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REVIEW ARTICLE

Functional architecture of behavioural thermoregulation

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Abstract The human thermoregulatory system relies primarily on behavioural adaptation and secondarily on autonomic and endocrine responses for thermal homeostasis. This is because autonomic and endocrine responses have a limited capacity in preventing hyper/hypothermia in extreme environments. Until recently, the neuroanatomy of behavioural thermoregulation as well as the neuroanatomic substrate of the various thermoregulatory behaviours remained largely unknown. However, this situation has changed in recent years as behavioural thermoregulation has become a topic of considerable attention. The present review evaluates the current knowledge on behavioural thermoregulation in order to summarize the present state-of-the-art and to point towards future research directions. Findings on the fundamental distinction between thermal (dis)comfort and sensation are reviewed showing that the former drives behaviour while the latter initiates autonomic thermoregulation. Moreover, the thermosensitive neurons and thermoeffector functions of behavioural thermoregulation are presented and analysed in a detailed discussion.

Keywords Thermal discomfort · Thermal sensation · Temperature · Conscious response · Heat · Psychophysical mechanism

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Introduction

Understanding the complex interactions amongst biological, psychological, and environmental factors in homoeothermic organisms represents the primary goal of behavioural thermoregulatory research. In this light, this area has served as a bridge between thermal physiology, psychology, neurophysiology, and bioengineering. Since its initial years, research on behavioural thermoregulation has evolved from a primarily qualitative study of conscious homoeothermic behaviour (Pieron 1913; Kleitman and Doktorsky 1933) into a comprehensive science that combines observational methods with analytic techniques to describe the complex behavioural mechanisms by which homoeothermic thermoregulation is achieved (Gagge et al. 1967; Cabanac and Serres 1976; Caputa and Cabanac 1980). Following a phase of quasistasis, the field of behavioural thermoregulation is evolving yet again influenced by advances in neurophysiology, biology, and thermal physiology and is acquiring a more fundamental theme that is supported by advances in technology (Nagashima 2006; Dimicco and Zaretsky 2007). This evolution is led by both neuroscience reductionists as well as physiology integrationists who perform research by combining cognitive psychology and thermobehavioural physiology with fields such as neurophysiology, molecular biology, biochemistry, pharmacology, and genetics.

The neuroanatomy of behavioural thermoregulation as well as the physiological basis of the various thermoregulatory behaviours remained largely unknown until a few years ago. However, much progress has been recently achieved as behavioural thermoregulation has become a topic of considerable attention. Examples of this progress include the seminal finding that behavioural thermoregulatory responses may not require an intact preoptic area and

anterior hypothalamus [PO/AH (Mercer and Simon 2001; Guest et al. 2007)] as well as the related discoveries of several cerebral loci involved in behavioural thermoregulation including the insular, cingulate, primary and secondary somatosensory, and orbitofrontal cortex (Craig et al. 1994; Davis et al. 1998; Becerra et al. 1999; Sawamoto et al. 2000), the amygdala (Kanosue et al. 2002; Verhagen et al. 2004), as well as the dorsomedial hypothalamus (Dimicco and Zaretsky 2007).

The recent attention directed at behavioural thermoregulation stems from the aforementioned evolution in this field as well as the realization of its significance in human thermoregulation. Indeed, thermal homeostasis in humans and other homoeothermic organisms is based primarily on behavioural and secondarily on autonomic and endocrine mechanisms (Attia 1984). This is because the latter mechanisms have a finite capacity in preventing hyper/hypothermia, whereas behavioural thermoregulation is a very powerful mechanism that relentlessly triggers conscious decisions in order to preserve thermal balance when it is possible (e.g., sun shade in a hot environment).

The present review evaluates the current knowledge on behavioural thermoregulation in order to summarize the present state-of-the-art and to point towards future research directions. While some of the cited research involves different homoeothermic species, this review focuses on mammalian behavioural thermoregulatory responses and particularly those of humans. Thermosensation, including general thermosensors (i.e., those implicated in autonomic, endocrine and behavioural thermoregulatory responses) in the brain and the periphery as well as thermosensitive neurons that have been shown to play a specific role in behavioural thermoregulation, is reviewed first. Subsequent sections review behavioural thermoregulation as a thermoeffector together with experiments investigating the functioning and effectiveness of behaviour in maintaining the organism's thermal integrity.

Thermosensation

Thermoregulatory behaviour has been defined as "an attempt to avoid what humans call thermal discomfort or displeasure and to obtain thermal pleasure" (Cabanac and Serres 1976). Thermal constancy is restricted to the body's core, while tissues of the body's shell vary in temperature as blood flow may be increased or decreased in order to augment or limit thermal insulation. With respect to central thermosensors, various behavioural thermoregulatory responses have been reported during thermal stimulation in the medulla oblongata, pons, midbrain (Holmes et al. 1960), the orbitofrontal, the insular, and the somatosensory cortex (Craig et al. 1994) as well as the amygdala (Kanosue et al. 2002; Verhagen et al. 2004). These thermosensitive brain areas have been recognized for more than a century as key components of thermoregulation based on observations from humans suffering brain damage and from the effect of experimental lesions in other mammalian models (Holmes et al. 1960; Simon 1974).

