal sensation in the spinal cord may reflect the activation of TRP channels in the central end of sensory neurons located in the spinal dorsal horn

(45). Temperature transduction mechanisms for receptive neurons that exist in the viscera (abdominal blood vessels, esophagus, and stomach amongst other organs) are also less well elucidated. However, animal studies have revealed several TRP channels, similar to the skin afferent nerves, are expressed in abdominal vagal afferent nerves (82).

### **Afferent pathways**

Cool and warm temperature information stimulates separate populations of primary somatosensory afferents in the skin. These enter the spinal (or trigeminal) dorsal horn to synapse with second-order ascending neurons in lamina 1. There are subtypes of ascending spinothalamic fibres that relay temperature information from the skin to the CNS and it is likely that fibres carrying information from innocuous cool or warm receptors provide the majority of the thermoregulatory information, rather than those relaying noxious hot or cold sensations (18).

More recent experiments by Morrison and Nakamura (43, 44) have incorporated labelling of neurons, to delineate projections, and electrophysiological recordings from the same neurons, to examine their responses to peripheral thermal stimulation. They have provided much more detailed information regarding central projections from the lateral parabrachial nucleus (LPB) where these second order neurons synapse. The LPB receives spinal input from cold-sensitive neurons (external lateral subnucleus of the LPB) and warm sensitive neurons (the dorsal subnucleus of the LBP). Third-order LPB neurons arise from these regions which then project to the median preoptic nucleus (MnPO) of the preoptic area of the hypothalamus (POA; 45, 47). Activation of these pathways will initiate either heat gain or heat loss mechanisms (45, 47). Other second-order neurons travel to the thalamus and then to cortex to allow conscious sensation of temperature (Figs. 3 & 4).

Afferents arising in the viscera travel to the CNS mainly in vagus and splanchnic nerves. The majority of this sensory information, including temperature, converges at the level of the nucleus tractus solitarius before passing to the LPB, so the LPB may integrate both skin and visceral thermal information (45, 47).

### **Central control of thermoregulatory responses**

Previously, temperature control was taught as involving integration of central and peripheral thermal signals coordinated in the POA and somehow involving a comparison of this integrated signal with a 'set-point' signal. If an error between the input temperatures and the set-point occurs, then this would trigger appropriate heat gain or heat-loss mechanisms. Although part of this model was based on the observation of thermal responses to heating and cooling of the skin and discrete regions of the hypothalamus (26), evidence of the central circuitry necessary for this model has been lacking. The application of several techniques has allowed these concepts to be updated. What appears to be emerging is a model in which an individual set-point within the hypothalamus is no longer necessary. Evidence is accumulating that central and peripheral temperatures influence individual effector circuits independently (45, 47, 57). Thermoreceptive neurons are activated when the appropriate temperature threshold for that neuron is reached, and action potentials ascend, via synaptic relays, to the POA. These signals, along with thermoreceptive signals arising within the POA, act upon the several effector outputs, and the influence of central and peripheral signals varies between different effectors (47, 57). Cold responses in general are more sensitive to skin temperature (potentially reflecting the preponderance of cold receptors), while hot responses are more sensitive to core temperature (where warm receptors are more numerous; 57). Indeed, there are distinguishable variations in the sensitivity of specific effector mechanisms to skin and core temperature. For example, the shivering response and BAT activation is most responsive to skin temperature, compared to the cutaneous circulation being influenced more by core temperature changes (41).

There is evidence that the individual effector circuits have distinctly different threshold temperatures. By carefully recording simultaneously the neural drive to individual effector organs, it has been possible to determine a threshold hierarchy for activation of each effector (41). For example, activation of cutaneous sympathetic vasoconstriction occurs slightly before (higher core temperature) the activation of BAT in rats (53, not confirmed in humans). Yet the contribution of all the relatively independent individual effector pathways collectively contributes to a steady core temperature of 37°C. In this way, the concept of 'set-point' has been updated with a more nuanced model, and the term 'balance-point' has been proposed as an alternative (57).

