REVIEW
Skin temperature: its role in thermoregulation

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Abstract

This review analyses whether skin temperature represents ambient temperature and serves as a feedforward signal for the thermoregulation system, or whether it is one of the body's temperatures and provides feedback. The body is covered mostly by hairy (non-glabrous) skin, which is typically insulated from the environment (with clothes in humans and with fur in non-human mammals). Thermal signals from hairy skin represent a temperature of the insulated superficial layer of the body and provide feedback to the thermoregulation system. It is explained that this feedback is auxiliary, both negative and positive, and that it reduces the system's response time and load error. Non-hairy (glabrous) skin covers specialized heat-exchange organs (e.g. the hand), which are also used to explore the environment. In thermoregulation, these organs are primarily effectors. Their main thermosensory-related role is to assess local temperatures of objects explored; these local temperatures are feedforward signals for various behaviours. Non-hairy skin also contributes to the feedback for thermoregulation, but this contribution is limited. Autonomic (physiological) thermoregulation does not use feedforward signals. Thermoregulatory behaviours use both feedback and feedforward signals. Implications of these principles to thermopharmacology, a new approach to achieving biological effects by blocking temperature signals with drugs, are discussed.

Keywords auxiliary feedback, body temperature, feedforward, thermopharmacology, TRPM8, TPRV1.

Our skin is the 2-m²-large organ that serves as a barrier between our internal and external environments and protects the former from diverse unfavourable factors of the latter, thus allowing us to maintain homeostasis. The skin is also the largest sensory organ in our body, and it further contributes to homeostasis by sensing various disturbances occurring at the border of the two environments, including thermal disturbances, and triggering defence responses. Amazingly, there is no agreement on which thermal disturbances are detected by the skin, external or internal. A large group of recent papers (Nakamura & Morrison 2008, 2010, Kanosue *et al.* 2010, Nakamura 2011) states that cutaneous nerves detect environmental temperature, and that environmental thermal signals from the skin serve as feedforward signals in the control of body temperature. The term 'feedforward' plays a central role in several of these papers: it is selected as a keyword and used to label the neural thermoregulatory pathway from skin. The second, smaller, group of recent papers (Romanovsky *et al.* 2009, Werner 2010) states that skin temperature is one of the body's temperatures, and that thermal cutaneous signals serve as feedback signals in the thermoregulation system. Further complicating the issue, several investigators, including this writer, treated it differently in different papers. For example, in the 2007 review (Romanovsky 2007b), following the examples of many before

me (Huckaba *et al.* 1971, Partridge & Partridge 1992, McAllen *et al.* 2006), I considered cutaneous thermal signals to be feedforward. Since then, I have realized that this treatment was erroneous, and in the next review, my co-authors and I treated skin temperature as a feedback signal (Romanovsky *et al.* 2009). I intend to justify this new treatment in the present paper.

Feedback vs. feedforward control

The typical reader of this article is well familiar with the feedback control: it is used by most physiological systems. In fact, the negative feedback control is the basis of homeostasis. We also often come across this type of control in our everyday life, with a house thermostat being an example. As the house is cooled by the environment on a freezing night, the air temperature inside the house drops below the thermostat's set value, and this turns on the heater, which starts warming the house. A feedforward control system would deal with the same issue differently. Imagine a system (and such systems do exist) that measures air temperature outside the house and turns the heater on when the outside temperature drops, before it affects the inside temperature. This example shows that in contrast to the feedback system, which reacts to a change in the controlled variable (reactive control, correction), the feedforward system responds to a disturbance without having the controlled variable being affected first (proactive control, avoidance). A feedback signal comes from the system's controlled variable; a feedforward signal does not depend on the controlled variable(s). A schematic of how a thermoeffector can be controlled via a feedback loop is shown in Figure 1a. Figure 1b shows how a feedforward signal can be added to the control of the same effector. A more detailed discussion of the feedback and feedforward control is presented by Werner (2010).

