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REVIEW ARTICLE

# Multiple thermoregulatory effectors with independent central controls

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**Abstract** This review first considers how mammalian body temperature regulation evolved, and how the brain's responses to thermoregulatory challenges are likely to be organised differently from the way an engineer would design them. This is because thermoregulatory effector mechanisms would have evolved one at a time, with each being superimposed on pre-existing mechanisms. There may be no functional need for the final ensemble of control loops to be coordinated by neural cross-connections: appropriate thermal thresholds would solve the problem sufficiently. Investigations first into thermoregulatory behaviours and later into unconscious thermoregulatory mechanisms (autonomic and shivering) have led investigators to the realisation that multiple control loops exist in the brain, with each effector system apparently regulated by its own central temperature sensors. This theme is developed with reference to data on four temperature-regulated neural outflows that have been studied on anaesthetized rats under standard conditions in the authors' laboratory. Direct comparisons were made between the behaviour of sympathetic nerves supplying the tail vasculature, vessels in the proximal hairy skin, interscapular brown adipose tissue (BAT) and fusimotor fibres to hind limb muscle. All four outflows were activated by cooling the skin, and all were silenced by neuronal inhibition in the medullary raphé. Their thermal thresholds were quite different, however, as were their relative responsiveness to core temperature. This was ranked as: tail > back skin > BAT > fusimotor. These and other data indicate that the four thermoeffector outflows are driven by separate neural pathways, each regulated by independent brain temperature sensors.

**Keywords** Rat tail · Cutaneous vasomotor · BAT · Fusimotor · Preoptic · Thermoregulation

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## Evolution of central temperature control in mammals

A number of mechanisms have evolved in mammals to regulate their body temperature, and different species may handle the same challenge in different ways. Evaporative cooling to lose heat in a hot environment, for example, occurs mainly by panting in dogs, by sweating in humans and by salivation with grooming in rats. On the cold-defence side, the relative importance of shivering versus non-shivering thermogenesis also varies across species. In humans and dogs, for example, shivering is the predominant mechanism, whilst in rodents, non-shivering thermogenesis by brown adipose tissue (BAT) is prominent. Although the presence of BAT in adult humans has been doubted, recent evidence clearly shows that it is present and activated by cold (Zingaretti et al. 2009; Saito et al. 2009; van Marken Lichtenbelt et al. 2009; Cypess et al. 2009). In all mammals, cutaneous vasoconstriction reduces heat loss.

Considering these matters, it has been noted that we should not expect evolution to generate natural control systems that operate exactly as an engineer would design them (Partridge 1982). All that is required for a new mechanism to be conserved is that it should improve the animal's chance of survival and reproduction; it does not matter how elegantly the physiological problem is solved (Partridge 1982; Gould 1983). The low occurrence rate of beneficial mutations results in new features being added one at a time, with each being superimposed on previous adaptations (Gould 1983). In the evolution of cold defences, for example, non-shivering thermogenesis by BAT is a mammalian 'invention' (Cannon and Nedergaard 2004) that would have been superimposed on pre-existing ancestral responses such as warm-seeking behaviour (Seebacher and Franklin 2005). Our reptilian ancestors may well have been able to control blood flow to their skin: modern reptiles such as crocodiles (Seebacher and Franklin 2005) and iguanas (Morgareidge and White 1969) are able to vasodilate their skin when basking in the warmth and to vasoconstrict in the cold. Those responses, however, appear to be mediated by local temperature rather than by vasomotor nerves (Morgareidge and White 1969). Whilst human cutaneous vessels also respond directly to temperature, dilating with heat and constricting with cold, their behaviour is generally dominated by neural drive from the CNS (Johnson and Proppe 1996). Successive evolutionary innovations may thus address a common challenge (in this case, defence against cold), and each will be conserved if its action is independently beneficial. As argued by Partridge, there may be no need for such mechanisms to be coordinated by common neural circuitry: only if neural coordination confers a further significant advantage is it likely to evolve (Partridge 1982).