Our knowledge of the peripheral mechanisms by which we sense hot and cold temperatures has been recently updated with the discovery that specific ion channels of the transient receptor potential (TRP) family are participating in thermosensation and are, direct or indirect, contributors to thermoregulation (Guler et al. 2002; Fink 2005). The mammalian TRP superfamily consists of approximately 30 channels that are divided into six subfamilies (Caterina 2007; Romanovsky 2007). A detailed discussion of the nature and functioning of these proteins as endogenous thermosensors is beyond the scope of this review and can be found elsewhere (Romanovsky 2007), yet it is noteworthy that certain invertebrate TRP channels are involved in the sensory process leading to thermal discomfort and, in turn, behavioural thermoregulatory responses. Indeed, a number of knockout mouse studies have confirmed that the TRP family V3 and V4 channels are active contributors in nocifensive behaviour and in thermotaxis (Caterina et al. 2000; Davis et al. 2000; Guler et al. 2002; Liedtke and Friedman 2003; Suzuki et al. 2003; Moqrich et al. 2005). Three recent experiments also showed that the V8 channel is actively involved in thermoregulation and that V8 knockout mice demonstrate a lack of preference for a comfortably warm zone compared with a cool environment, yet they retain the ability to avoid noxious cold (Bautista et al. 2007; Colburn et al. 2007; Dhaka et al. 2007). The V8 channel also appears to be involved in acute nocifensive reactions to painful or uncomfortable stimuli (Bautista et al. 2007; Colburn et al. 2007; Dhaka et al. 2007). However, much remains to be learned regarding the involvement of specific TRP channels in behavioural thermoregulation and in the multitude of homoeothermic thermosensory functions.

Distinction between thermal comfort and sensation

Human thermal comfort is defined as the state of mind that expresses satisfaction with the surrounding environment, while thermal sensation is the perception of a given peripheral stimulus resulting from the stimulation of peripheral and central thermosensors (ASHRAE 1997). In this light, it has been observed that, irrespective of absolute body temperature, comfort levels improve in circumstances where the environment allows the return of body temperature towards a physiological 'normal' level but sensation levels remain unchanged (Gagge et al. 1967). For instance, when an individual reports as 'hot/uncomfortable' (i.e., thermal

sensation/thermal comfort) and is subsequently cooled, skin temperatures that are normally perceived as 'cold/uncomfortable' are sensed as 'cold/comfortable' (Gagge et al. 1967). Consequently, it has been postulated that thermal discomfort drives behavioural thermoregulation, while thermal sensation initiates autonomic thermoregulatory responses (Gagge et al. 1967; Taylor et al. 1995). This is supported by previous research showing that behavioural thermoregulatory responses to alter ambient temperature conditions are elicited only when thermal discomfort/displeasure occurs (Taylor et al. 1995). Based on these notions, it is worthwhile to explore the basis of thermal discomfort.

Data presented thus far suggest that thermal discomfort is affected by the thermal status of the entire body (Attia et al. 1980; Attia and Engel 1982; Kuno et al. 1987; Flouris and Cheung 2008; Flouris 2009). For instance, as mentioned in the previous paragraph, similar levels of hand warming in humans produce feelings of comfort and discomfort depending on whether the body is hypothermic or hyperthermic (Gagge et al. 1967). Hence, a thermal stimulus is felt agreeable when it serves to minimize body heat storage, and felt un-agreeable when it acts to increase body heat storage. The term 'alliesthesia' has been proposed to describe this concept of a given temperature stimulus producing pleasure or displeasure depending on the deep body thermal state (Cabanac 1971). These notions allude to a central control of thermal discomfort and, in turn, behavioural thermoregulation, suggesting that local thermal stimuli are integrated centrally and perceived as comfortable or uncomfortable depending on the thermal status of the body. The processing of afferent signals for thermal (dis)comfort is discussed in detail in the following paragraph.

Thermosensors involved in behavioural thermoregulatory responses

Understanding the underlying psychophysical mechanism(s) that controls thermal discomfort and, in turn, behavioural thermoregulation has been the objective of many of experiments to date. Data from thermal stimulation experiments in rats suggested that different thermoregulatory behaviours such as thermoregulatory grooming (i.e., spreading saliva on the skin to increase evaporative heat loss), relaxed postural extension, and locomotion use distinct neural circuitries (Roberts 1988), while neurons in the median preoptic nucleus are implicated in moving to a reward zone during heat exposure to trigger a breeze of cold air, at least during osmotic stimuli (Konishi et al. 2007).

An important distinction between thermal (dis)comfort and sensation and, in turn, autonomic/endocrine and behavioural thermoregulatory responses is that the latter may not require an intact PO/AH (Mercer and Simon 2001; Guest et al. 2007). Indeed, the participation of non-PO/AH areas in behavioural thermoregulation is supported by experiments using functional magnetic resonance imaging (fMRI) or positron emission tomography demonstrating that several areas in the cerebral cortex are involved in behavioural thermoregulatory signals (Craig et al. 1994; Guest et al. 2007). More specifically, neural activations in response to non-noxious oral thermal stimuli have been found in the orbitofrontal, the insular, and the somatosensory cortex (Craig et al. 1994) as well as in the amygdala (Kanosue et al. 2002; Verhagen et al. 2004) with different neurons having increasing, decreasing, or tuned responses as a function of body temperature. Notably, some of these neurons are thermo-specific, while others combine thermal sensitivity with responses to taste, and/or oral texture (Kadohisa et al. 2004; Verhagen et al. 2004; Kadohisa et al. 2005a; Kadohisa et al. 2005b). A recent fMRI investigation reported that activations of the mid-orbitofrontal and pregenual cingulate cortex as well as the ventral striatum correlate with subjective thermal (dis)comfort (Rolls et al. 2008). Specifically, the (dis)comfort of thermal stimuli was correlated with activations in the lateral and some more anterior parts of the orbitofrontal cortex, while the intensity of the thermal stimuli was correlated with activations in the somatosensory cortex and ventral posterior insula (Rolls et al. 2008). Based on these findings, the authors proposed that the processing of thermal stimuli occurs in different brain areas depending on whether it is related to sensory properties (such as their intensity) or to the affective value and associated subjective emotional experience (Rolls et al. 2008).