The feedforward hypothesis is appealing

It is widely agreed that the deep (core) body temperature is the main control variable of the thermoregulation system, and that, as such, it also represents a feedback signal (Fig. 1). To serve as a feedforward signal, skin temperature should not depend on the activity of the thermoregulation system; it should represent not one of the body's temperatures, but the ambient temperature. Our everyday experience shows that skin temperatures differ drastically from the deep body temperature. The most obvious difference is that the deep body temperature is relatively constant, while skin temperatures are not. When we step outdoors on a freezing day and have any portion of the skin
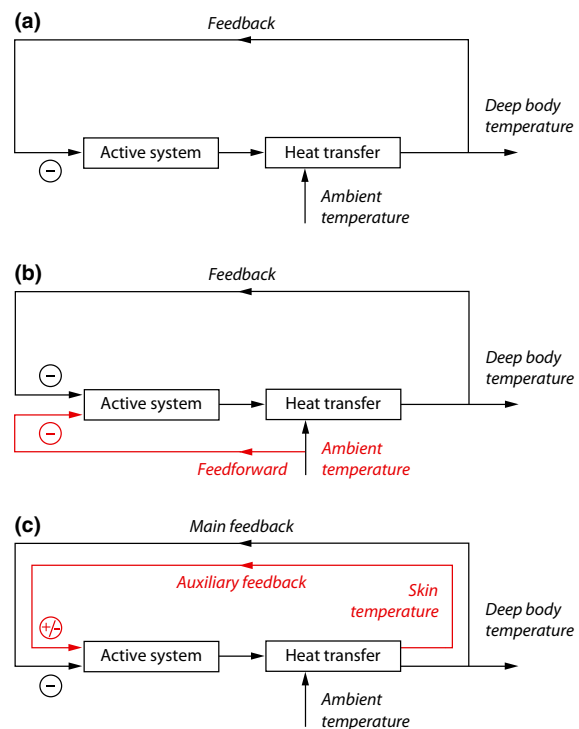

Figure 1 Feedback and feedforward in thermoregulation. The multisensory, multieffector thermoregulation system can be described as a federation of relatively independent thermo-effector loops (Romanovsky 2007b). The three hypothetical schematics show how body temperature may be regulated within an individual thermoeffector loop. The active elements of each loop (in principal, thermoreceptors and the thermoeffector) are marked as the active system; the passive system (processes of heat transfer) is marked as heat transfer. (a) Deep body temperature is controlled via a negative (−) feedback loop. (b) Deep body temperature is controlled by the same negative feedback loop (from deep body temperature) supplemented by a feedforward signal (ambient temperature). The feedforward control signal is shown in red. (c) The same negative feedback control loop (as in panel a) is supplemented by auxiliary feedback control (from skin temperature). The auxiliary feedback (which can be negative or positive, +/−) is shown in red.

exposed (usually the face and the hands), the exposed areas soon become cold, even though any skin protected by clothes remains warm. Hence, it is tempting to think that skin temperature, at least that of the exposed areas, reflects our external, rather than internal, thermal environment. Moreover, the skin temperature is often used by our brain specifically for assessing temperatures in our external environment. An example of such a use would be testing water by dipping our fingers in it before entering a bathtub. Furthermore, thermoreceptors have been found in the organs that serve predominantly for investigating the external environment, such as the antennae of differ-

ent insects, including cockroaches (Loftus 1968); such a location is poorly suited for measuring temperature of the body but is ideal for measuring ambient temperature. Based on the above, it seems logical to view thermal cutaneous signals as measures of ambient temperature and, consequently, as feedforward signals for the control of deep body temperature (Fig. 1b). Although this intuitive view is popular, it may be erroneous.