## Multiple control mechanisms

It has been known for some time that thermoregulatory behaviours are organised by the brain independently of autonomic mechanisms, and indeed survive brain lesions of the preoptic area that disable the latter (Satinoff and Rutstein 1970; Almeida et al. 2006). Moreover, it became evident that distinct pathways *with anatomically distinct central thermosensors* regulate different heat-defence behaviours, such as locomotion, saliva spreading and postural extension in rats (Roberts 1988). Evidence also shows that involuntary control mechanisms (i.e. autonomic and shivering) are multiple and parallel rather than unitary. In 1978, Gilbert and Blatteis showed that preoptic knife cuts could disable cutaneous vasoconstriction, but shivering was left unaffected (Gilbert and Blatteis 1977). In the 1990s, Kanosue et al. pointed to a series of differences in the descending pathways from preoptic warm-sensitive neurons to different effectors (Kanosue et al. 1994a, 1994b; Chen et al. 1998; Zhang et al. 1995). The logical inference was that, instead of a single central 'thermostat' regulating a suite of heat loss and heat gain mechanisms, the preoptic region contains a number of independent groups of temperature-sensitive neurons, each regulating individual effector mechanisms (Nagashima et al. 2000; Romanovsky 2007). The present study extends this theme of multiple independent controllers operating via distinct efferent pathways. Regardless of whether this principle applies universally to mammalian body temperature control, it is clear that one cannot transfer lessons learnt from one thermoeffector control system directly to another.

The principal difficulty with this view is that the mechanisms regulating body temperature appear to act seamlessly together as a precisely coordinated control system seeking a 'set point'. This applies not only to the basal state, but parallel threshold shifts can cause a regulated 'resetting' of body temperature upwards or downwards with (e.g.) diurnal body temperature variation, fever and hypoxia (Cabanac 2006). On some occasions, however, this coordination can break down: for example, high doses of endotoxin cause a regulated hypothermia that involves cold-seeking behaviour and a substantially reduced temperature threshold for thermogenesis, but only a minimal change in cutaneous vasoconstrictor threshold (Almeida et al. 2006; Romanovsky et al. 1996). Divergence of thresholds between different thermoeffector responses has also been noted in the later phases of fever (Vybiral et al. 1987). Our view is that the occurrence of parallel threshold shifts between the various thermoeffectors is a beguiling phenomenon that requires further explanation. It does not amount to compelling evidence for the control of multiple effectors by a single brain centre.

## The medullary raphé

From the late 1990s, it became apparent from the work in several laboratories that a critical role in cold defence was played by neurons in a small region of the ventral medullary raphé, at the rostrocaudal level of the caudal part of the facial nucleus (Rathner and McAllen 1999; Blessing et al. 1999; Morrison et al. 1999; Morrison 1999; Rathner et al. 2001; Tanaka et al. 2002). Inhibition of neurons in this small brainstem region could suppress both non-shivering thermogenesis by BAT and cutaneous vasoconstriction in response to cold exposure or experimental fever (Tanaka et al. 2002; Nakamura et al. 2002; Morrison 2003; Madden and Morrison 2003; Nakamura and Morrison 2007; Korsak and Gilbey 2004; Ootsuka et al. 2004; Rathner et al. 2008; Tanaka et al. 2007). In conscious rats, inactivating neurons

of this raphe region rendered the animals unable to defend their body temperature against cold (Zaretsky et al. 2003). Neurons in this same region had previously been implicated as mediating the gastric secretory and motility responses characteristic of rats exposed to cold (Tache et al. 1995; Yang et al. 2000). Could there be, after all, a coordinating centre in this discrete brainstem region for multiple cold-defence responses? Others (Rathner et al. 2008) and we (Tanaka et al. 2006, 2007; Ootsuka and McAllen 2006) investigated this possibility by directly comparing several cold-defence effector pathways in anaesthetized rats.

