Journal of Thermal Biology 83 (2019) 37–46

Contents lists available at ScienceDirect

Journal of Thermal Biology

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

Thermoeffector threshold plasticity: The impact of thermal pre-conditioning on sudomotor, cutaneous vasomotor and thermogenic thresholds

Nigel A.S. Taylor*, Åsa Nykvist, Nicholas Powers, Joanne N. Caldwell[1]

Centre for Human and Applied Physiology, School of Medicine, University of Wollongong, Wollongong, NSW, 2522, Australia

ARTICLE INFO

Keywords:
Shivering
Sudomotor
Thermoeffector thresholds
Thermogenesis
Vasoconstriction
Vasodilatation

ABSTRACT

To better understand the relationships between changes in body temperature and displacements of the thermoeffector thresholds (critical temperatures), the passive cooling (and heating) of pre-heated (and pre-cooled) individuals was investigated. Such experiments are necessary to understand the inter-dependence of those thresholds, and may possibly yield human evidence for the existence of separate central controllers. Eight males participated in four trials; two when normothermic, one following pre-experimental heating and the fourth following pre-cooling. Subjects were exposed to passive, whole-body cooling and heating when normothermic (the control trials), and again following pre-heating and pre-cooling (respectively). Cutaneous vasomotor, thermogenic, as well as precursor and discharged sudomotor thresholds from different body segments were compared across those dynamic thermal states. Following pre-heating, the critical mean body temperatures for vasoconstriction (0.37 °C ± 0.10) and thermogenesis (0.67 °C ± 0.20) were significantly elevated during passive cooling, relative to the corresponding control trial (both $P < 0.05$). When passive heating followed pre-cooling, the thresholds for vasodilatation were reduced (0.37 °C ± 0.07; $P < 0.05$). Conversely, but with the exception of forehead precursor sweating, the sudomotor thresholds were elevated (averaging 0.16 °C ± 0.02; $P < 0.05$). Most thermoeffectors revealed unique and adjustable activation thresholds, with the threshold displacements for thermogenesis and vasomotion appearing to be linked to the change in mean body temperature. Following pre-cooling, the critical temperatures for vasodilatation and sudomotor activation varied independently, with the exception of forehead precursor sweating. Collectively, those observations are consistent with the presence of independent central controllers for thermally dependent vasomotor and sudomotor responses, and perhaps also for shivering thermogenesis.

1. Introduction

When the stability of the internal environment is challenged, species that regulate the physical characteristics of their *milieu intérieur* invoke behavioural and autonomic regulatory mechanisms designed to restore the *status quo*. One of those regulatory processes deals with the thermal energy content of the deep-body and peripheral tissues (the passive system; Werner, 1977; Stolwijk and Hardy, 2011). Indeed, mammals and birds (physiological regulators) defend body temperatures between lower and upper boundaries that optimise physiological function. As those threshold (critical) temperatures are crossed, autonomically controlled structures act to conserve (cutaneous vasoconstriction) and produce heat (thermogenesis) during cooling, or to dissipate heat (cutaneous vasodilatation and evaporation) when body temperatures are rising (Werner et al., 2008; Stolwijk and Hardy, 2011). The focus of this manuscript is on the mean body temperature thresholds at which those thermoeffectors are activated in humans, and the possibility that such points are neither unitary nor fixed (set), but are independently moveable.

The once prevailing dogma was that mammalian temperature regulation was based upon the existence of an adjustable set point (Hammel et al., 1963). We now recognise that concept to have been a sometimes misleading simplification, for reference signals and anatomical structures that might contain such information have neither been identified, nor are they required within proportional, feedback control systems (Mitchell et al., 1970; Werner et al., 2008, Werner 2010). Indeed, whilst a single threshold temperature has been described (Cabanac and Massonnet, 1977), others found that those critical temperatures not only differed across (Mekjavić et al., 1991; Caldwell et al., 2015), but also within thermoeffectors (McCook et al., 1965; Hellstrøm

* Corresponding author.
E-mail address: nigelastaylor@gmail.com (N.A.S. Taylor).
[1] Current address: Department of Physiology, Monash University, Clayton, VIC 3800, Australia.

https://doi.org/10.1016/j.jtherbio.2019.05.001
Received 2 May 2019; Accepted 2 May 2019
Available online 03 May 2019

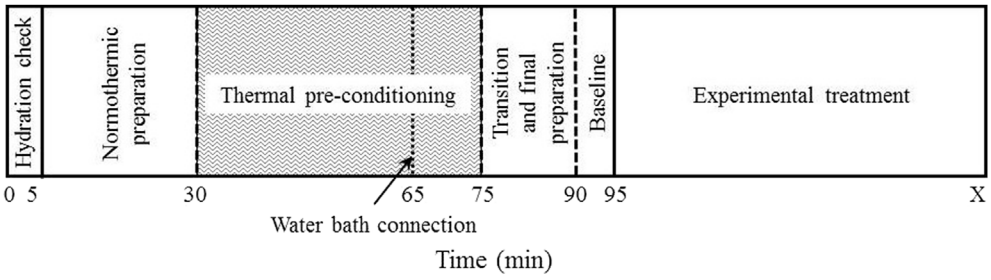

Fig. 1. Experimental overview with a typical time line. Each of the four trials followed an identical sequence, commencing with hydration-state confirmation and pre-experimental, normothermic preparation (0–30 min; seated). One of three thermal pre-conditioning water immersions then followed (30–75 min; supine): normothermic (Trials A and B), pre-heated (Trial C) and pre-cooled (Trial D). The duration of those pre-conditioning phases varied among individuals, but during the final 10 min of both the warm and cool immersions (~65–75 min), warm (or cool) water was passed from a water bath through the water-perfusion suit worn by all participants. Immediately thereafter, subjects were transferred to a pre-conditioned climate chamber and prepared for the experimental treatment. Baseline data collection followed (90–95 min), with the experimental treatment then commencing (~95-final min).

and Hammel, 1967; Kenny et al., 1998), and convincing evidence for the existence of a single threshold (set point) does not exist (Mekjavić et al., 1991; Werner et al., 2008). Instead, human thermoregulation is best described as a series of regulatory zones (Giaja, 1938; Mekjavic and Eiken, 2006), the ends of which are defined by the lower and upper critical temperatures for thermoeffector activation. The questions of interest for this investigation were whether or not the temperatures that define those zones are fixed and inter-dependent. One outcome from this experiment is the possible provision of integrated physiological evidence for the existence of multiple, central thermoeffector controllers.

With regard to the stability of the thermoeffector thresholds, it has been repeatedly demonstrated that heat adaptation lowers both the resting deep-body temperature and the sudomotor threshold (Ladell, 1951; Fox et al., 1967; Wyndham, 1967; Henane and Valatx, 1973). That is, the threshold for sweating seemed to possess some degree of plasticity, although relatively few have suggested a mechanistic link between those temperatures changes (Werner, 1994; Buono et al., 1998; Patterson et al., 2004; Kenny et al., 2010). Moreover, artificially lowering mean body temperature (pre-cooling), prior to exercise in the heat, can also elicit a downward displacement of the sudomotor threshold (MacDonald et al., 2000; Booth et al., 2004). Those, perhaps serendipitous, observations prompted further exploration of those phenomena, and it was a relatively small step to contemplate the possibility that the thermoeffector thresholds may be more tightly coupled with the size of the change in mean body temperature from its basal state, than with its arrival at some pre-ordained absolute value. That possibility formed the working hypothesis behind this experiment. It was also of interest to explore the inter-dependence of those critical temperatures across several thermoeffectors.

Since cutaneous vasomotion and sudomotion are modulated via mechanisms in addition to temperature regulation (Blair et al., 1961; van Beaumont and Bullard, 1963; Machado-Moreira and Taylor, 2012), then a critical design objective was to minimise non-thermal influences. For example, neural feedforward (central command) accompanying exercise elevates constrictor tone while simultaneously stimulating sweating, making the identification, and subsequent interpretation, of the vascular and sudomotor critical temperatures rather difficult. Therefore, an experiment was designed in which passive thermal treatments were used, with the resulting autonomic responses reflecting changes that might be observed when resting individuals are exposed to thermal states on either side of thermoneutrality. The critical (mean body) temperatures for vasomotion, thermogenesis and sudomotion were identified and compared during both the cooling and heating of normothermic participants, the cooling of those same individuals following pre-heating and when passive heating followed pre-cooling.

2. Methods

2.1. Participants

This experiment was performed on eight physically active, healthy males (23.6 y [standard deviation (SD) 4.0], 74.9 kg [SD 7.9], 1.79 m [SD 0.04]). Each was screened to ensure that none had a history of cardiovascular, respiratory or thermoregulatory disorders. The procedures used were approved by a Human Research Ethics Committee (University of Wollongong) in accordance with national regulations (National Health and Medical Research Council, Australia). Every subject provided written, informed consent prior to participation.