The combination of immunohistochemical identification, other identification techniques, such as the use of cFos, along with electrophysiological recording from identified neurons has allowed the identification of neuronal substrates that corroborate this emerging viewpoint from a number of leading researcher groups in this area (41, 45, 47, 53). The following is a summary of the control mechanisms for several of the temperature effector systems that have been elucidated in recent



years. Cold-sensitive neurons within the MnPO are activated by cutaneous/visceral afferent activity as well as direct stimulation of the MnPO neurons themselves (see Fig. 3). These activated inhibitory neurons project to the medial preoptic hypothalamus (MPO). In the case of neural control of blood vessels, these activated inhibitory neurons reduce activity in inhibitory projections to the rostral raphe pallidus (rRPa). Disinhibition allows full expression of on-going activity in the sympathetic vasoconstrictor outflow (via spinal cord, pre-ganglionic and post-ganglionic sympathetic nerves). Similarly, disinhibition occurs in outflow to skeletal muscle and BAT but at the level of the dorsomedial hypothalamus (DMH), allowing unimpeded activity in neurons arising in DMH and projecting to these targets via rRPa. This induces heat production by shivering in skeletal muscle, and increased metabolism in BAT.

Figure 3 here

Warm-sensitive neurons within the MnPO are activated by cutaneous/visceral afferent activity as well as direct stimulation of MnPO neurons themselves (see Fig. 4). These neurons project to the MPO where they activate inhibitory input which travels to the rRPa, via the dorsal medial hypothalamus (where there may be one further synapse in the case of outflow to skeletal muscle and BAT). Finally, this inhibitory signal slows or stops ongoing activity arising in neurons that project to the spinal cord to control output to cutaneous blood vessels, BAT and skeletal muscle.

Although the importance of the role of active vasodilatation has been established and several mechanisms by which it may be achieved have been found, there is still little or no information as to the central pathways responsible for its control.

The role of the POA in coordinating the fever response has been accepted for many years (26). But in recent years further detail of the mechanism of fever has emerged with the details of the thermoregulatory circuitry outlined above. It is likely that fever is induced by production of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) within the brain in response to various inflammatory mediators, such as cytokines, that are released as a result of infection. PGE<sub>2</sub> binds to receptors specifically on warm-sensitive MnPO and MPO cells within the POA and inhibits their activity (see Fig. 4). The resultant disinhibition of several individual pathways for thermoeffectors causes activation of shivering and BAT thermogenesis, along with cutaneous vasoconstriction (45), so that the raised 'balance point' of these effectors results in heat gain. This contrasts with a vague notion of single 'set-point' or thermostat simply being turned up, with no anatomical substrate. Non-steroidal anti-inflammatory drugs reduce fever by inhibiting the enzymes that are responsible for the production prostaglandins (Fig 3).

It should be emphasised that the majority of the studies that have allowed the development of these new models of temperature control have been carried out in animals, particularly rats. The extent to which these models are applicable in humans remains to be seen. However, the models of thermoregulation currently in our textbooks similarly rely on conclusions drawn from animal experimentation, largely because of the impracticality of examining these models in humans.

Figure 4 here

## **Conclusion**

The major advances in our understanding of thermoregulation that are outlined here are

- i. on the sensory side, several membrane channel proteins (TRPs) have been identified that may transduce specific temperature ranges
- ii. elucidation of discrete neuroanatomical circuitry for several of the thermoregulatory effectors within the hypothalamic region that updates the concept of the 'set-point'
- iii. recognition of a potential role for BAT in thermoregulation and metabolism
- iv. advances in the understanding of thermoregulatory control of have been paralleled by advances in the mechanisms that determine vasomotor tone (dilation and constriction), particularly in the roles played by the myriad of vasoactive neurotransmitters, locally released and systemic factors.