Skin temperature of heat-exchange organs reflects local vasomotor tone

So far, we have not taken into account the fact that, from the thermoregulation point of view, our skin is heterogeneous. The first type of skin is the non-hairy (glabrous) skin. This skin covers specialized organs for insensible heat loss ('radiators'), such as the human palm, rat tail, rabbit ear or chicken comb. These heat-exchange organs are characterized by several common features, including the absence of hair, dense vascularization, the presence of arteriovenous anastomoses and a large surface-to-volume ratio. To meet the latter requirement, many of these organs are located distally, far from the geometric centre of the body. Because of all these features, the biological radiators are capable of mounting two opposite responses. The first response, rapid dumping of heat into the environment, occurs when the blood flow through these organs is increased (cutaneous vasodilation) and directed to the anastomoses. Remarkably, in the human finger, the flow can increase by 500% (Nagasaka *et al.* 1987). The second, abrupt cessation of heat loss, occurs when the anastomoses shut, and the cutaneous blood flow decreases to nearly 0 (cutaneous vasoconstriction). When this happens, for example, in the rat tail, the skin temperature behaves as if no cutaneous blood flow were present at all, that is, as in a dead body (Szekely & Szelenyi 1979).

In contrast to other heat-defence responses (such as sweating in humans, panting in dogs or thermoregulatory salivation in rats), cutaneous vasodilation does not result (at least not directly) in loss of water. In contrast to other cold-defence responses (such as shivering or non-shivering thermogenesis), cutaneous vasoconstriction does not require the burning of fuel. Because thermoregulatory vasodilation and vasoconstriction in the non-hairy skin do not impede on the body's reserves of either water or energy, these responses are used as the first-line autonomic defences against heat and cold, respectively. As such, these responses are recruited in thermoregulation very often. Within the zone of thermal neutrality (Romanovsky 2007b), the regulation of body temperature relies on them exclusively (or almost exclusively, if behavioural

thermoregulation is also accounted for). Accordingly, within the thermoneutral zone, the skin temperature in these organs fluctuates widely, reflecting always changing vasomotor tone (Savage & Brengelmann 1996, Romanovsky *et al.* 2002). At one point in time, the skin is vasoconstricted, and the skin temperature approaches ambient temperature; a few seconds later, the skin is vasodilated, and its temperature approaches deep body temperature. Clearly, the skin temperature in the heat-exchange organs is not a reliable measure of the ambient temperature. It depends primarily on the local vasomotor tone, which depends on, among other factors, deep body temperature. Because thermal signals from the heat-exchange organs are not independent of body temperature and do not represent ambient temperature, they cannot be used as feedforward thermal signals from the environment.

Non-hairy skin covering the forehead in humans deserves a special consideration. Through convective and conductive heat transfer, forehead temperature is 'contaminated' by the temperature of the underlying metabolically active brain, as the effective heat transfer coefficient for the forehead is higher than for the rest of the body (Sessler & Sessler 1998). In addition to arteries (which show on the infrared thermograms of the forehead as spots having temperatures approaching deep body temperature), the high rate of heat transfer across the forehead tissues can be aided by the system of emissary veins with their bidirectional blood flow (Cabanac 1995). In fact, parents all over the world believe that a high forehead temperature (as determined by touching their child's forehead) is an indicator of fever (i.e. an indicator of a high deep body temperature). This belief, however, has found limited support in clinical studies (Katz-Sidlow *et al.* 2009). Infrared measurements of forehead temperature proposed for mass detection of febrile subjects in airports and other places also produced largely disappointing results (Hausfater *et al.* 2008). Nevertheless, if one accepts that the forehead skin is heated by the underlying brain, this would make this area of non-hairy skin an even worse indicator of ambient temperature.

Exploring the environment: feedforward signals for behaviours

Discussions about thermoregulation tend to include autonomic (physiological) regulation only. Behavioural thermoregulation, which has different control mechanisms and pathways (Romanovsky 2007b, Nakamura & Morrison 2008, Flouris 2011), is often not considered at all, whereas occasionally it is treated in a special way, subservient to autonomic thermoregulation (Kanosue *et al.* 2010). Many simple