Relatively recent neurophysiological developments revealed that neurons of the dorsomedial hypothalamic nucleus and fibres passing through the paraventricular hypothalamic nucleus are involved in cold-seeking behaviour (Dimicco and Zaretsky 2007). Additional experiments demonstrated that disinhibition of neurons in the dorsomedial hypothalamus by local microinjection of the $GABA_A$ receptor antagonist bicuculline methiodide evokes a host of behavioural, autonomic, and endocrine thermoregulatory responses (Dimicco and Zaretsky 2007). It appears that neurons in the dorsomedial hypothalamus activate premotor sympathetic neurons in the rostral raphe pallidus that are involved in elevating body temperature, in cold defence, and in fever (Dimicco and Zaretsky 2007). Based on these findings it has been proposed that neurons in the dorsomedial hypothalamus play a vital role in a variety of thermoregulatory responses, including behaviour (Nagashima 2006; Dimicco and Zaretsky 2007). Indeed, it has been known for some time that the dorsomedial hypothalamus is involved in chemical signals related to food consumption

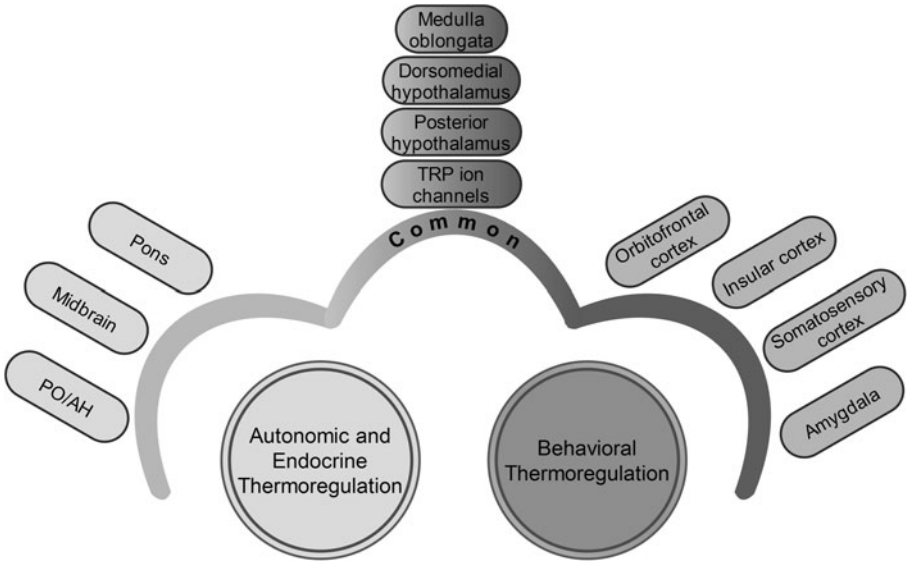

Fig. 1 Neural thermosensation centres involved in autonomic/endocrine thermoregulation and behavioural thermoregulation. PO/AH, preoptic area, and anterior hypothalamus

and ingestive behaviour both of which represent hypothalamic functions linked with thermoregulation (Hamilton and Ciaccia 1971). For instance, leptin, a peptide involved in feeding behaviour, raises body temperature in mice and rats (Stehling et al. 1997) and is implicated in the human behavioural, autonomic, and endocrine control of nycthemeral body temperature rhythm (Simon et al. 1998). Administration of two other peptides, vasopressin and oxytocin, through intracerebroventricular injection induces grooming behaviour, characteristic of heat loss (Drago et al. 1997). The neural thermosensation centres involved in autonomic/endocrine thermoregulation and behavioural thermoregulation are illustrated in Fig. 1.

The notion of extra-PO/AH thermosensitivity has received support from several experiments demonstrating that behavioural thermoregulation is primarily regulated by alterations in mean shell temperature (Cheng et al. 1995; Grahn et al. 1998; Flouris et al. 2006b; Flouris et al. 2006c) and that a rise in body temperature during exercise triggers behavioural responses to lower work rate (Tucker et al. 2004, 2006). According to this notion, mean shell temperature may carry important information to the brain to regulate exercise behaviour—and thus metabolic rate—independently of core body temperature (Tucker et al. 2004, 2006). Indeed, it appears that thermal discomfort may depend more on shell temperature signals from peripheral thermosensors than core temperature signals from central thermosensors (Romanovsky 2007). In contrast, deep core body temperature is comparatively more important for eliciting autonomic and endocrine responses. This arrangement mirrors the fact that behavioural responses are most often prescient in that they are aimed at preventing an anticipated thermal insult (Nagashima 2006; Cheung and Flouris 2009). On the other hand, autonomic and endocrine thermoregulatory responses are usually employed when body temperature starts to change because behavioural responses were inadequate or could not be used due to conflicting behavioural demands (Cheung and Flouris 2009).