2.2. Procedures

2.2.1. Procedural overview

Every subject completed four trials, each performed on a separate day, and administered in a unique sequence for each individual (Latin square). Within each trial, an identical experimental sequence was followed (Fig. 1). On presentation, the required euhydrated state was evaluated (urine specific gravity) and adjusted if required, followed by instrumentation and the donning of a water-perfusion suit over a swimming costume. Thermal pre-conditioning then commenced (whole-body water immersion), with three thermal states being established across the four trials: normothermia (two trials), whole-body heating prior to experimentation (pre-heated) and whole-body, pre-experimental cooling (pre-cooled). Once those states were achieved and stabilised, subjects were wrapped in heavily insulated clothing, transferred to a pre-conditioned, climate-controlled chamber and prepared for the experimental phase (Fig. 1), which took the form of either passive, whole-body cooling or heating. Those experimental treatments involved the gradual removal (or addition) of thermal energy, by modifying the temperature of water passing through the perfusion garment. When normothermic, subjects were exposed to both the passive cooling (Trial A) and heating treatments (Trial B); these were the control trials. Gradual, whole-body cooling was also implemented following pre-heating (Trial C), with whole-body heating again applied after participants had been pre-cooled (Trial D). Since the aim of this project was to evaluate the impact of thermal pre-conditioning on the critical temperatures for cutaneous vasoconstriction and shivering (Trials A and C), as well as those for cutaneous vasodilatation and sweating (Trials B and D), then each trial was terminated 10 min following the establishment of the trial-specific thermoeffector responses.

2.2.2. Experimental standardisation

To ensure that variations in neither metabolic nor hydration state would introduce experimental artefacts, participants were required to refrain from strenuous exercise, alcohol and tobacco for 12 h, and caffeine for 2 h, prior to testing. Subjects were also instructed to eat high-carbohydrate and low-fat meals on the evening before, and in the morning of experimentation. In addition, the within-subject timing of

these trials was matched to minimise circadian influences, with testing not occurring on consecutive days. Finally, subjects were requested to drink 15 mL kg^{-1} of additional water before retiring. Pre-experimental hydration status was evaluated, on arrival, from urine specific gravity (Clinical Refractometer, Model 140, Shibuya Optical, Tokyo, Japan), with subjects presenting, on average, in a euhydrated state: Trial A = 1.019 (SD 0.01), Trial B = 1.022 (SD 0.01), Trial C = 1.016 (SD 0.01) and Trial D = 1.018 (SD 0.01). However, on six of the 32 occasions, some individuals had values > 1.029 (the hypohydration threshold), and immediately consumed supplementary water (10 mL kg^{-1}), 90 min before baseline data collection (Fig. 1). Supervised recovery followed every trial, ensuring the restoration of normothermia. Following the heating trials, participants consumed isotonic drinks during recovery, equal to 150% of their body-mass loss.

2.2.3. Thermal pre-conditioning

The three pre-experimental thermal states were achieved and stabilised using supine (head out) immersion in a stirred water tank (4500 L). Every immersion lasted 45 min to ensure the hydrostatic impact on body-fluid distribution was standardised across all trials (Stocks et al., 2004). That pre-conditioning was aimed at producing a uniform and stable normothermic state across individuals, or at achieving controlled displacements of the mean body temperature of approximately 0.5 °C above and below its normothermic level. Pilot testing was used to identify the water temperatures necessary to achieve those states (Fig. 2). For the normothermic trials, the water was regulated at 33–34 °C. Pre-heating was induced using a water temperature of 39 °C. Pre-cooling was achieved by gradually reducing the water temperature from 28° to 23 °C over 45 min, with ice added (2.0–2.5 kg) at 5-min intervals beyond 25 min. That method gradually extracts heat without eliciting a thermogenic response (Booth et al., 2004).

In addition, during the final 10 min of each immersion (Fig. 1), water was pumped through the water-perfusion suit from a water bath (Type VFP, Grant instruments, U.K.) positioned next to the immersion tank, and regulated at either of two temperatures: 48 °C (pre-heating) or 15 °C (pre-cooling). That suit was constructed from a network of tubing (~180 m Tygon® tubing: I.D. = 1.58 mm; O.D. = 3.0 mm) arranged from 140 parallel, 1-m lengths to form anterior and posterior jacket and trouser segments (Paul Webb Associates, Yellow Springs, U.S.A.). Such a configuration enabled ~90% of the skin to be covered, with skin between adjacent tubes being fully exposed, and thereby provided an effective means for establishing and sustaining a range of whole-body thermal states.

To prevent the impact of postural changes on body-fluid distribution (Maw et al., 1995), a supine posture was sustained throughout all immersions (feet ~5° below the horizontal plane), during the transition to the climate chamber and then during every experimental treatment. The transition from the immersion tank, which was contained within an air-conditioned laboratory (20–22 °C), to the adjacent chamber (5 m) necessitated the use of pre-heated (or pre-cooled) and heavily insulated clothing and blankets to minimise unwanted heat exchanges.

Once removed from the water (electronic winch), perfusion of the suit ceased and each participant was rapidly and carefully towelled dry, covered with pre-conditioned, insulated clothing and transferred to the chamber on a gurney (mobile bed). That climate chamber was initially equilibrated to either warm (cooling trials) or temperate conditions (heating trials) to minimise heat exchange: Trial A: 29.6 °C; Trial B: 22.7 °C; Trial C: 29.8 °C; and Trial D: 22.3 °C. Once inside the chamber, each participant was gently moved onto a wire-mesh bed to maximise skin exposure to the air. The insulating clothing was maintained and water was again pumped through the suit, but now from a second water bath (Type VFP, Grant instruments, U.K.), whilst subject preparations were completed.

2.2.4. Experimental treatments

Each experimental (thermal) treatment commenced with removal of the insulated clothing. Those treatments were of a passive nature, thereby avoiding artefacts associated with exercise-related feedforward, and consisted of either passive (forced) whole-body cooling (Trials A and C; Fig. 2A) or heating (Trials B and D; Fig. 2B), by manipulating the temperatures of water perfusing the suit and of the air within the chamber. Radiant heating was also used in Trials B and D. Pilot testing permitted the identification of air and water temperatures necessary to both induce gradual changes in mean body temperature, and to minimise the impact of dynamic peripheral thermoreceptor feedback (Mekjavić et al., 1991). For whole-body cooling, chamber air temperature was reduced in a step-wise manner to 17 °C, and water perfusing the suit was similarly reduced to 10 °C. For the heating trials, the air temperature was immediately elevated to 36 °C, the water-bath temperature was elevated to 48 °C and radiant heating was applied to the torso (three, 500-W infra-red lamps). Since the objective was to initiate either cutaneous vasoconstriction and shivering (Trials A and C), or cutaneous vasodilatation and sweating (Trials B and D), then trials ended following the recruitment of those thermoeffector pairs and their continuous activity for another 10 min.

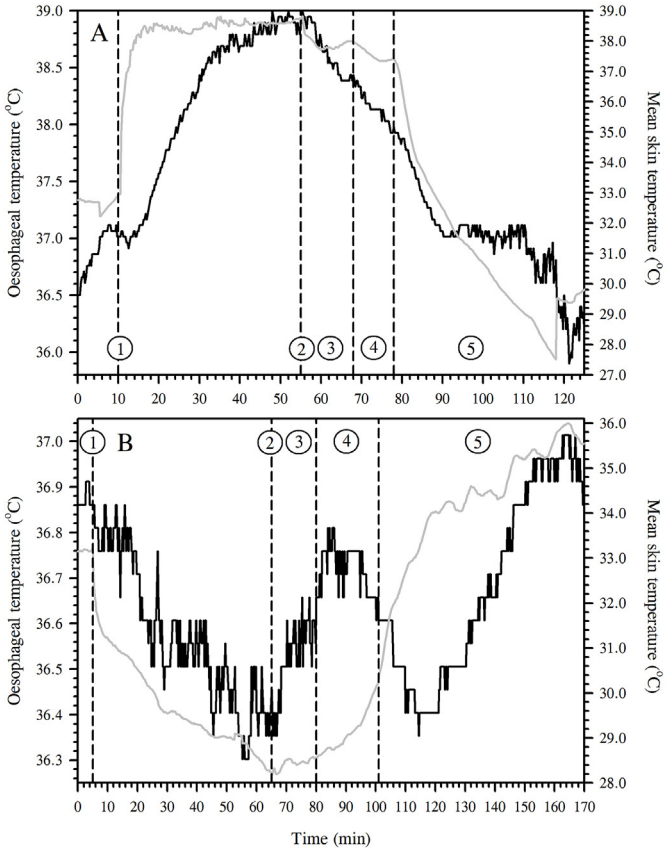

Fig. 2. Representative deep-body (oesophageal; black lines) and mean skin temperature (grey lines) profiles from the same individual during Trial C (Fig. 2A: pre-experimental heating followed by whole-body cooling) and Trial D (Fig. 2B: pre-cooled followed by whole-body heating). The vertical (dashed) lines define the following steps (moving left to right): (1) initiating the pre-experimental water immersion, (2) terminating immersion, (3) transition into the climate chamber, (4) further subject preparation inside the chamber and (5) the whole-body thermal treatments by reducing air and water-perfusion suit temperatures (Trial C), or by increasing air and water temperatures and activating radiant heating (Trial D). Experimental data collection commenced at the fourth dashed line.