behaviours are primarily thermoregulatory in their nature; moving towards a preferred ambient temperature is an example. In addition, there are many complex behaviours that have thermoregulatory consequences, for example nest building in rats or the construction of a space shuttle by humans (Romanovsky 2007a). Thermal signals are also used for non-thermoregulatory behaviours, such as avoidance behaviour caused by noxious heat or cold. So far, we have been looking primarily at autonomic thermoregulation, and the heat-exchange organs are important effectors of (but not a source of feedforward control signals for) autonomic thermoregulation. However, many organs that are covered by non-hairy skin, such as the human palm and face or the rat paw and snout, are not only radiators. In agreement with the most distal location of these organs, animals use them to touch and otherwise explore various objects in the environment. When we touch objects to determine their temperature, as in the example with the water in a bathtub, we are interested in the specific objects explored – not in the overall heat exchange between our body and the environment at that moment. The information obtained from the skin of the hand in the bathtub example is used to assess and, if necessary, adjust the temperature to which we will be exposed in the future; it serves as a feedforward signal for a complex behaviour with a thermoregulatory component. Different uses of thermal information require different neural pathways. Thermal signals that control most thermoregulatory behaviours do not travel through the pre-optic hypothalamus (Roberts 1988, Almeida et al. 2006) and, in general, do not follow the autonomic pathways (Nakamura & Morrison 2008). Instead, they (at least some of them) follow the pathway used for discriminative temperature sensation (Craig 2002).

Temperature of hairy skin: feedback for thermoregulation

Whereas the specialized heat-exchange organs (most distal portions of our body) are covered by non-hairy skin, the rest of the body (more proximal area) is covered by hairy (non-glabrous) skin. The hairy skin is characterized by the lack of arteriovenous anastomoses and by the presence of hair follicles. Both features make this skin better suited to serve as a thermal insulator, rather than a radiator. There are many examples of studies, both in rats (Vianna & Carrive 2005, Tanaka et al. 2007) and in humans (Saad et al. 2001, Kondo et al. 2003), showing that the vasomotor tone in hairy and non-hairy skin is regulated differently. Accordingly, temperatures of these two types of skin behave differently. The temperature of the non-hairy

skin varies widely, as described previously. The hairy skin is thermally more stable, as it is typically insulated from the environment by clothes in humans or by fur or feathers in other endothermic animals. In fact, using unclothed humans and closely shorn domestic animals in thermoregulation research has been criticized for artificially creating a paradigm in which the hairy skin becomes strongly affected by ambient temperature (Kitzing et al. 1972). But even in those cases when the hairy skin is not insulated with hair, it still has a thermal profile different from the glabrous skin. An infrared image of the body can readily reveal the two skin types (Fig. 2).

The proximally located and insulated hairy skin seems to be a bad place to assess ambient temperature. Indeed, no one would think that putting a thermometer under the clothes of a warmly dressed man on a cold day would give an accurate reading of the ambient temperature. Sticking a thermometer under the fur of a polar bear may not work well either. Furthermore, temperature in some areas of the hairy skin, for example the rostral back in the rat, is strongly affected by the thermogenesis in the underlying brown adipose tissue (Marks et al. 2009) (also see Fig. 2). An important fact from the clinical point of view is that temperature of hairy skin in the body's nooks and crannies (e.g. the external acoustic meatus and axilla) often approaches

Figure 2 Two types of skin in a rat. Two images of a genetically hairless (Crl:CD-Hrhr) rat exposed to cold are overlaid. The bottom layer is a regular (visible spectrum) photograph. The top layer is a transparent infrared thermogram. In the thermogram, temperatures from 31.0 to 37.0 °C are coded with yellow (from dark to light respectively), temperatures below 31.0 °C are coded with black, and temperatures above 37.0 °C are coded with purple. As a result, the vasoconstricted skin over the heat-exchange organs shows as black, whereas the skin over the rest of the body is yellow. The external acoustic meatus and the skin over interscapular brown adipose tissue have higher temperatures and show as purple.

deep body temperature. In fact, despite their widely acknowledged shortcomings [see e.g. Romanovsky et al. (1997)], both tympanic and axillary temperatures are used as measures of deep body temperature in many countries, both by people taking their temperature at home and by medical personnel in hospitals. Interestingly, the meatus temperature of the cold-exposed rat shown in Figure 2 is higher than 36.0 °C. It is hard to dispute, therefore, that temperature of hairy skin is not an ambient temperature; it is a body temperature. As such, it is used as a feedback signal driving autonomic effectors, but also for the perception of thermal comfort and thermoregulatory behaviours.