Another line of evidence in favour of extra-PO/AH control of behavioural thermoregulation comes from hypoxia experiments. Hypoxia has been shown to significantly alter the thermoregulatory behaviour in animals by lowering their preferred ambient temperature (Hicks and Wood 1985; Gordon and Fogelson 1991; Gordon 1997). In humans, however, the evidence is less straightforward. Some (Johnston et al. 1996; Golja et al. 2004) but not all (Golja and Mekjavic 2003; Malanda et al. 2008) human studies have shown that hypoxia significantly decreases the sensation of cold in humans which, in turn, may predispose individuals to cold injury in cold hypoxic environments by interfering with temperature receptors. These findings mirror earlier evidence in primates that a local reduction in oxygen supply either through arterial blood flow to the skin or via blood oxygenation diminishes the firing rate of cutaneous cold receptors (Iggo and Paintal 1977). Hence, hypoxia may attenuate afferent thermal information through a neural membrane function blockade since increasing levels of hypoxia result in serial shutdowns of the energy-requiring nerve cell functions, with synaptic transmission failing first (Astrup 1982). With further reductions in oxygen supply, nerve cell membranes become inept and, ultimately, as the cellular ATP stores become depleted, the Na^+/K^+ATP-ase transport fails and the net ion current through the cell membrane results in membrane depolarisation and complete loss of neural cell function (Astrup 1982). Since the hypoxia-induced synaptic transmission blockade has been confirmed in vivo (Findlater et al. 1987), it is logical to suggest that the effect of hypoxia on synaptic transmission should be more potent in the most complex polysynaptic circuits. Therefore, hypoxia should affect the

behavioural thermoregulatory pathway before any alteration of autonomic and endocrine thermoregulatory responses would occur. However, further research is required to fully elucidate the effects of hypoxia in human behavioural thermoregulation.

Within the aforementioned challenges, the majority of the evidence presented to date suggests that thermal comfort/behavioural thermoregulation relies more on shell than core temperatures (Frank et al. 1999). Moreover, recent attempts to address the aforementioned limitations in humans have used various paradigms whereby individuals are given thermo-behavioural choices without knowing they are being monitored (Flouris and Cheung 2008; Schlader et al. 2009). Results have shown that behaviour acts on shell temperature alterations to prevent or 'buffer' changes in core temperature (Schlader et al. 2009) as well as a general trend to cool the head in the heat and to maintain the warmth of the abdomen in the cold, yet in a balanced fashion [i.e., cooling and/or heating other regions of the body (Nakamura et al. 2008)] resulting in a stable mean body temperature rather than a specific body region (Flouris et al. 2006a; Flouris and Cheung 2008). These findings suggest, therefore, that the stimulus for thermal discomfort and, in turn, behavioural thermoregulation is a change in mean body temperature/body heat content, implicating peripheral thermosensors as the primary thermal input for thermal (dis)comfort/behavioural thermoregulation.

Behaviour as a thermoeffector

Given that autonomic and endocrine responses have a finite capacity for preventing hyper/hypothermia, behavioural thermoregulation is assiduously active as the primary thermoregulatory mechanism triggering conscious decisions in order to preserve thermal homeostasis (Attia 1984). Simple behavioural thermoregulatory responses found in a multitude of species include changes in orientation to the direction of the wind/sun, positional measures like curling up, cuddling, and huddling in order to alter the surface/mass ratio and, hence, the rate of heat exchange between the organism and the environment, as well as search for sunny, dry, warm, wind-sheltered environments, and avoidance of dangerous/hostile environmental temperatures (Nakamura et al. 2008). More complex behavioural thermoregulatory responses include building a nest, spreading saliva on the skin to increase evaporative heat loss (i.e., grooming), the creation and application of clothing, or, simply, turning on or off the air conditioner. Furthermore, primary alterations of food consumption behaviour can significantly alter body temperature and are, thus, considered behavioural thermoregulatory responses (Riddell 2008). For instance, it has been shown that food intake increases in the cold in order to increase metabolic rate and compensate for the excessive heat loss in order to maintain body temperature homeostasis (Szekely and Szelenyi 2005). At the other end of the spectrum, febrile illnesses, seen as principally thermoregulatory phenomena, are accompanied by anorexia (Szekely and Szelenyi 2005). Unfortunately, the physiology of this behaviourally based regulation remains to be elucidated.

Behavioural thermoeffector responses have been employed as the basis of many bioengineering applications including 'smart' buildings (Cena and de Dear 2001) and microclimate liquid conditioning systems worn underneath protective clothing (Flouris and Cheung 2006). Yet, the efficacy of these applications is limited as our knowledge on the underlying psychophysical mechanism(s) controlling thermal (dis)comfort remains incomplete. Possible reasons for this may be the lack of appropriate techniques to measure directly thermal comfort and/or sensation in animals and humans as well as the complexity in the body's responses to different stimuli and the difficulty to explicitly identify behavioural thermoregulation and isolate it from other systems within the body, as well as from external dynamics (Flouris and Cheung 2008; Nakamura et al. 2008). It is also important to note that thermal (dis)comfort may be significantly altered by the environment leading to variations between perceptual and physiological strain which may result in inappropriate behavioural thermoregulatory responses (Cheung and Mekjavic 1995). Moreover, specific non-thermal factors interfere with neural information at one or more levels of behavioural thermoregulation. For instance, research has shown that ageing (Collins et al. 1977; Collins and Exton-Smith 1983; Collins et al. 1985), hypoglycaemia (Passias et al. 1996), inert-gas narcosis (Pertwee et al. 1986; Cheung and Mekjavic 1995; Mekjavic et al. 1995), as well as physical condition (Tikuisis et al. 2002) can alter thermal (dis)comfort.