2.2.5. Measurements

Three indices of deep-body temperature were used: oesophageal temperature (transnasal insertion; Edale instruments Ltd., Cambridge,

U.K.), insulated auditory canal temperature (Edale instruments Ltd., Cambridge, U.K.) and rectal temperature (10 cm beyond the anal sphincter; Edale instruments Ltd., Cambridge, U.K.). Skin temperatures were measured from eight sites (Type EU, Yellow Springs Instruments Co. Ltd., Yellow Springs, OH, U.S.A.): forehead, right scapula, right chest, right upper arm, left dorsal forearm, left dorsal hand, right anterior thigh and left posterior calf. Those thermistors were secured using a single layer of adhesive tape, with all temperatures recorded at 15-s intervals (Grant Instruments Ltd., 1206 Series Squirrel, U.K.).

An area-weighted summation of those skin temperatures was used to derive mean skin temperature (Hardy and DuBois, 1938). Whilst those weighting can be modified to reflect regional differences in cutaneous thermosensitivity, experimental evidence does not support that approach (Cotter and Taylor, 2005; Burdon et al., 2017), with the possible exception of the face during locally applied thermal stimuli. Mean skin temperatures were combined with oesophageal temperature, with the following temperature-specific coefficients used to approximate mean body temperature (Vallerand et al., 1992). It is acknowledged that index may not provide a perfect reflection of thermoafferent flow (Taylor et al., 2014b), but the omission of sites providing peripheral feedback (skin temperatures) during externally applied thermal treatments was considered a further step away from reality. It is also recognised that a combination of several deep-body temperatures may, under steady-state conditions, yield a superior index of heat storage (Taylor et al., 2014b). However, in the current experiment, dynamic responses were of primary interest, and so the most dynamically responsive index was used for estimating mean body temperature (oesophageal temperature; Taylor et al., 2014b).

Heating: Mean body temperature = (0.90∗oesophageal) + (0.10∗skin) (1)

Cooling: Mean body temperature = (0.65∗oesophageal) + (0.35∗skin) (2)

Cutaneous vasomotor activity was quantified using both venous-occlusion plethysmography (left finger and left calf) and laser-Doppler flowmetry (right dorsal forearm). Those body segments were not covered by the water-perfusion garment, and, in the absence of local thermal clamping, possible artefactual affects associated with localised thermal influences cannot be excluded, although they were most unlikely under such stable ambient conditions. The assumption of the former technique was that, within resting individuals, vascular changes would primarily reflect those of the cutaneous vasculature (Edholm et al., 1956; Detry et al., 1972). Whilst that premiss is generally accepted, particularly for the finger, it may not always be valid for the calf or forearm (Crandall and Wilson, 2015). Therefore, both vascular techniques were used, with plethysmography applied to different segments of the upper and lower limbs. That combination of techniques and measurement sites provided a comprehensive evaluation of cutaneous vasomotor activity across different spinal segments during each of the experimental treatments.

Mercury-in-silastic strain gauges were positioned at the middle phalanx of the left index finger, and at the widest girth of the left calf. To negate measurement artefacts associated with variations in foot blood flow, a pressure cuff was also placed around the left ankle and inflated to 160 mm Hg prior to each measurement block. Occlusion cuffs were positioned on the left arm and thigh, and intermittently inflated to 50 mm Hg (8 s inflated, 12 s deflated) over a 2-min period (EC 4 Plethysmograph with AG 101 Cuff inflator air source, D.E. Hokanson, Inc., Bellevue, U.S.A.). That cyclical pattern was repeated at 5-min intervals from the pre-treatment baseline through to the end of each trial, with data collected at 20 Hz using an analog-to-digital converter (Computer Boards Inc., PPIOA18, Mansfield, OH, U.S.A.), and saved to a computer. Laser-Doppler data were collected from the right dorsal forearm (TSI Laserflo BPM2 with a P-435 laser fibre optic probe, Vasamedics Inc., St. Paul, U.S.A.; 37 internal refresh rate ~7 Hz), with probe positioning standardised across trials. That location provides a representative index of forearm cutaneous blood flow (Cotter et al., 1993). Data were collected in 2-min blocks every 5 min, and sampled at 20 Hz (Computer Boards Inc., PPIOA18, Mansfield, OH, U.S.A.).

Arterial blood pressures were measured (right upper arm) prior to each blood-flow measurement period (Omron SEM-2, Omron Healthcare Inc., Kyoto, Japan), with mean arterial pressure calculated as systolic pressure plus 0.33 times the difference between the systolic and diastolic pressures. Vascular conductances were derived as the ratio of local blood flow to mean arterial pressure. Cardiac frequency data were obtained at 15-s intervals (Polar Electro Sports Tester, Kempele, Finland).

Thermogenesis was estimated from whole-body oxygen consumption (respirometry). Subjects wore an oronasal mask from which expired air was sampled and airflow measured, with those data analysed continuously to derive oxygen consumption as 15-s averages (TrueOne 2400, ParvoMedics Inc., Utah, USA). Analysers were calibrated using *alpha* gas standards (15.97% oxygen, 4.03% carbon dioxide, balance nitrogen) and room air.

Sudomotor responses were also evaluated using two techniques: skin conductance was used to detect the onset of primary (precursor) sweat production, while secondary (discharged) secretion was quantified using capacitance hygrometry. Since precursor sweat does not always reach the skin surface, then threshold detection errors can occur when one relies wholly upon discharged sweat measurements (Machado-Moreira et al., 2015). To minimise that possibility, both sudomotor indices were simultaneously recorded from the finger, forearm and forehead. This provided a within-site measurement verification for this effector. In addition, it enabled the comparison of vasomotor and sudomotor activity within two matched sites (fingers and forearm), and well as one between-site comparison (calf and forehead). As with the indices of vasomotor activity, those three body regions were not covered by the water-perfusion garment.

Precursor sweat production was evaluated from changes in the electrodermal responses of three segments: the dorsal surfaces of the second and third fingers (right hand), the right dorsal forearm and the forehead. Pairs of Ag/AgCl surface electrodes (1081 FG) were attached to those sites (0.05 M sodium chloride in an inert ointment base), and a constant voltage (0.5 V) was applied across each electrode pair. The resulting data were sampled at 10 Hz (UFI Bioderm model 2701-SC Simple Scope and SCL/SCR Data Collection System, UFI, Morrow Bay, CA, U.S.A.). For comparative purposes, sweat capsules were positioned next to those sites, except for the fingers, with the dorsal surface of the right index finger used due to the limited surface areas of the phalanges.

Sweat capsules were used to measure local discharged sweat rates from the right index finger (1.40 cm^2), forehead and the left dorsal forearm (3.16 cm^2). Capsules were glued to the skin to prevent pressure artefacts (Collodion U.S.P., Mavidon Medical Products, U.S.A.), with pre-capsular airflows independently regulated (300 mL min^{-1} [smaller capsule] and 600 mL min^{-1} [larger capsules]). Inlet relative humidity was maintained at 12% by passing room air over a saturated lithium chloride solution, whilst post-capsular humidity was measured using capacitance hygrometers, all of which were components of a sweat-monitor system (Clinical Engineering Solutions, NSW, Australia). Temperatures of the pre- and post-capsular air, as well as the relative humidity of the post-capsular air, were sampled at 1-s intervals (DAS1602, Keithley Instruments, Inc., Cleveland, U.S.A.), and used to compute local sweat rates. Hygrometer calibration, using three saturated salt solution standards, preceded experimentation.