It has been recognized for some time that, theoretically, the thermal receptive fields influencing thermoeffectors (including the cutaneous blood flow) should be located remotely from the radiator organs, that is, in the hairy skin (Aschoff & Wever 1958). In practice, however, thermal signals from non-hairy skin also contribute to driving various effector mechanisms to the extent that varies widely across skin areas, species and thermoeffector responses (Jessen 1985); they also contribute to the perception of thermal comfort (Nakamura et al. 2013). In the case of cold-induced shivering in humans, the contribution of thermal signals from the face and hands has been shown to be negligible (Doufas et al. 2003). However, the exploration organs, especially the face, have a high concentration of thermoreceptors, and their sensitivity to both cold and warmth is high (Stevens & Choo 1998). Hence, even though the human face has the surface area of perhaps 4–5% of the total skin area, it accounts for the unproportionally large share of the total skin signal driving some thermoeffectors. For example, in the case of thermoregulatory sweating in humans, the face accounts for 20% of the total drive from the skin (Nadel et al. 1973). But even in such cases, the vast majority of thermal cutaneous signals that drive autonomic thermoeffectors (at least 80%) originate in the hairy skin. This can be expected, because almost the entire body is covered by hairy skin. In humans and other primates, the non-hairy skin covers only the palms of the hands, the soles of the feet, the ear pinnae and areas of the face. The ratio of the areas of hairy and non-hairy skin in the rat can be assessed by comparing the yellow and black skin areas, respectively, in Figure 2. It is the expansive hairy skin of the trunk and proximal extremities (most importantly of the abdomen), not the scarce non-hairy skin, that is the primary source of thermosensory information used for thermoregulation. In the cold, thermal signals from the abdomen are also of primary importance for the perception of thermal comfort by humans (Nakamura et al. 2013). In a recent study in our laboratory (Almeida et al. 2012), before applying a menthol ointment to rats, the investigators tested it on their own skin. Menthol is an agonist of the transient receptor potential melastatin-8 (TRPM8, formerly known as the cold and menthol receptor 1) channel, which serves as a cutaneous thermosensor for several cold-defence responses (Almeida et al. 2012). When the ointment with this TRPM8 agonist was applied to the hands, it caused almost no cooling sensation. In contrast, when a comparable amount of ointment was applied to the abdomen, it caused cold discomfort and triggered shivering (M.C. Almeida, T.B. Nucci & A.A. Romanovsky, unpublished observation).

A different feedback: skin temperature signals are auxiliary

It may be difficult to accept that cutaneous temperature represents a feedback signal, because deep body temperature is indisputably a feedback signal, and the roles of the two temperatures in thermoregulation are clearly not identical. Can the idea of skin temperature being a feedback signal be reconciled with the idea that its role in thermoregulation is different from the role of deep body temperature?

It is stated above that the deep body temperature is the main control variable of the thermoregulation system. A more precise statement would be that the regulated variable in the thermoregulation system is an integrative, spatially distributed temperature signal, which incorporates deep (core) body temperatures (those of the brain and viscera) and shell (peripheral) temperatures (those of the skin and subcutaneous tissues) (Werner 1979, 2010, Romanovsky 2007b). Different effectors within the thermoregulation system are driven by different combinations of core and shell temperatures; experimental demonstrations of such differences go back to the 19th century [reviewed by Bligh (1966)]. Peripheral temperatures are relatively more important for driving most (but not all) thermoregulatory behaviours (Roberts 1988), whereas deep body temperatures are relatively more important for triggering autonomic responses (Jessen 1981, Sakurada et al. 1993). As summarized elsewhere (Romanovsky 2007b), such an organization reflects the fact that behavioural responses are often aimed at escaping forthcoming thermal insults. Even though skin temperature is generally not a good measure of ambient temperature, it is still more responsive to changes in the thermal environment than deep body temperature. In contrast, autonomic cold defences (energetically expensive) and heat defences (water-consuming) are often recruited only when deep body temperatures start changing after any behavioural mechanisms and vasomotor responses in the heat-exchange organs recruited appeared ineffective.