The debate regarding the psychophysical mechanism(s) controlling thermoregulation is, probably, at its peak when exercise in the heat is considered. The human capacity to perform prolonged exercise is clearly impaired in high ambient temperatures (Roelands et al. 2008). The classical—and most widely accepted—'cardiovascular/anaerobic model' view holds that the heart's pumping capacity is the factor limiting effort during exercise in the heat (Brink-Elfegoun et al. 2007). In contrast, the 'central governor model' argues that humans circumvent the physiological impact of exercise-induced hyperthermia through feedforward and feedback voluntary control of effort at the start or during heat stress (Noakes and Marino 2009). In this context, fatigue is viewed as a conscious or unconscious behavioural command to lower or cease work rate in order to prevent the body from reaching a thermal point of near-collapse (Noakes and Marino 2009). The issue whether fatigue development during exercise in the heat is based on

circulatory limitations or behavioural commands is currently under discussion (Brink-Elfegoun et al. 2007; Noakes and Marino 2009), and different opinions have been expressed on the merits and the weaknesses of the 'cardiovascular/anaerobic' and the 'central governor' hypotheses (Brink-Elfegoun et al. 2007; Cheung and Flouris 2009; Noakes and Marino 2009). The majority of the published data thus far suggest that the 'central governor' hypothesis is supported mainly in the original papers that proposed it. From a philosophical standpoint, it is possible that the two measures of control can harmoniously coexist within a system, the 'central governor' being a prescient behavioural mechanism preventing imminent myocardial ischaemia by limiting peripheral blood flow, and the 'cardiovascular/anaerobic model' being a safety measure employed when behavioural means are insufficient. This arrangement fits precisely the organization of the homoeothermic thermoregulatory system with behavioural responses, depending on shell temperature signals from peripheral thermosensors, deployed to prevent anticipated thermal insults (Flouris and Cheung 2008), while autonomic and endocrine responses, based more on core temperature signals from central thermosensors, employed when body temperature changes because behavioural responses were inadequate or could not be used due to conflicting behavioural demands (Romanovsky 2007). However, this integrated model is, most likely, incomplete because it eliminates the possibility of healthy adults exercising themselves into a state of heat stroke. Unfortunately, exertional heat illness and death among exercising individuals continue to surface during exposure to hot environments while heat stroke is a leading cause of death in athletes, second only to head and spinal injuries (Ficarra 1996). These notions exemplify the need for further research and, possibly, debate in order to increase our understanding of the psychophysical mechanism(s) controlling thermoregulation during exercise in the heat.

Concluding remarks

A review of the germane literature shows that in recent years there has been remarkable progress in the area of behavioural thermoregulation with basic and applied experiments providing novel evidence on the underlying psychophysical mechanism(s) controlling human behavioural thermoregulation. Prominent new insights include the important distinction between autonomic/endocrine and behavioural thermoregulatory responses whereby the latter do not require an intact PO/AH (Mercer and Simon 2001; Guest et al. 2007) and the relevant discoveries of several cerebral loci involved in behavioural thermoregulation including the insular, cingulate, primary and secondary somatosensory, and orbitofrontal cortex (Craig et al. 1994; Davis et al. 1998; Becerra et al. 1999; Sawamoto et al. 2000), the amygdala (Kanosue et al. 2002; Verhagen et al. 2004), as well as the dorsomedial hypothalamus (Dimicco and Zaretsky 2007). These findings are supported by integrated experiments providing strong evidence for the involvement of peripheral thermosensitivity in thermal (dis)comfort and the role of shell (Cheng et al. 1995; Grahn et al. 1998; Schlader et al. 2009) and mean body (Tucker et al. 2004, 2006; Flouris et al. 2006a, 2007; Flouris and Cheung 2008) temperature in behavioural thermoregulatory responses. Based on this evidence, it can be postulated that behavioural thermoregulation is based on extra-PO/AH cerebral integration of signals originating primarily from peripheral shell thermosensors and acts to maintain mean body temperature.

Notwithstanding the recent attention on behavioural thermoregulation and the excitement for the new discoveries in this area, we remain largely naive to the principles governing the psychophysical mechanism(s) of human thermoregulation. Many pertinent questions remain unanswered including the role of individual ion TRP channels in the control of different behavioural thermoeffectors, the afferent and efferent neural circuits of behavioural thermoregulatory reactions, and the neuroanatomy of behavioural thermoregulation, as well as the psychophysical mechanism(s) controlling thermoregulation during exercise in the heat. These include potential avenues of future research which will increase our knowledge on the principles that govern behavioural thermoregulation.