This information can be incorporated into current teaching of thermoregulation to take into account several of the more recent advances in the field. We anticipate that the overall teaching would not differ greatly, but the factual content would be more up-to-date. The main conceptual difference is the replacement of the 'set-point' model with the 'balance point'. Although 'set-point' has served as an effective and convenient concept to explain central control of core temperature, particularly in explaining thermoregulatory responses to fever, we now have a replacement model that is much more firmly based on experimental data, and yet is conceptually no more complicated.

Figure 1. Control of peripheral blood flow to glabrous skin. With permission from (69).

Note the presence of arteriovenous anastomoses, which have a rich supply of sympathetic vasoconstrictive fibers. The arteriovenous anastomoses connect arterioles directly to the venous plexus. Increased sympathetic tone in response to a decrease in core temperature constricts arterioles and reduces blood flow through arteriovenous anastomoses to almost nothing, thereby reducing heat loss from the surface of the skin. In response to an increase in body temperature, the withdrawal of sympathetic tone leads to passive dilation of arterioles and arteriovenous anastomoses and enables heat loss by increasing blood flow to the venous plexus. Precapillary sphincters are only sparsely innervated by sympathetic nerves. At rest, there is a high degree of sympathetic tone to the skin.

Figure 2. Discharge frequencies at different skin temperatures of thermoreceptors, along with potential TRP channels associated with receptor function (reproduced with permission from 26)

Figure 3. Central circuitry mediating the response to cold

POA – pre-optic area of the hypothalamus; MnPO – Median preoptic nucleus; MPO – medial preoptic area; DMH – dorsomedial hypothalamus; rRPa – rostral raphe pallidus nucleus; LPB – lateral parabrachial nucleus; BAT – brown adipose tissue (after 45, which also gives details of putative/known central neurotransmitters in these pathways).

Figure 4. Central circuitry mediating responses to warm

Abbreviations as in Fig. 3, in addition, PGE<sub>2</sub> – Prostaglandin E<sub>2</sub> (after 45). Non-steroidal anti-inflammatory drugs have an anti-pyretic affect by inhibiting the enzyme (cyclooxygenase) responsible for producing prostaglandin E<sub>2</sub> (PGE<sub>2</sub>).