Among the autonomic defences, different thermoeffectors are also triggered by different combinations of skin and deep body temperatures (Bligh 1966). Because peripheral thermosensors are mostly cold sensors, information from the periphery is relatively more important for triggering cold-defence effectors (Sakurada *et al.* 1993, Bratincsak & Palkovits 2005, Tanaka *et al.* 2006, Nakamura & Morrison 2007) than heat defences (Sakurada *et al.* 1993). Because central thermosensors are mostly warmth sensors, information from body's core is relatively more important for triggering heat-defence responses (Sakurada *et al.* 1993). Nevertheless, if core temperature is high (near the threshold for sweating) and constant, changes in skin temperature become sufficient to drive the sweat rate in a rather spectacular fashion (McCaffrey *et al.* 1979, Fealey 2013). Overall, however, there is consensus that deep body temperatures contribute to thermoregulation with a higher weight than skin temperatures.

Translating the described organization into an engineering control concept, a feedback thermal signal represented by heavily weighted core temperatures and lightly weighted skin temperatures is equivalent to a control system with deep body temperature being the main controlled variable, and also serving as the main feedback signal, and skin temperature being a secondary (auxiliary) feedback signal (Romanovsky *et al.* 2009, Werner 2010). Here, auxiliary means supplementary, supporting control of the main variable, deep body temperature. The auxiliary variable (skin temperature) is not defended. A control system with auxiliary feedback is shown in Figure 1c. Werner (2010) points at two characteristics that engineers find desirable for an auxiliary control variable.

First, they prefer to select, as the auxiliary variable, a variable that responds to disturbances more quickly than the main control variable. This reduces the system's response time (delay), an effect similar to that of auxiliary feedforward control. Skin temperature clearly possesses this first characteristic. Furthermore, some skin thermoreceptors respond not to the temperature, but to the rate of temperature change (Hensel 1974), and there may also be a mechanism for detecting a spatial temperature gradient in the superficial skin layer (Slepchuk & Ivanov 1992). Both mechanisms may contribute to reducing the response time.

Second, in contrast to the main variable, which is almost always used with a negative feedback, the auxiliary variable is often used with a positive feedback. According to Werner (2010), this may be beneficial in the steady state, as the use of positive feedback can reduce or even eliminate what is known as the load error. The load error is the deviation of a feedback-controlled variable (body temperature in the thermo-regulation system), observed in the presence of disturbances, as compared to the value of this variable in the absence of disturbances (i.e. in a thermoneutral state). The load error is the minimum deviation in the controlled variable that produces the system's response (a thermoeffector response). A reduced load error in the thermoregulation system means a more stable body temperature. Skin temperature possesses the second Werner's characteristic, as it can be used as a positive feedback signal, for example, in the thermoregulatory control of skin vasoconstriction in a cool environment: low skin temperature → vasoconstriction → lower skin temperature. Hence, the skin temperature is well suited for playing the role of an auxiliary feedback control signal (Fig. 1c). This role is somewhat different from the role of the main feedback signal played by the deep body temperature and contributes to the overall thermoregulation by reducing both the response time and load error.

Perspective: the birth and future of thermopharmacology

During the past two decades, several temperature-sensitive transient receptor potential (TRP) channels, including the above-mentioned TRPM8, have been discovered and cloned, which has triggered a remarkable surge of interest in thermosensation (Jordt *et al.* 2003, Bandell *et al.* 2007, Caterina 2007, Pogorzala *et al.* 2013). Pharmaceutical companies further propelled this surge by synthesizing, within a short period of time, a plethora of highly selective and potent TRP antagonists (Romanovsky *et al.* 2009, Preti *et al.* 2012). Because several TRP channels are profoundly expressed in sensory neurones and epithelia, they immediately became prime suspects for the roles of cutaneous thermosensors. Furthermore, the activation of TRP channels results in an inward, non-selective cationic current and, consequently, membrane depolarization; this electrophysiological mechanism agrees with a possible role of TRP channels in peripheral thermosensitivity (Okazawa *et al.* 2002). To the contrary, when thermosensitive neurones are exposed to different temperature changes, the effects evoked (changes in brief ionic currents of the depolarizing pre-potential, but not in the resting membrane potential) seem incompatible with a pivotal role of TRP channels in central thermosensitivity (Boulant 2006).