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References

ASHRAE (1997) Thermal comfort. In: ASHRAE handbook of fundamentals, chapter 8. American Society of Heating, Refrigerating and Air-Conditioning Engineers, Atlanta

Astrup J (1982) Energy-requiring cell functions in the ischemic brain. Their critical supply and possible inhibition in protective therapy. J Neurosurg 56:482–497

Attia M (1984) Thermal pleasantness and temperature regulation in man. Neurosci Biobehav Rev 8:335–342

Attia M, Engel P (1982) Thermal pleasantness sensation: an indicator of thermal stress. Eur J Appl Physiol 50:55–70

Attia M, Engel P, Hildebrandt G (1980) Quantification of thermal comfort parameters using a behavioural indicator. Physiol Behav 24:901–909

Bautista DM, Siemens J, Glazer JM, Tsuruda PR, Basbaum AI, Stucky CL, Jordt SE, Julius D (2007) The menthol receptor TRPM8 is the principal detector of environmental cold. Nature 448:204–208

Becerra LR, Breiter HC, Stojanovic M, Fishman S, Edwards A, Comite AR, Gonzalez RG, Borsook D (1999) Human brain activation under controlled thermal stimulation and habituation to noxious heat: an fMRI study. Magn Reson Med 41:1044–1057

Brink-Elfegoun T, Kaijser L, Gustafsson T, Ekblom B (2007) Maximal oxygen uptake is not limited by a central nervous system governor. J Appl Physiol 102:781–786

Cabanac M (1971) Physiological role of pleasure. Science 173:1103–1107

Cabanac M, Serres P (1976) Peripheral heat as a reward for heart rate response in the curarized rat. J Comp Physiol Psychol 90:435–441

Caputa M, Cabanac M (1980) Muscular work as thermal behavior in humans. J Appl Physiol 48:1020–1023

Caterina MJ (2007) Transient receptor potential ion channels as participants in thermosensation and thermoregulation. Am J Physiol Regul Integr Comp Physiol 292:R64–R76

Caterina MJ, Leffler A, Malmberg AB, Martin WJ, Trafton J, Petersen-Zeitz KR, Koltzenburg M, Basbaum AI, Julius D (2000) Impaired nociception and pain sensation in mice lacking the capsaicin receptor. Science 288:306–313

Cena K, de Dear R (2001) Thermal comfort and behavioural strategies in office buildings located in a hot-arid climate. J Thermal Biol 26:409–414

Cheng C, Matsukawa T, Sessler DI, Ozaki M, Kurz A, Merrifield B, Lin H, Olofsson P (1995) Increasing mean skin temperature linearly reduces the core-temperature thresholds for vasoconstriction and shivering in humans. Anesthesiology 82:1160–1168

Cheung S, Flouris AD (2009) Maximal oxygen uptake regulation as a behavioral mechanism. J Appl Physiol 106:345

Cheung SS, Mekjavic IB (1995) Human temperature regulation during subanesthetic levels of nitrous oxide-induced narcosis. J Appl Physiol 78:2301–2308

Colburn RW, Lubin ML, Stone DJ Jr, Wang Y, Lawrence D, D'Andrea MR, Brandt MR, Liu Y, Flores CM, Qin N (2007) Attenuated cold sensitivity in TRPM8 null mice. Neuron 54:379–386

Collins KJ, Exton-Smith AN (1983) 1983 Henderson award lecture. Thermal homeostasis in old age. J Am Geriatr Soc 31:519–524

Collins KJ, Dore C, Exton-Smith AN, Fox RH, MacDonald IC, Woodward PM (1977) Accidental hypothermia and impaired temperature homoeostasis in the elderly. Br Med J 1:353–356

Collins KJ, Easton JC, Belfield-Smith H, Exton-Smith AN, Pluck RA (1985) Effects of age on body temperature and blood pressure in cold environments. Clin Sci (Lond) 69:465–470

Craig AD, Bushnell MC, Zhang ET, Blomqvist A (1994) A thalamic nucleus specific for pain and temperature sensation. Nature 372:770–773

Davis KD, Kwan CL, Crawley AP, Mikulis DJ (1998) Functional MRI study of thalamic and cortical activations evoked by cutaneous heat, cold, and tactile stimuli. J Neurophysiol 80:1533–1546

Davis JB, Gray J, Gunthorpe MJ, Hatcher JP, Davey PT, Overend P, Harries MH, Latcham J, Clapham C, Atkinson K, Hughes SA, Rance K, Grau E, Harper AJ, Pugh PL, Rogers DC, Bingham S, Randall A, Sheardown SA (2000) Vanilloid receptor-1 is essential for inflammatory thermal hyperalgesia. Nature 405:183–187

Dhaka A, Murray AN, Mathur J, Earley TJ, Petrus MJ, Patapoutian A (2007) TRPM8 is required for cold sensation in mice. Neuron 54:371–378

Dimicco JA, Zaretsky DV (2007) The dorsomedial hypothalamus: a new player in thermoregulation. Am J Physiol Regul Integr Comp Physiol 292:R47–R63

Drago F, Stanciu M, Salehi S, Scapagnini U (1997) The block of central vasopressin V1 but not V2 receptors suppresses grooming behavior and hypothermia induced by intracerebroventricular vasopressin in male rats. Peptides 18:1389–1392

Ficarra BJ (1996) Diseases and injuries in athletes. A review. J Med 27:241–275

Findlater GS, Cooksey EJ, Anand A, Paintal AS, Iggo A (1987) The effects of hypoxia on slowly adapting type I (SAI) cutaneous mechanoreceptors in the cat and rat. Somatosens Res 5:1–17