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Fig1

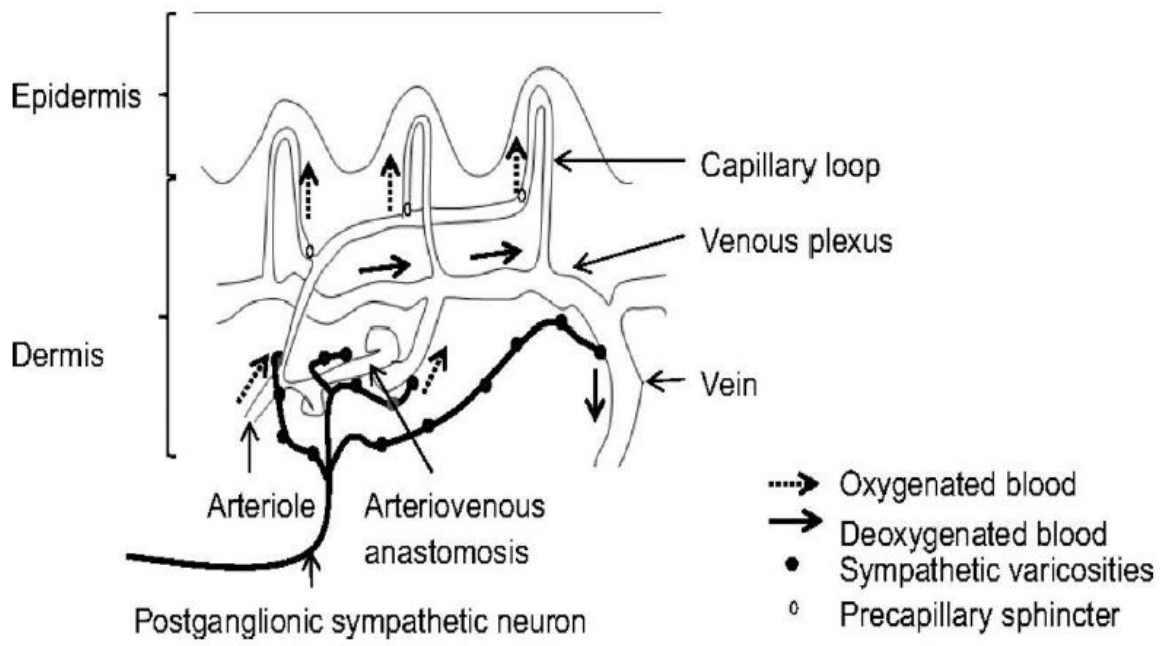
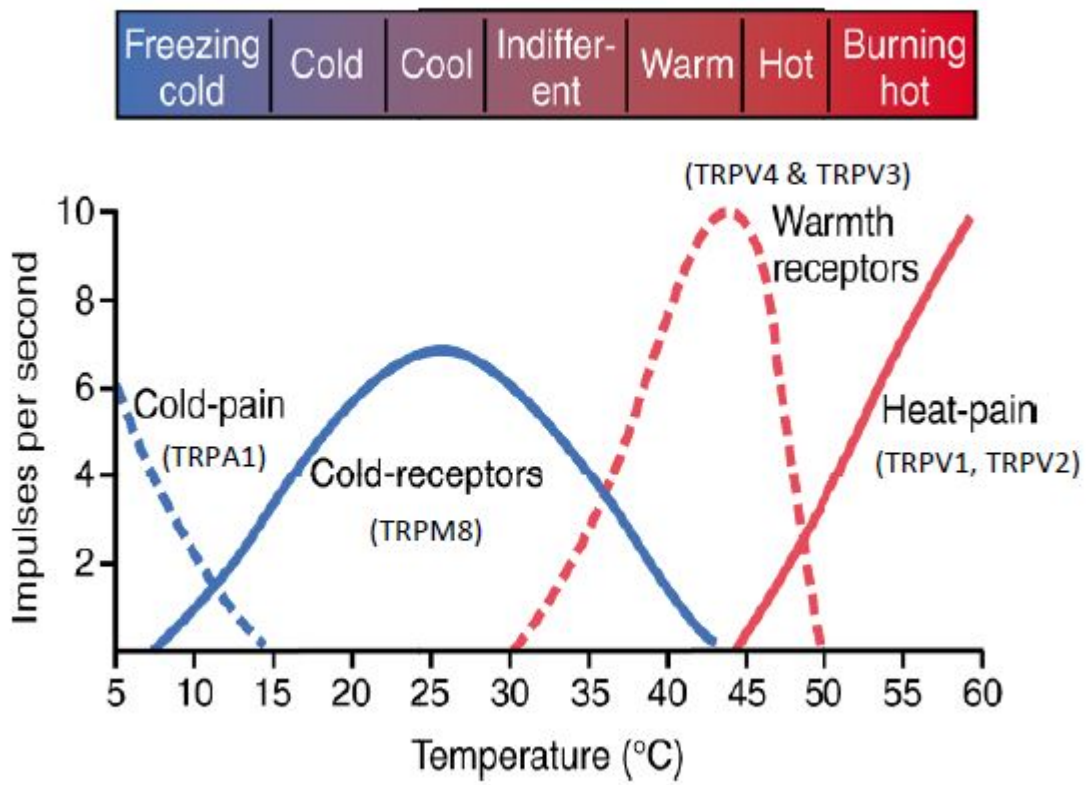