2.2.6. Design and analysis

This experiment was based on a repeated-measures design, with subjects completing every trial and acting as their own controls (Trials A and B). Since the primary focus was determining the thermoeffector thresholds during both cooling and heating, then, for each effector, preconditioned baselines were established over a 5-min period (Fig. 1:

90–95 min). An approximation of each threshold (critical temperature) was initially identified visually, as determined by a clear, and continued deviation of each effector response away from its baseline. To minimise the influence of experimenter bias, separate baseline and treatment data were isolated. To achieve those data sets, values were removed from 15 to 30 s immediately preceding, and then directly following, each visually determined threshold. In addition, data beyond the early (linear) phase of effector activation were excluded. That process yielded separate baseline and treatment data sets for each effector, to which linear regression analyses were applied, and used to describe the relationship between mean body temperature and each thermoeffector response. Intersections of those regression lines were resolved (simultaneous equations), and used to define each of 13 thermoeffector activation thresholds (Regan et al., 1996). Due to technical problems with the sweat capsules for two individuals during either Trial B or D, some data sets were incomplete. In those instances, the corresponding data for that location in the other trial pair were omitted. Repeated-measures Analysis of Variance was used to evaluate differences in the vasomotor, thermogenic and sudomotor thresholds within the two experimental treatments, and across the three pre-conditioned thermal states. Tukeys HSD *post hoc* tests were used to isolate sources of significant differences between trials, with *alpha* set at the 0.05 level, and with data presented as means with either standard errors of those means (±), or standard deviations (SD) when describing distributions.

3. Results

3.1. Thermal pre-conditioning

Critical to the design of this experiment was the establishment of normothermia (the control condition: Trials A and B), as well as the mildly heated (Trial C) and mildly cooled, pre-treatment states (Trial D). Those pre-conditioned levels of heat storage were successfully achieved, as reflected within the three deep-body temperatures, and shown on an individual basis for oesophageal temperature (Table 1). The respective baseline deep-body temperatures for Trials A and B averaged 36.8 °C (SD 0.1) and 36.9 °C (SD 0.2) for the oesophagus, 36.7 °C (SD 0.2) and 36.1 °C (SD 0.3) for the auditory canal, and 36.8 °C (SD 0.3) and 37.1 °C (SD 0.5) for the rectum. The corresponding mean body temperatures averaged: Trial A: 36.0 °C (SD 0.1); Trial B: 36.2 °C (SD 0.1). The within-site, deep-body temperature differences were not significant for either of the control trials ($P > 0.05$).

All deep-body temperatures were significantly elevated prior to commencing Trial C (passive cooling; Table 1: $P < 0.05$) and significantly depressed prior to Trial D (Table 1: $P < 0.05$). For the auditory canal, those displacements were also significant relative to the control trials (Trial C: 37.7 °C [SD 0.4]; Trial D: 36.2 °C [SD 0.1]; both $P < 0.05$), with the same pattern evident for the rectal temperatures (Trial C: 38.4 °C [SD 0.4]; Trial D: 36.6 °C [SD 0.4]; both $P < 0.05$). The corresponding mean body temperatures were: Trial C: 38.2 °C (SD 0.4); Trial D: 35.6 °C (SD 0.2; both $P < 0.05$). On the basis of those observations, it was concluded that thermal pre-conditioning was successfully and uniformly achieved across participants.

Table 1
Baseline oesophageal temperatures (°C) for each participant, averaged across the 5-min period prior to commencing the experimental treatments. *Symbols:* † = significantly different from Trial A ($P < 0.05$); ‡ = significantly different from Trial B ($P < 0.05$); and § = significantly different from Trial C ($P < 0.05$).

Subject	Trial A	Trial B	Trial C	Trial D
1	36.8	36.8	37.7	36.1
2	36.8	36.7	37.2	36.7
3	37.1	37.2	38.2	36.5
4	36.6	37.1	37.3	36.7
5	36.9	37.0	37.9	36.6
6	36.9	36.9	37.7	36.7
7	36.8	36.6	38.1	36.1
8	36.7	36.9	37.6	36.2
Mean	36.8§	36.9§	37.7†,‡	36.4†,‡,§
SD	0.2	0.2	0.3	0.3

3.2. Experimental treatments

To eliminate differences in dynamic thermoreceptor feedback that might affect the critical temperatures, it was essential that the passive cooling (Trials A and C) and heating rates (Trials B and D) were matched within those trial pairs. This was successfully achieved, with the corresponding rates of mean body temperature change being: $-2.16\ ^{\circ}C.h^{-1}$ (SD 1.0) for Trial A and $-2.15\ ^{\circ}C.h^{-1}$ (SD 0.7) for Trial C ($P > 0.05$); and $0.47\ ^{\circ}C.h^{-1}$ (SD 0.3) for Trial B and $0.52\ ^{\circ}C.h^{-1}$ (SD 0.2) for Trial D ($P > 0.05$). It was therefore concluded that inter-trial differences in thermoeffector activation would not result from variations in the rates of either cooling or heating.

3.3. Thermoeffector thresholds and regulatory zones

For the normothermic (control) trials in which participants were passively cooled (Trial A), none of the critical mean body temperatures for the cutaneous vasoconstriction indices (forearm, calf and finger) differed significantly from one another (Fig. 3; $P > 0.05$), reflecting the similarity of those measures across three spinal segments. Nevertheless, each threshold occurred at a significantly higher mean body temperature than, and therefore preceded, the threshold for thermogenesis (Fig. 3; $P < 0.05$). During passive heating from that normothermic state (Trial B), the three thresholds for cutaneous vasodilatation were also of equivalent magnitudes (Fig. 4; $P > 0.05$), as were those for both precursor and discharged sweating (Fig. 5; $P > 0.05$). In that control trial, however, the thresholds for vasodilatation and sweating were numerically, but not significantly different (Figs. 4 and 5; $P > 0.05$). For comparative purposes with other investigations, Table 2 contains the corresponding oesophageal temperature thresholds for each trial, although, in the absence of skin temperatures, those data do not reflect all sources of thermoafferent flow during externally

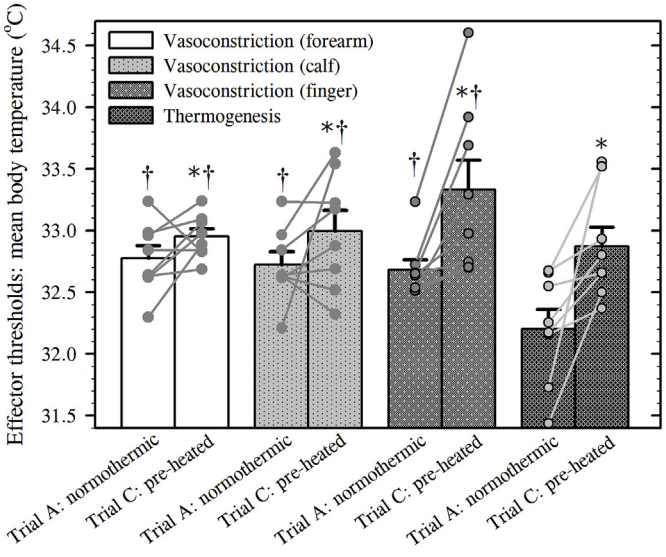

Fig. 3. Vasomotor and thermogenic thresholds, relative to mean body temperature, observed during the passive, whole-body cooling of normothermic (Trial A: $N = 8$) and pre-heated individuals (Trial C: $N = 8$). Data are presented for each individual, with the bar plots providing means and standard errors of those means. *Symbols:* † = significant differences between the within-trial vasomotor and thermogenic thresholds ($P < 0.05$); * = significant between-trial differences (Trial A versus Trial C) for each thermoeffector index ($P < 0.05$).

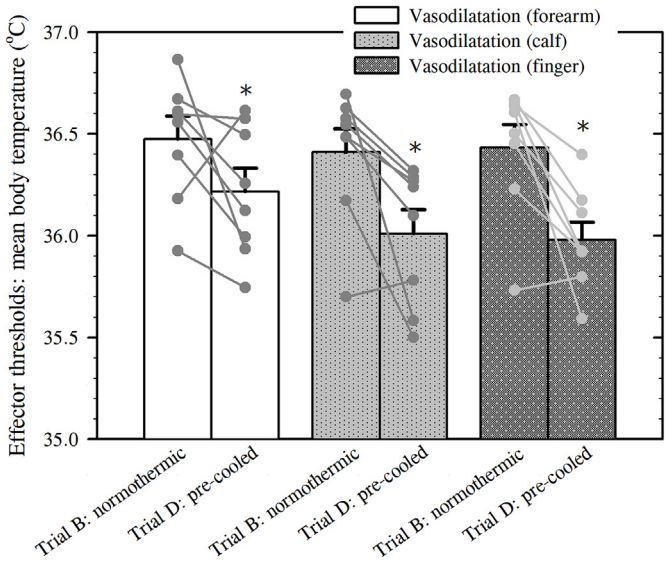

Fig. 4. Vasodilatory thresholds observed during passive, whole-body heating of normothermic (Trial B: $N = 8$) and pre-cooled individuals (Trial D: $N = 8$). Data are presented for each individual, along with means and standard errors of those means (bar plots). *Symbols:* * = significant between-trial differences (Trial B versus Trial D) within each vasomotor index ($P < 0.05$). Significant differences between the vasomotor and sudomotor thresholds for Trial B did not exist ($P > 0.05$), yet the former generally preceded the latter during Trial D ($P < 0.05$), except for forehead precursor sweating ($P > 0.05$).

driven cooling and heating.