Fink GD (2005) Hypothesis: the systemic circulation as a regulated free-market economy. A new approach for understanding the long-term control of blood pressure. Clin Exp Pharmacol Physiol 32:377–383

Flouris AD (2009) Fundamental principles governing behavioral thermoregulation. In: Cisneros AB, Goins BL (eds) Body temperature regulation. Nova Science Publishers, Inc, Hauppauge

Flouris AD, Cheung SS (2006) Design and control optimization of microclimate liquid cooling systems underneath protective clothing. Ann Biomed Eng 34:359–372

Flouris AD, Cheung SS (2008) Human conscious response to thermal input is adjusted to changes in mean body temperature. Br J Sports Med 43:199–203

Flouris AD, Cheung SS, Fowles JR, Kruisselbrink LD, Westwood DA, Carrillo AE, Murphy RJ (2006a) Influence of body heat content on hand function during prolonged cold exposures. J Appl Physiol 101:802–808

Flouris AD, Cheung SS, Fowles JR, Murphy RJ, Westwood DA, Kruisselbrink LD (2006b) A pre-heating approach to preserve manual dexterity and neuromuscular function of the hands during cold exposures. Habitation 10:142–143

Flouris AD, Westwood DA, Cheung SS (2006c) Influence of thermal body state on vigilance during prolonged cold exposures. Appl Physiol Nutr Metab 31:S26

Flouris AD, Westwood DA, Cheung SS (2007) Thermal balance effects on vigilance during 2-hour exposures to −20°C. Aviat Space Environ Med 78:673–679

Frank SM, Raja SN, Bulcao CF, Goldstein DS (1999) Relative contribution of core and cutaneous temperatures to thermal comfort and autonomic responses in humans. J Appl Physiol 86:1588–1593

Gagge AP, Stolwijk JA, Hardy JD (1967) Comfort and thermal sensations and associated physiological responses at various ambient temperatures. Environ Res 1:1–20

Golja P, Mekjavic IB (2003) Effect of hypoxia on preferred hand temperature. Aviat Space Environ Med 74:522–526

Golja P, Kacin A, Tipton MJ, Eiken O, Mekjavic IB (2004) Hypoxia increases the cutaneous threshold for the sensation of cold. Eur J Appl Physiol 92:62–68

Gordon CJ (1997) The role of behavioral thermoregulation as a thermoeffector during prolonged hypoxia in the rat. J Therm Biol 22:315–324

Gordon CJ, Fogelson L (1991) Comparative effects of hypoxia on behavioral thermoregulation in rats, hamsters, and mice. Am J Physiol 260:R120–R125

Grahn D, Brock-Utne JG, Watenpaugh DE, Heller HC (1998) Recovery from mild hypothermia can be accelerated by mechanically distending blood vessels in the hand. J Appl Physiol 85:1643–1648

Guest S, Grabenhorst F, Essick G, Chen Y, Young M, McGlone F, de Araujo I, Rolls ET (2007) Human cortical representation of oral temperature. Physiol Behav 92:975–984

Guler AD, Lee H, Iida T, Shimizu I, Tominaga M, Caterina M (2002) Heat-evoked activation of the ion channel, TRPV4. J Neurosci 22:6408–6414

Hamilton CL, Ciaccia PJ (1971) Hypothalamus, temperature regulation, and feeding in the rat. Am J Physiol 221:800–807

Hicks JW, Wood SC (1985) Temperature regulation in lizards: effects of hypoxia. Am J Physiol 248:R595–R600

Holmes RL, Newman PP, Wolstencroft JH (1960) A heatsensitive region in the medulla. J Physiol 152:93–98

Iggo A, Paintal AS (1977) The metabolic dependence of primate cutaneous cold receptors [proceedings]. J Physiol 272:40P–41P

Johnston CE, White MD, Wu M, Bristow GK, Giesbrecht GG (1996) Eucapnic hypoxia lowers human cold thermoregulatory response thresholds and accelerates core cooling. J Appl Physiol 80:422–429

Kadohisa M, Rolls ET, Verhagen JV (2004) Orbitofrontal cortex: neuronal representation of oral temperature and capsaicin in addition to taste and texture. Neuroscience 127:207–221

Kadohisa M, Rolls ET, Verhagen JV (2005a) Neuronal representations of stimuli in the mouth: the primate insular taste cortex, orbitofrontal cortex and amygdala. Chem Senses 30:401–419

Kadohisa M, Verhagen JV, Rolls ET (2005b) The primate amygdala: neuronal representations of the viscosity, fat texture, temperature, grittiness and taste of foods. Neuroscience 132:33–48

Kanosue K, Sadato N, Okada T, Yoda T, Nakai S, Yoshida K, Hosono T, Nagashima K, Yagishita T, Inoue O, Kobayashi K, Yonekura Y (2002) Brain activation during whole body cooling in humans studied with functional magnetic resonance imaging. Neurosci Lett 329:157–160

Kleitman N, Doktorsky A (1933) The effect of the position of the body and sleep on rectal temperature in man. Am J Physiol 104:340–343

Konishi M, Kanosue K, Kano M, Kobayashi A, Nagashima K (2007) The median preoptic nucleus is involved in the facilitation of heat-escape/cold-seeking behavior during systemic salt loading in rats. Am J Physiol Regul Integr Comp Physiol 292:R150–R159

Kuno S, Ohno H, Nakahara N (1987) A two-dimensional model expressing thermal sensation in transitional conditions. ASHRAE Trans 93:396–406