It was anticipated that the molecular substrate of peripheral thermoreception would be promptly identified, for example, by showing that pharmacological blockade of some TRP channel would eliminate responses driven by thermal cutaneous signalling. And although certain progress has been achieved, the picture that is now emerging is less certain and more

complex. Some of the complexity stems from the functional architecture of the thermoregulatory system discussed in the present review and elsewhere (Romanovsky 2007b). In agreement with the fact that signals used for behavioural thermoregulation can differ from signals for autonomic thermoregulation (Flouris 2011), antagonists of the TRP channel vanilloid-1 (TRPV1; formerly known as the capsaicin receptor, or vanilloid receptor 1) readily affect autonomic thermoeffectors in rats (Steiner *et al.* 2007, Garami *et al.* 2010), but fail to affect the selection of preferred ambient temperature in the same species, at least as concluded from one study (Steiner *et al.* 2007). Non-thermoregulatory responses that are driven by thermal signals (e.g. thermal pain responses) may receive sensory information from different TRP channels than those involved in thermoregulation, whether autonomic or behavioural. In agreement with this, the TRP channel ankyrin-1 (TRPA1; formerly ANKTM1) may be involved in nocifensive responses to cold (Story *et al.* 2003, del Camino *et al.* 2010, Nilius *et al.* 2012), at least in some species (Chen & Kym 2009), but it is probably not involved in autonomic thermoregulation (at least not in a near-thermoneutral environment) (Chen *et al.* 2011) or behavioural thermoregulation (Bautista *et al.* 2007). Such functional diversification is due, at least in part, to the fact that different TRP channels are sensitive to temperature in different ranges (Romanovsky 2007b).

One of the difficulties in studying the thermosensory roles has been assessing whether an effect observed following the blockade of a particular TRP channel is because of changes in thermal signalling via this TRP. For example, many TRPV1 antagonists cause hyperthermia by triggering skin vasoconstriction in the heat-exchange organs and activating thermogenesis (Steiner *et al.* 2007, Gavva *et al.* 2008, Garami *et al.* 2010). These effects are often interpreted as evidence of the physiologically significant role of TRPV1 as a thermosensor for autonomic thermoregulation. However, Steiner *et al.* (2007) have shown that TRPV1-mediated signals that drive autonomic thermoeffectors originate in the abdominal viscera, not in the skin. Furthermore, the same study has found that the magnitude of the hyperthermic response to a TRPV1 antagonist does not increase at high ambient, skin or deep body temperatures, thus suggesting that TRPV1-mediated visceral signals are non-thermal. The latter conclusion agrees with the fact that the hyperthermic response is caused only by antagonists that are potent blockers of the proton (low pH) activation of TRPV1; the hyperthermic response does not depend on the antagonist's ability to block the thermal (high temperature) activation of TRPV1 (Garami *et al.* 2010). Experimental evidence for any involvement of TRPV1-mediated thermal signals in thermoregulation is lacking; the TRPV1 channel is probably not a thermosensor for the thermoregulation system, at least not in the absence of profound hyperthermia (Romanovsky *et al.* 2009), although it is a thermosensor for nocifensive responses to noxious heat.

In contrast to TRPV1, the TRPM8 channel is a physiologically important thermosensor for the thermoregulation system. TRPM8 antagonists cause hypothermia in rats and mice (Knowlton *et al.* 2011, Almeida *et al.* 2012), and the magnitude of the hypothermic response increases with a decrease in the ambient and body temperatures, including skin temperature – when the thermal activation of TRPM8 is stronger, the blockade of this activation with an antagonist causes a stronger response (Almeida *et al.* 2012).