The uniformity of the thresholds for the three vasomotor indices during the control trials, as well as those for each of the sudomotor indices, provides confidence in the inter-segmental reliability of those measurements. The lower precursor sweat thresholds at each site are physiologically correct, and reflect time differences between the initial production of sweat and its eventual appearance at the skin surface. Collectively, those observations demonstrate the strength and veracity of the methods. Moreover, significant differences between the vasomotor and thermogenic thresholds reinforce previous evidence that, at least during passive cooling, those thermoeffectors have different critical temperatures.

Following pre-heating (Trial C), the mean body temperature thresholds (Fig. 3) during whole-body cooling were significantly elevated for each vasomotor index (averaging 0.37 °C across those indices [± 0.10]; $P < 0.05$), and also for thermogenesis (0.67 °C ± 0.20; $P < 0.05$). Vasoconstriction again preceded shivering (Fig. 3; $P < 0.05$), confirming the thermal independence of recruitment. On average, those four thresholds now occurred at a mean body temperature 0.44 °C (± 0.04) higher, whilst the elevation in the pre-experimental baseline mean body temperature was 2.30 °C (± 0.01). Thus, those threshold changes were qualitatively, but not quantitatively similar, to the pre-experimental manipulation of mean body temperature. Not every subject followed that pattern, with six revealing an elevation in the vasoconstriction threshold at the forearm, five had higher thresholds at the calf while all eight showed higher thresholds for finger vasoconstriction (Fig. 3). Every participant experienced an elevated thermogenic threshold (Fig. 3).

During Trial D (passive heating following pre-cooling), the pre-experimental baseline mean body temperature was reduced by 0.59 °C (± 0.10). On average, the thresholds for cutaneous vasodilatation were now 0.37 °C lower (± 0.07; $P < 0.05$; Fig. 4), with seven participants showing reduced thresholds at the forearm, six at the calf and seven at the finger. Those thresholds also occurred significantly earlier than the corresponding sudomotor thresholds (Figs. 4 and 5; $P < 0.05$), with the only exception being precursor sweating at the forehead. Therefore,

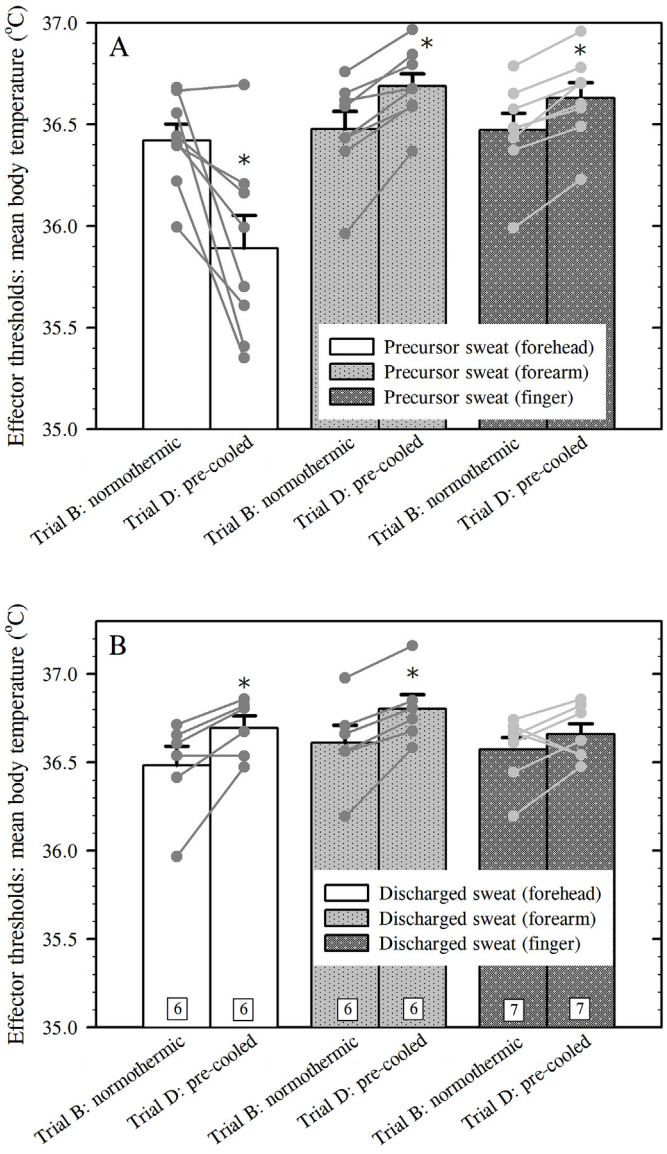

Fig. 5. Precursor (A) and discharged sweat thresholds (B) observed during the passive, whole-body heating of normothermic (Trial B) and pre-cooled individuals (Trial D). Data are presented for each individual, with means and standard errors of the means (bar plots). Numbers show incomplete data sets (otherwise $N = 8$). *Symbols:* * = significant between-trial differences (Trial B versus Trial D) within each sudomotor index ($P < 0.05$).

when those thermoeffectors were compared within the same body segments (finger and forearm), pre-cooling was found to elicit independent and divergent threshold displacements.

Unlike the vasomotor thresholds, the sweat thresholds were generally significantly elevated following pre-cooling ($P < 0.05$; Fig. 5A and B), except for precursor sweating at the forehead (reduced [$P < 0.05$]; Fig. 5A) and discharged sweating from the finger (elevated [$P > 0.05$]; Fig. 5B). The mean sudomotor threshold increase for the forearm and finger, averaged across those precursor and discharged indices, was 0.16 °C (± 0.02; $P < 0.05$). On an individual basis, the following participant numbers conformed with the averages shown in Fig. 5: precursor sweating (forehead [seven], forearm [eight], finger [eight]) and discharged sweating (forehead [five], forearm [six], finger [five]). Notwithstanding some variability, it was evident that not only did the thresholds for these vasomotor and sudomotor thermoeffectors move, but they moved independently. Furthermore, the displacement of the vasomotor threshold was now close to the experimentally

Table 2
For comparative purposes with previous research, the critical deep-body temperatures (oesophageal [°C]: upper values) are provided, as well as the mean skin temperatures at those thresholds (°C: lower values). Trials A and B involved the whole-body cooling and heating (respectively) of normothermic individuals (the control trials), whilst in Trials C and D the same treatments were repeated when participants were pre-heated and pre-cooled (respectively). Data are means with standard deviations in parentheses (N = 8).

Thermoeffector	Trial A	Trial C	Trial B	Trial D
Vasomotor (forearm)	36.8 (0.2)	37.0 (0.2)	36.8 (0.2)	36.5 (0.2)
	25.3 (0.7)	25.5 (0.4)	33.9 (2.2)	33.3 (2.6)
Vasomotor (calf)	36.8 (0.2)	37.1 (0.4)	36.8 (0.1)	36.3 (0.3)
	25.1 (0.6)	25.4 (0.7)	33.3 (2.8)	33.3 (1.1)
Vasomotor (finger)	36.8 (0.2)	37.2 (0.3)	36.8 (0.2)	36.4 (0.3)
	25.1 (0.4)	26.2 (1.8)	33.1 (2.4)	32.5 (2.1)
Thermogenesis	36.4 (0.5)	37.0 (0.4)		
	24.4 (0.7)	25.2 (0.9)		
Precursor sweat (forehead)			36.8 (0.3)	36.6 (0.3)
			33.0 (2.0)	29.2 (3.3)
Discharged sweat (forehead)			36.9 (0.2)	36.7 (0.2)
			32.9 (1.7)	37.1 (1.2)
Precursor sweat (forearm)			36.8 (0.3)	36.8 (0.2)
			33.3 (2.5)	35.9 (1.0)
Discharged sweat (forearm)			36.9 (0.2)	36.7 (0.1)
			34.0 (2.2)	37.7 (1.7)
Precursor sweat (finger)			36.8 (0.2)	36.7 (0.2)
			33.5 (1.7)	36.0 (0.8)
Discharged sweat (finger)			36.8 (0.2)	36.8 (0.2)
			34.3 (1.9)	35.8 (0.5)

induced mean body temperature manipulation.