Fig2



**Fig3**

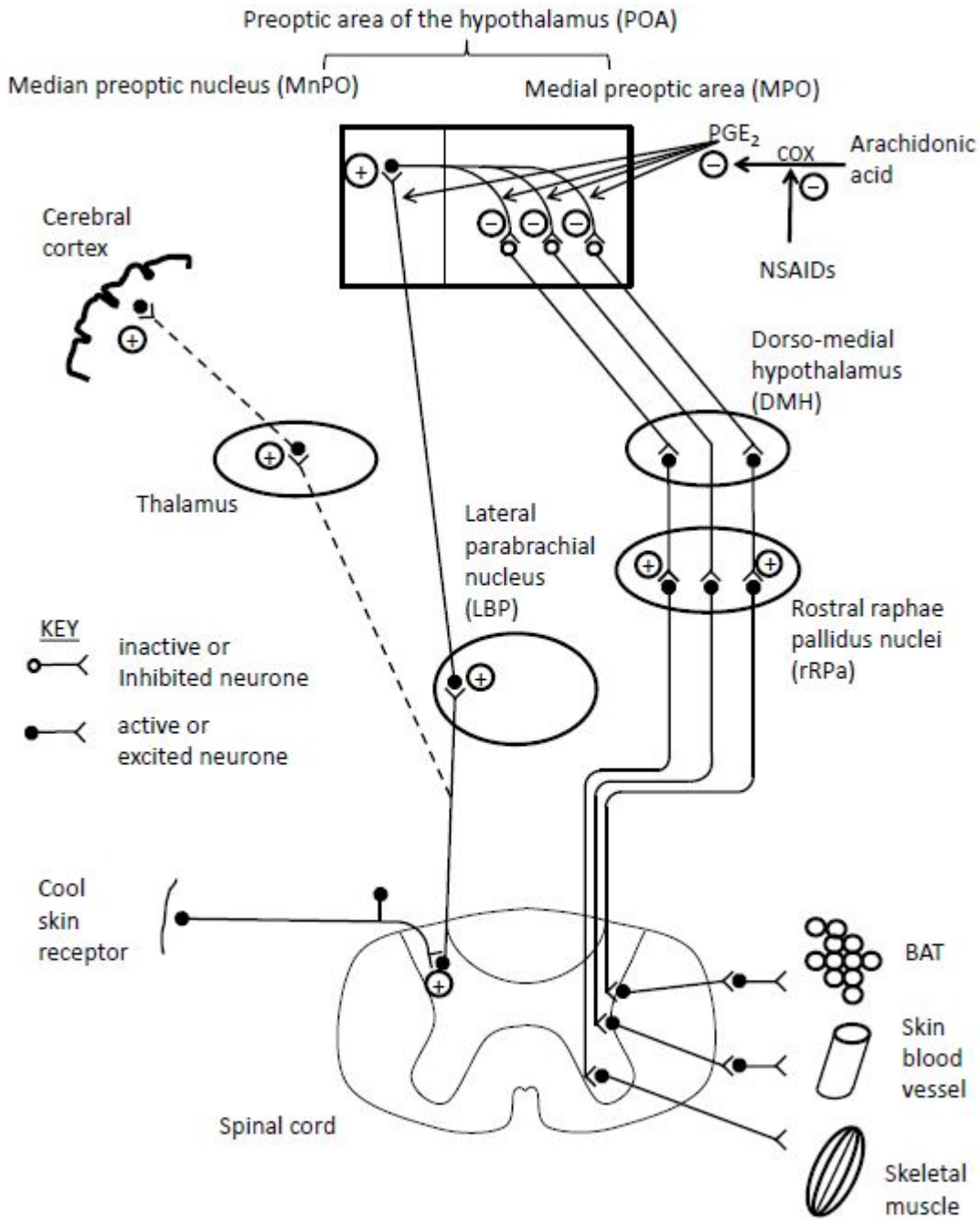


Fig 4