Blocking cutaneous thermal signals with selective pharmacological compounds opens a new approach to modulate body temperature, thermal comfort and possibly even the activity of individual thermoeffectors. Almeida *et al.* (2012) have coined a term for this approach: thermopharmacology. It is tempting to speculate about potential applications of thermopharmacology, with the induction of therapeutic hypothermia being the most obvious and clinically important application. However, understanding the roles played by cutaneous thermal signals in thermoregulation limits such speculations.

Because peripheral thermal signals are more important for behaviours than for autonomic thermoeffector responses, blocking these signals with pharmacological tools is likely to affect behavioural responses more than physiological defences. Furthermore, because the skin temperature is a more important driver for cold defences than for heat defences, it has been relatively easy to establish the thermosensory role of the TRPM8 channel in thermoregulation (Almeida *et al.* 2012); it may be more difficult to establish such roles for warmth-sensitive molecules that participate in the control of heat defences. Because skin signals only complement deep body temperature signals, the magnitude of body temperature responses to TRP antagonists is likely to be limited, as in the case with TRPM8 antagonists (Knowlton *et al.* 2011, Almeida *et al.* 2012). When effects of TRP-active compounds on body temperature are profound, such as the hypothermic effect of TRPV1 agonists, these effects are unrelated to thermosensation (Romanovsky *et al.* 2009).

Perhaps, the most disappointing limitation of thermopharmacology derives from the fact that cutaneous thermal signals are less important for thermoregulation in larger animals, such as humans (Mercer & Simon 1984). The greater thermal inertia of larger

animals makes transient thermal exposures less threatening, which decreases the importance of auxiliary feedback signals from the skin. Hence, blocking peripheral thermosensation with TRP antagonists in humans is likely to have smaller effects on body temperature than in rodents.

With this in mind, the thermopharmacology can reach its true potential only when pharmacological tools to block central, presumably non-TRP-mediated, thermosensitivity become available. As for blocking peripheral thermosensitivity with TRP antagonists, the most promising direction would be to modulate responses to cold, especially behavioural responses. Because auxiliary feedback control decreases the response time and, when it involves positive feedback, decreases the load error, responses to cold under the conditions of pharmacological blockade of peripheral thermosensors are expected to occur with a longer delay in time and at lower body temperatures – like some cold defences in rats treated with a TRPM8 antagonist in the study by Almeida *et al.* (2012).

Summary

(1) Non-hairy, glabrous skin covers most distal body parts, which have evolved to explore the environment and to exchange heat with it. The main thermosensory-related role of non-hairy skin is to assess local temperatures, that is, those of various objects explored. Thermal information about these objects can serve as feedforward signals for various behaviours, some of which may have thermoregulatory consequences. Thermal signals from non-hairy skin also serve as the negative and positive auxiliary feedback for the control of autonomic and behavioural thermoeffector responses, but the contribution of these signals is limited both by the small total area of the non-hairy skin and by the fact that the skin temperature of these organs is heavily affected by the local vasomotor tone.

(2) Hairy, non-glabrous skin covering the rest of the body is typically insulated from the environment by hair or clothes, and thermal signals from this skin reflect the temperature of the insulated superficial layer of the body, rather than the ambient temperature. The area covered by hairy skin is vast, and thermal signals from this vast area serve as important negative and positive auxiliary feedback signals in the control of autonomic and behavioural thermoeffectors.

(3) The autonomic thermoregulation does not use thermal feedforward signals; all thermal signals used are feedback signals. Thermoregulatory behaviours use similar feedback signals. In addition, some complex behaviours use feedforward signals.

(4) Overall, the main thermoregulatory role of thermal cutaneous signals is to provide negative and positive auxiliary feedback to the thermoregulation system, thus both reducing the system's response time and making body temperature more stable.

(5) The outlined roles of cutaneous thermal signals are neither arbitrary nor a matter of linguistic preferences. They are deeply rooted in the dynamic functional architecture of the thermoregulatory system.

(6) Thermopharmacology – a new approach to regulate bodily functions by modulating thermal signals pharmacologically – has emerged. Its development will be limited by the functional architecture of the thermoregulation system, but it will also facilitate the acquisition of new knowledge about body temperature regulation.

Conflict of interest

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