4. Discussion

The current experiment represents one of the most comprehensive investigations of human thermoeffector thresholds thus far performed. Not only were vasomotor and sudomotor indices measured simultaneously from within the same body segment, but they were studied across different skin types and spinal segments. Moreover, the thermal equivalence of each pre-treatment state was ensured, whilst the changes in mean body temperature within each treatment pair were matched. In addition to reconfirming that a unitary critical temperature for heat production and dissipation does not exist, three novel outcomes arose. Firstly, each of the three, site-specific vasomotor thresholds differed significantly from that observed for shivering thermogenesis. Secondly, the cold-induced critical temperatures were all elevated following pre-heating, with that outcome implying that those thresholds seemed to be qualitatively coupled with the change in body temperature, rather than with the attainment of some absolute body temperature. Thirdly, when passive heating followed whole-body pre-cooling, the vasomotor and sudomotor thresholds varied independently, with a reduction in the former and an elevation in the latter, with one notable exception. Collectively, those outcomes are consistent with the presence of independent central controllers for the thermally dependent vasomotor and sudomotor responses, and perhaps also for thermogenesis.

Notwithstanding the suggestion of some (Benzinger et al., 1963; Cabanac and Massonnet, 1977), Burton and Bazett (1936) and DuBois (1939) had hypothesised that a single threshold for thermogenesis and evaporative thermolysis would not exist, with Jessen and Ludwig (1971), Mekjavić et al. (1991) and Bligh (2006) eventually providing the necessary empirical support. The current experiment has extended that evidence, with different thermoeffector thresholds observed between the heating and cooling phases, regardless of whether the participants were normothermic or thermally pre-treated. Furthermore, significant differences existed in the activation of those effectors within those treatments. That is, the cutaneous vascular responses always preceded thermogenesis during passive cooling, regardless of the pre-experimental mean body temperature (Fig. 3). Following pre-cooling, the critical temperatures for vasodilatation (Fig. 4) were lower than those for sweating (Fig. 5), with the exception of precursor sweat production at the forehead.

Those unique thresholds are summarised in Fig. 6, with two thermoeffector zones being apparent, each with different dimensions as well as unique lower and upper critical temperatures. Those critical temperatures defined both a cutaneous vasomotor zone (between vasoconstriction and vasodilatation) and a wider inter-threshold zone (separating thermogenesis from thermolysis). If separate effector controllers do exist, then those critical temperatures, and therefore the sizes of those zones, would seem to be merely (conceptual) by-products of the independent influences on those controllers.

The vasomotor zone, as derived from simultaneous measurements across three spinal segments using two measurement techniques, spanned a mean body temperature range of 3.7 °C (± 0.1 °C; Fig. 6). Inside those critical temperatures, there is a continual fine tuning of the cutaneous vascular heat exchanges, particularly at the hands and feet (Taylor et al., 2014a). When those exchanges match heat production, the mean body temperature reaches an operating or balance point (Werner, 2010) that corresponds with thermal comfort. Similarly, the six inter-threshold zones covered a mean body temperature range of 4.3 °C (± 0.1 °C; Fig. 6). When the size of those zones, with respect to oesophageal temperature (Table 2), was compared with the observations of Mekjavić et al. (1991), there was agreement across both experiments (0.40° versus 0.47 °C, respectively). However, due to the methods used for deriving mean body temperature within this experiment, the sizes of those two zones will necessarily be larger than those

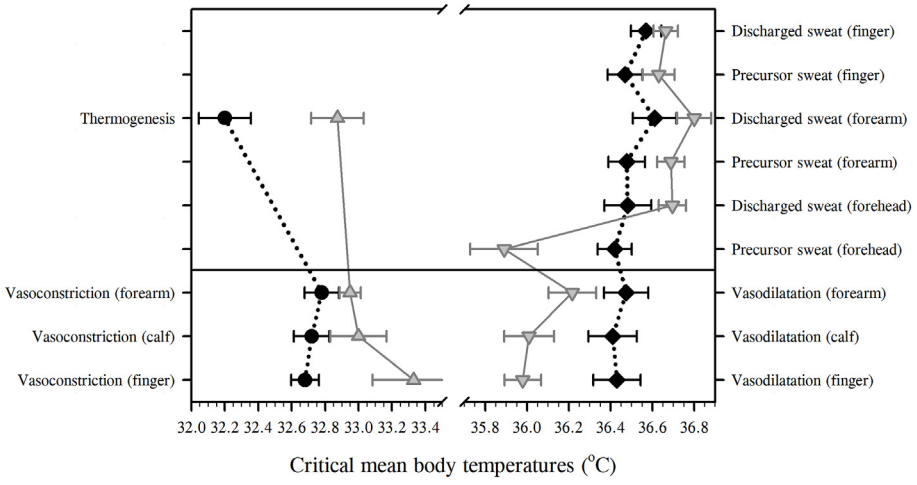

Fig. 6. Critical mean body temperatures for thermogenesis, cutaneous vasomotion and sudomotion determined during the passive cooling of normothermic (left side; Trial A [circles]: N = 8) and pre-heated individuals (Trial C [triangles]: N = 8), and then during the heating of those same participants in both normothermic (right side; Trial B [diamonds]: N = 8) and pre-cooled states (Trial D [inverted triangles]: N = 8). Data are means and standard errors of the means, with data from each trial being joined. Below the horizontal line, distances between the site-specific vasoconstriction and vasodilatation thresholds define the local vasomotor zones for the control (black symbols) and thermal pre-conditioning trials (grey symbols). The corresponding inter-threshold zones (above the horizontal line) are bordered by the single critical temperature for whole-body (shivering) thermogenesis and the six indices of sudomotor activation.

determined using only a deep-body temperature index.

If not already recognised from previous evidence (Mitchell et al., 1970; Mekjavić et al., 1991; Mekjavic and Eiken, 2006), then these data render the set-point concept indefensible, but what about the stability of those critical temperatures (Hammel et al., 1963)? Many have reported effector threshold plasticity following heat adaptation (Ladell, 1951; Fox et al., 1967; Wyndham, 1967; Henane and Valatx, 1973; Werner, 1994; Buono et al., 1998; Patterson et al., 2004; Kenny et al., 2010), and it is herein shown that this phenomenon also accompanies thermal pre-conditioning, possibly with a mechanistic connection. Thus, the three thermoeffectors have both unique and variable thresholds. Moreover, those thresholds appear capable of independent movement (Fig. 6), with displacements of the thermogenic, and each of the vasomotor thresholds appearing to be qualitatively related to mean body temperature changes. How do we reconcile those observations?

Perhaps the most simple explanation lies with the possibility that each group of thermoeffectors is independently modulated by a separate central controller. In considering that possibility, it is helpful to reflect upon the phylogenetic progression of effector acquisition. The first effector to be acquired was a capacity to modulate cutaneous blood flow, which presumably arose when our reptilian ancestors diverged from amphibians (> 300 million years ago: Carroll, 1970; Templeton, 1970). About 110 million years ago, endothermic monotremes evolved from amphibious reptiles (Phillips et al., 2009), providing mammals with a thermogenic capacity. Finally, eccrine sweat glands appeared in early primates (3–4 million years ago; Best and Kamilar, 2018). Against that background, one can imagine that each regulatory mechanism might have appeared with its own central controller, but that is only circumstantial evidence.

For empirical support, we turn to neurological evidence. Using bilateral incisions of the preoptic-anterior hypothalamus (rats), Gilbert and Blatteis (1978) eliminated cutaneous vasoconstriction during cold-air exposure. However, thermogenesis was minimally affected, leading to the conclusion that different central control centres existed for those thermoeffectors. Ootsuka and McAllen (2006) provided further evidence for independent central controllers of thermogenesis and cutaneous vasoconstriction (rats), and then for different vasoconstrictor thresholds for the glabrous (hairless) and non-glabrous skin (rats; Tanaka et al., 2007). Those outcomes, along with the current observations, support the existence of separate central controllers (McAllen et al., 2010), although several questions remain.

For instance, following pre-heating (Trial C), the thresholds for vasoconstriction and shivering were displaced to higher mean body temperatures relative to control Trial A. Was that elevated, pre-experimental heat content then retained, as if a new temperature was being defended? That possibility might be read into those threshold displacements (Fig. 6), although the authors do not support that interpretation. Instead, it means only that the critical temperatures, which signify effector activation and not response intensity, were displaced. It need not indicate, nor is it implied, that the intensities of heat conservation and production were equivalent to those seen during passive cooling from normothermia (Trial A). Instead, it is speculated that less powerful effector responses would more gradually dissipate heat. Following pre-cooling (Trial D), leftward displacements of the three vasomotor thresholds may similarly be explained, and there was some evidence supporting those possibilities in Trials C and D. Those data came from modelling the initial thermoeffector sensitivities (~30 s), which were used to determine the effector thresholds. However, none of those sensitivities differed significantly between trials ($P > 0.05$), with the durations over which they were collected limiting their use in this regard, and therefore leaving that hypothesis to be further investigated.