Liedtke W, Friedman JM (2003) Abnormal osmotic regulation in trpv4−/− mice. Proc Natl Acad Sci USA 100:13698–13703

Malanda UL, Reulen JP, Saris WH, van Marken Lichtenbelt WD (2008) Hypoxia induces no change in cutaneous thresholds for warmth and cold sensation. Eur J Appl Physiol 104:375–381

Mekjavic IB, Savic SA, Eiken O (1995) Nitrogen narcosis attenuates shivering thermogenesis. J Appl Physiol 78:2241–2244

Mercer JB, Simon E (2001) Lessons from the past—human and animal thermal physiology. J Therm Biol 26:249–253

Moqrich A, Hwang SW, Earley TJ, Petrus MJ, Murray AN, Spencer KS, Andahazy M, Story GM, Patapoutian A (2005) Impaired thermosensation in mice lacking TRPV3, a heat and camphor sensor in the skin. Science 307:1468–1472

Nagashima K (2006) Central mechanisms for thermoregulation in a hot environment. Ind Health 44:359–367

Nakamura M, Yoda T, Crawshaw LI, Yasuhara S, Saito Y, Kasuga M, Nagashima K, Kanosue K (2008) Regional differences in temperature sensation and thermal comfort in humans. J Appl Physiol 105:1897–1906

Noakes TD, Marino FE (2009) Point: maximal oxygen uptake is limited by a central nervous system governor. J Appl Physiol 106:338–339 (discussion 341)

Passias TC, Meneilly GS, Mekjavic IB (1996) Effect of hypoglycemia on thermoregulatory responses. J Appl Physiol 80:1021–1032

Pertwee RG, Marshall NR, Macdonald AG (1986) Effects of subanesthetic doses of inert gases on behavioral thermoregulation in mice. J Appl Physiol 61:1623–1633

Pieron H (1913) Le probleme physiologique du sommeil (The physiological problem of the sleep). Masson and Cie, Paris

Riddell MC (2008) The endocrine response and substrate utilization during exercise in children and adolescents. J Appl Physiol 105:725–733

Roberts WW (1988) Differential thermosensor control of thermoregulatory grooming, locomotion, and relaxed postural extension. Ann N Y Acad Sci 525:363–374

Roelands B, Goekint M, Heyman E, Piacentini MF, Watson P, Hasegawa H, Buyse L, Pauwels F, De Schutter G, Meeusen R (2008) Acute norepinephrine reuptake inhibition decreases performance in normal and high ambient temperature. J Appl Physiol 105:206–212

Rolls ET, Grabenhorst F, Parris BA (2008) Warm pleasant feelings in the brain. Neuroimage 41:1504–1513

Romanovsky AA (2007) Thermoregulation: some concepts have changed. Functional architecture of the thermoregulatory system. Am J Physiol Regul Integr Comp Physiol 292:R37–R46

Sawamoto N, Honda M, Okada T, Hanakawa T, Kanda M, Fukuyama H, Konishi J, Shibasaki H (2000) Expectation of pain enhances responses to nonpainful somatosensory stimulation in the anterior cingulate cortex and parietal operculum/posterior insula: an event-related functional magnetic resonance imaging study. J Neurosci 20:7438–7445

Schlader ZJ, Prange HD, Mickleborough TD, Stager JM (2009) Characteristics of the control of human thermoregulatory behavior. Physiol Behav 98:557–562

Simon E (1974) Temperature regulation: the spinal cord as a site of extrahypothalamic thermoregulatory functions. Rev Physiol Biochem Pharmacol 1–76

Simon C, Gronfier C, Schlienger JL, Brandenberger G (1998) Circadian and ultradian variations of leptin in normal man under continuous enteral nutrition: relationship to sleep and body temperature. J Clin Endocrinol Metab 83:1893–1899

Stehling O, Doring H, Nuesslein-Hildesheim B, Olbort M, Schmidt I (1997) Leptin does not reduce body fat content but augments cold defense abilities in thermoneutrally reared rat pups. Pflugers Arch 434:694–697

Suzuki M, Mizuno A, Kodaira K, Imai M (2003) Impaired pressure sensation in mice lacking TRPV4. J Biol Chem 278:22664–22668

Szekely M, Szelenyi Z (2005) Regulation of energy balance by peptides: a review. Curr Protein Pept Sci 6:327–353

Taylor NA, Allsopp NK, Parkes DG (1995) Preferred room temperature of young versus aged males: the influence of thermal sensation, thermal comfort, and affect. J Gerontol A Biol Sci Med Sci 50:M216–M221

Tikuisis P, McLellan TM, Selkirk G (2002) Perceptual versus physiological heat strain during exercise-heat stress. Med Sci Sports Exerc 34:1454–1461

Tucker R, Rauch L, Harley YX, Noakes TD (2004) Impaired exercise performance in the heat is associated with an anticipatory reduction in skeletal muscle recruitment. Pflugers Arch 448:422–430

Tucker R, Marle T, Lambert EV, Noakes TD (2006) The rate of heat storage mediates an anticipatory reduction in exercise intensity during cycling at a fixed rating of perceived exertion. J Physiol 574:905–915

Verhagen JV, Kadohisa M, Rolls ET (2004) Primate insular/opercular taste cortex: neuronal representations of the viscosity, fat texture, grittiness, temperature, and taste of foods. J Neurophysiol 92:1685–1699