Why were five sudomotor thresholds elevated while the forehead precursor sweat threshold was reduced? We know that precursor sweat production precedes its eventual discharge (Ogawa and Bullard, 1972). In this experiment, seven participants revealed a reduced critical temperature for precursor sweat production at the forehead (Fig. 5A). Since none of the sweat measurement sites was beneath the water-perfusion garment, then this implies altered neural activation, rather than local thermal affects. Moreover, whilst data showing an elevated discharged sweat threshold for that site can be trusted, as it was observed in five of six subjects (with technical difficulties in two [Fig. 5B]), one cannot exclusively rely upon those data to evaluate the neurological significance of that threshold shift. Indeed, such an interpretation would be wrong, as it presumably relates to the time taken for fluid secretion to exceed reabsorption within the sweat duct (Taylor and Machado-Moreira, 2013). Therefore, those differences highlight the need for caution when analysing sweat data collected without precursor indices, particularly when measured from only one or two sites. On that basis, an opposite shift in the discharged threshold can be disregarded.

Since steady-state sweat oscillations are synchronised across the current measurement sites (Ogawa and Bullard, 1972; Taylor and Machado-Moreira, 2013), then it is assumed the glands of the forehead, forearm and finger share a common central controller. This leads to the possibility that the facial sweat glands may have different excitatory and inhibitory influences, downstream of the hypothalamus. The similarity of the forearm and finger precursor and discharged thresholds (Fig. 5), relative to those of the forehead, is consistent with such differences, which were only revealed following thermal pre-conditioning. To our knowledge, there is no other evidence of either this site-specific separation of the sudomotor thresholds, or the divergence of the vasomotor and sudomotor thresholds (within and between spinal segements), although Hellstrøm and Hammel (1967) reported an upward displacement of the evaporative cooling (panting) threshold in unanaesthetised dogs following pre-cooling.

Which mechanisms might explain the effects of thermal pre-conditioning on these thermoeffector thresholds (Trials C and D; Fig. 6)? Firstly, immersion-induced pre-cooling and pre-heating modified the thermal energy content of the peripheral tissues in directions opposite to those encountered during the experimental trials. Therefore, when each treatment was applied, the temperatures of those tissues would change more rapidly than during the control trials (heat-transfer law; Newton, 1700). Feedback from the cutaneous thermoreceptors, which possess powerful dynamic characteristics, would be significantly stronger.

Secondly, that feedback could influence neural traffic from the central controllers. Whilst neurological speculation must necessarily be limited, the neuronal model of Bligh (1998) provides a capacity to hypothesise on the impact of that thermoreceptor feedback. That model contains evidence-based excitatory and inhibitory interneurons. Therefore, an elevation of the lower critical temperatures for vasoconstriction and shivering could result following pre-heating (Trial C) if peripheral thermoreceptor feedback activated one of the excitatory interneurons within those separate neural pathways. That same mechanism might explain reduced vasodilatation thresholds, and perhaps also forehead sweating, when passive heating followed pre-cooling (Trial D).

Finally, there are two mechanisms that might explain the elevated forearm and finger sudomotor thresholds. Using the Bligh (1998) model again, an inhibitory influence within those sudomotor paths may have been activated. Alternatively, sudomotor activation may have been delayed during passive heating because the pre-cooled peripheral tissues, in combination with locally mediated cutaneous vasodilatation, delayed the accumulation of heat, and thereby reduced the need to sweat. The step that must follow this experiment is the independent verification of these observations. In addition, more invasive animal experiments are needed to continue the unravelling of our phylogenetically acquired regulatory mechanisms and their neural control.

4.1. Conclusion

Critical mean body temperatures for the activation of most

thermoeffectors investigated in this experiment were neither unitary points nor were they fixed. Instead, they represented unique and adjustable thresholds. The displacement of those critical temperatures following thermal pre-conditioning seemed more closely related to the change in mean body temperature than to some pre-ordained, absolute body temperature. Furthermore, following whole-body pre-cooling, the vasomotor and sudomotor thresholds varied independently. Those outcomes are interpreted to signify the presence of independent central controllers for thermally dependent vasomotor and sudomotor responses, and possibly also for thermogenesis. Such a conclusion is consistent with both the phylogenetic acquisition of those thermoeffectors and neurological evidence from animal studies.

Conflict of interest

There are no conflicts of interest.

Acknowledgments

Joanne Caldwell was supported by an Australian Postgraduate Award (Department of Innovation, Industry, Science and Research, Australia). Åsa Nykvist and Nicholas Powers participated during research internships conducted at the University of Wollongong, and were supported by their respective home institutions (Karolinska Institutet [Stockholm, Sweden] and Grand Valley State University [Allendale, U.S.A.], respectively). Parts of this manuscript have been published elsewhere in abstract form (Caldwell et al., 2011; 2015; Taylor and Caldwell, 2016). The authors gratefully acknowledge the editorial comments of Christopher Gordon, Sean Notley and Jürgen Werner during the preparation of this manuscript.

References

Benzinger, T.H., Kitzinger, C., Pratt, A.W., 1963. The human thermostat. In: In: Hardy, J.D. (Ed.), Temperature - its Measurement and Control in Science and Industry, vol. 3. Reinhold Publishing Corp, New York, pp. 637–665 Part 3.
Best, A., Kamilar, J.M., 2018. The evolution of eccrine sweat glands in human and non-human primates. J. Hum. Evol. 117, 33–43.
Blair, D.A., Glover, W.E., Roddie, I.C., 1961. Vasomotor responses in the human arm during leg exercise. Circ. Res. 9, 264–274.
Bligh, J., 1998. Mammalian homeothermy: an integrative thesis. J. Therm. Biol. 23, 143–258.
Bligh, J., 2006. A theoretical consideration of the means whereby the mammalian core temperature is defended at a null zone. J. Appl. Physiol. 100, 1332–1337.
Booth, J.D., Wilsmore, B.R., MacDonald, A.D., Zeyl, A., Storlien, L.H., Taylor, N.A.S., 2004. Intramuscular temperatures during exercise in the heat following pre-cooling and pre-heating. J. Therm. Biol. 29, 709–715.
Buono, M.J., Heaney, J.H., Canine, K.M., 1998. Acclimation to humid heat lowers resting core temperature. Am. J. Physiol. 274, R1295–R1299.
Burdon, C.A., Tagami, K., Park, J., Caldwell, J.N., Taylor, N.A.S., 2017. Indirect hand and forearm vasomotion: regional variations in cutaneous thermosensitivity during normothermia and mild hyperthermia. J. Therm. Biol. 65, 95–104.
Burton, A.C., Bazett, H.C., 1936. A study of the average temperature of the tissues, of the exchanges of heat and vasomotor responses in man by means of a bath calorimeter. Am. J. Physiol. 117, 36–54.
Cabanac, M., Massonnet, B., 1977. Thermoregulatory responses as a function of core temperature in humans. J. Physiol. 265, 587–596.
Caldwell, J.N., Nykvist, Å., Powers, N., Notley, S.R., Lee, D.S., Peoples, G.E., Taylor, N.A.S., 2011. An investigation of forearm vasomotor and sudomotor thresholds during passive heating, following whole-body cooling. In: Kounalakis, S.N., Koskolou, M. (Eds.), Proceedings of the Fourteenth International Conference on Environmental Ergonomics. Nafplio, Greece. July 10th-15th, 2011, pp. 132–135.
Caldwell, J.N., Nykvist, Å., Powers, N., Notley, S.R., Taylor, N.A.S., 2015. The impact of thermal pre-conditioning on cutaneous vasomotor and shivering thresholds. Extreme Physiol. Med. 4, A117.
Carroll, R.L., 1970. The ancestry of reptiles. Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci. 257, 267–308.
Crandall, C.G., Wilson, T.E., 2015. Human cardiovascular responses to passive heat stress. Compr. Physiol. 5, 17–43.
Cotter, J.D., Mark, A.J., Regan, J.M., Taylor, N.A.S., 1993. Optimal sites for the measurement of human skin blood flow using laser Doppler velocimetry. Proc. Aust. Physiol. Pharmacol. Soc. 24 184P.
Cotter, J.D., Taylor, N.A.S., 2005. The distribution of cutaneous sudomotor and alliesthesial thermosensitivity in mildly heat-stressed humans: an open-loop approach. J. Physiol. 565, 335–345.
Detry, J.M., Brengelmann, G.L., Rowell, L.B., Wyss, C., 1972. Skin and muscle components of forearm blood flow in directly heated resting man. J. Appl. Physiol. 32, 506–511.
DuBois, E.F., 1939. Heat loss from the human body. Bull. N. Y. Acad. Med. 15, 143–173.
Edholm, O.G., Fox, R.H., Macpherson, R.K., 1956. The effect of body heating on the circulation in skin and muscle. J. Physiol. 134, 612–619.
Fox, R.H., Goldsmith, R., Hampton, I.F.G., Hunt, T.J., 1967. Heat acclimatization by controlled hyperthermia in hot-dry and hot-wet climates. J. Appl. Physiol. 22, 39–46.
Giaja, J., 1938. Homéothermie et thermorégulation I - L'homothermie. Hermann & Cie, Paris.
Gilbert, T.M., Blatteis, C.M., 1978. Hypothalamic thermoregulatory pathways in the rat. J. Appl. Physiol. 43, 770–777.
Hammel, H.T., Jackson, D.C., Stolwijk, J.A.J., Hardy, J.D., Stromme, S.B., 1963. Temperature regulation by hypothalamic proportional control with an adjustable set-point. J. Appl. Physiol. 18, 1146–1154.
Hardy, J.D., DuBois, E.F., 1938. The technic of measuring radiation and convection. J. Nutr. 15, 461–475.
Hellstrøm, B., Hammel, H.T., 1967. Some characteristics of temperature regulation in the unanesthetized dog. Am. J. Physiol. 213, 547–556.
Henane, R., Valatx, J.L., 1973. Thermoregulatory changes induced during heat acclimatization by controlled hypothermia in man. J. Physiol. 230, 255–271.
Jessen, C., Ludwig, O., 1971. Spinal cord and hypothalamus as core sensors of temperature in the conscious dog. II. Addition of signals. Pflügers Archiv 324, 205–216.
Kenny, G.P., Chen, A.A., Nurbakhsh, B.A., Denis, P.M., Proulx, C.E., Giesbrecht, G.G., 1998. Moderate exercise increases postexercise thresholds for vasoconstriction and shivering. J. Appl. Physiol. 85, 1357–1361.
Kenny, G.P., Gagnon, D., Dorman, L.E., Hardcastle, S.G., Jay, O., 2010. Heat balance and cumulative heat storage during exercise performed in the heat in physically active younger and middle-aged men. Eur. J. Appl. Physiol. 109, 81–92.
Ladell, W.S., 1951. Assessment of group acclimatization to heat and humidity. J. Physiol. 115, 296–312.
MacDonald, A.D., Groeller, H., Fogarty, A.L., Armstrong, K.A., Booth, J.D., Hahn, A., Taylor, N.A.S., 2000. Exercise in the heat: cardiovascular consequences of whole-body and head-torso pre-cooling. In: Abstracts of the Ninth International Conference on Environmental Ergonomics. Dortmund, Germany. July 30th-August 4th, 2000, pp. 3.
Machado-Moreira, C.A., Barry, R.J., Vosselman, M.J., Ruest, R.M., Taylor, N.A.S., 2015. Temporal and thermal variations in site-specific thermoregulatory sudomotor thresholds: precursor versus discharged sweat production. Psychophysiology 52, 117–123.
Machado-Moreira, C.A., Taylor, N.A.S., 2012. Sudomotor responses from glabrous and non-glabrous skin during cognitive and painful stimulations following passive heating. Acta Physiol. 204, 571–581.
Maw, G.J., Mackenzie, I.L., Taylor, N.A.S., 1995. Redistribution of body fluids during postural manipulations. Acta Physiol. Scand. 155, 157–163.
McAllen, R.M., Tanaka, M., Ootsuka, Y., McKinley, M.J., 2010. Multiple thermoregulatory effectors with independent central controls. Eur. J. Appl. Physiol. 109, 27–33.
McCook, R.D., Wurster, R.D., Randall, W.C., 1965. Sudomotor and vasomotor responses to changing environmental temperature. J. Appl. Physiol. 20, 371–378.
Mekjavic, I.B., Eiken, O., 2006. Contribution of thermal and nonthermal factors to the regulation of body temperature in humans. J. Appl. Physiol. 100, 2065–2072.
Mekjavić, I.B., Sundberg, C.J., Linnarsson, D., 1991. Core temperature "null zone". J. Appl. Physiol. 71, 1289–1295.
Mitchell, D., Snellen, J.W., Atkins, A.R., 1970. Thermoregulation during fever: change of set-point or change of gain. Pflügers Archiv 321, 293–302.
Newton, I., 1700. Scala graduum caloris. Calorum descriptiones & figna. Phil. Trans. Roy. Soc. Lond. 22, 824–829.
Ogawa, T., Bullard, R.W., 1972. Characteristics of subthreshold sudomotor neural impulses. J. Appl. Physiol. 33, 300–305.
Ootsuka, Y., McAllen, R.M., 2006. Comparison between two rat sympathetic pathways activated in cold defense. Am. J. Physiol. 291, R589–R595.
Patterson, M.J., Stocks, J.M., Taylor, N.A.S., 2004. Humid heat acclimation does not elicit a preferential sweat redistribution towards the limbs. Am. J. Physiol. 286, R512–R518.
Phillips, M.J., Bennett, T.H., Lee, M.S., 2009. Molecules, morphology, and ecology indicate a recent, amphibious ancestry for echidnas. Proc. Natl. Acad. Sci. U.S.A. 106, 17089–17094.
Regan, J.M., Macfarlane, D.J., Taylor, N.A.S., 1996. An evaluation of the role of skin temperature during heat adaptation. Acta Physiol. Scand. 158, 365–375.
Stocks, J.M., Patterson, M.J., Hyde, D.E., Jenkins, A.B., Mittleman, K.D., Taylor, N.A.S., 2004. Effects of immersion water temperature on whole-body fluid distribution in humans. Acta Physiol. Scand. 182, 3–10.
Stolwijk, J.A.J., Hardy, J.D., 2011. Control of body temperature. In: Comprehensive Physiology. Supplement 26: Handbook of Physiology, Reactions to Environmental Agents, pp. 45–68 First published in print 1977.
Tanaka, M., Ootsuka, Y., McKinley, M.J., McAllen, R.M., 2007. Independent vasomotor control of rat tail and proximal hairy skin. J. Physiol. 582, 421–433.
Taylor, N.A.S., Caldwell, J.N., 2016. Thermoeffector threshold plasticity and its implications for temperature regulation. In: Physiology and Pharmacology of Temperature Regulation. Sixth International Meeting. Ljubljana, Slovenia. December 5th-9th, 2016, pp. 183.
Taylor, N.A.S., Machado-Moreira, C.A., 2013. Regional variations in transepidermal water loss, eccrine sweat gland density, sweat secretion rates and electrolyte composition in resting and exercising humans. Extreme Physiol. Med. 2 (4).
Taylor, N.A.S., Machado-Moreira, C.A., van den Heuvel, A.M.J., Caldwell, J.N., 2014a. Hands and feet: physiological insulators, radiators and evaporators. Eur. J. Appl. Physiol. 114, 2037–2060.

Taylor, N.A.S., Tipton, M.J., Kenny, G.P., 2014b. Considerations for the measurement of deep-body, skin and mean body temperatures. J. Therm. Biol. 46, 72–101.
Templeton, J.R., 1970. Reptiles. In: In: Wittow, G.C. (Ed.), Comparative Physiology of Thermoregulation, vol. I. Academic Press, New York, pp. 167–223.
Vallerand, A.L., Savourey, G., Hanniquet, A., Bittel, J.H.M., 1992. How should body heat storage be determined in humans: by thermometry or calorimetry? Eur. J. Appl. Physiol. 65, 286–294.
van Beaumont, W., Bullard, R.W., 1963. Sweating: its rapid responses to muscular work. Science 141, 643–646.
Werner, J., 1977. Mathematical treatment of structure and function of the human thermoregulatory system. Biol. Cybern. 25, 93–101.
Werner, J., 1994. Beneficial and detrimental effects of thermal adaptation. In: Zeisberger, E., Schönbaum, E., Lomax, P. (Eds.), Thermal Balance in Health and Disease. Birkhäuser Verlag, Basel. York, pp. 141–154.
Werner, J., 2010. System properties, feedback control and effector coordination of human temperature regulation. Eur. J. Appl. Physiol. 19, 13–25.
Werner, J., Mekjavic, I.B., Taylor, N.A.S., 2008. Concepts in physiological regulation: a thermoregulatory perspective. In: Taylor, N.A.S., Groeller, H. (Eds.), Physiological Bases of Human Performance during Work and Exercise. Churchill Livingstone Elsevier, Edinburgh, pp. 325–340.
Wyndham, C.H., 1967. Effect of acclimatization on the sweat rate/rectal temperature relationship. J. Appl. Physiol. 22, 27–30.