## Studies comparing four cold-defence effector pathways

The studies from our laboratory have been performed on animals under standard experimental conditions. Male Sprague–Dawley rats were anaesthetized with urethane (1–1.5 g/kg i.v.) after preparatory surgery under 2% isofluorane; they were ventilated artificially with oxygen via a tracheostomy. The animal's head was fixed in a stereotaxic frame and its shaved trunk was encased in a water-perfused silastic jacket. Body core temperature was measured from the rectum and skin temperature as the mean value of thermocouples placed at three sites under the water jacket. No paralysing agent was given. Nerve activity was recorded from peripheral thermoeffector nerves, usually in pairs. The standard cooling protocol started from warm conditions. Cold water was then pumped through the water jacket for successive brief (0.5–2 min) episodes that were separated by similar time intervals, during which warm water was reperfused. Core temperature fell in response to the repeated skin cooling episodes. The different time courses of skin and core temperature falls allowed the neural response to each to be distinguished and measured (Owens et al. 2002).

Whilst the use of general anaesthesia is a limitation, the use of parallel neural recordings and standard experimental conditions is an aid to interpreting the findings.

## Case 1: tail vasoconstrictior and BAT thermogenic nerve activity

Recordings of sympathetic nerves supplying the tail vasculature and interscapular BAT have revealed similarities and differences. Both nerves show little or no activity when skin and core were kept at warm temperatures (Johnson and Gilbey 1998; Owens et al. 2002; Morrison 2003; Ootsuka et al. 2004; Nakamura and Morrison 2008a). Both nerves may be activated by cooling and during experimental fever after prostaglandin $E_2$ (or $E_1$) injection into the brain (Johnson and Gilbey 1998; Owens et al. 2002; Morrison 2003; Collins et al. 2002; Ootsuka et al. 2004; Nakamura and Morrison 2008a; Tanaka and McAllen 2005). Tonic and evoked activity in both nerves may be eliminated by inhibiting neurons in the ventral medullary raphé at the level of the caudal part of the facial nucleus (Korsak and Gilbey 2004; Morrison 2003; Ootsuka et al. 2004; Nakamura and Morrison 2008a).

When their activity was compared in simultaneous recordings (Fig. 1a), both nerves were activated by cooling the skin of the trunk, but this occurred at different threshold temperatures (Fig. 1a). Further repeated skin cooling episodes caused the core temperature to fall, whereupon tail fibre activity started responding to this signal. As core temperature fell further, tail fibres were no longer silenced each time the skin was rewarmed. BAT nerve activity, however, continued to respond only to skin temperature until core temperature fell substantially further (Fig. 1a). The relative sensitivity of BAT nerve activity to core temperature was always much less than that of tail fibre activity, and in two out of seven cases examined in that study, no component of BAT nerve activity was attributable to core cooling (Ootsuka and McAllen 2006).

It is thus clear that the central mechanisms driving these two sympathetic outflows cannot be identical. Further corroboration of this point is provided by the lack of coherence between the frequency spectra of the two nerves' activity, other than a component associated with the ventilatory cycle (Ootsuka and McAllen 2006). Moreover, differences have been found between their central pathways. Tail fibre activity is supported by an auxiliary, excitatory drive from neurons in the rostral ventrolateral medulla (RVLM) (Ootsuka and McAllen 2005); BAT nerve activity, by contrast, is inhibited by RVLM neurons (Morrison 1999). Most strikingly, it has recently been shown that whilst BAT nerve activity depends on a critical synapse in the dorsomedial hypothalamus (DMH), tail activity is unaffected by inhibition of DMH neurons (Rathner et al. 2008).

## Case 2: tail and back skin cutaneous vasoconstrictor fibre activity

In humans, differences have been documented between the neural control of blood flow to the acral versus proximal skin regions (Johnson and Proppe 1996). In rats, the cutaneous vasomotor drives to the hind paw and tail are very similar (Smith and Gilbey 2000). Only one study has directly compared the neural activity supplying these distal sites with that to more proximal skin regions (Tanaka et al. 2007). Figure 1b is taken from that study and shows how the cutaneous vasoconstrictor (CVC) activity to the proximal hairy skin of the back has different thresholds for activation by both skin and core cooling. Moreover, the ratio of responsiveness to core versus skin temperature was quite

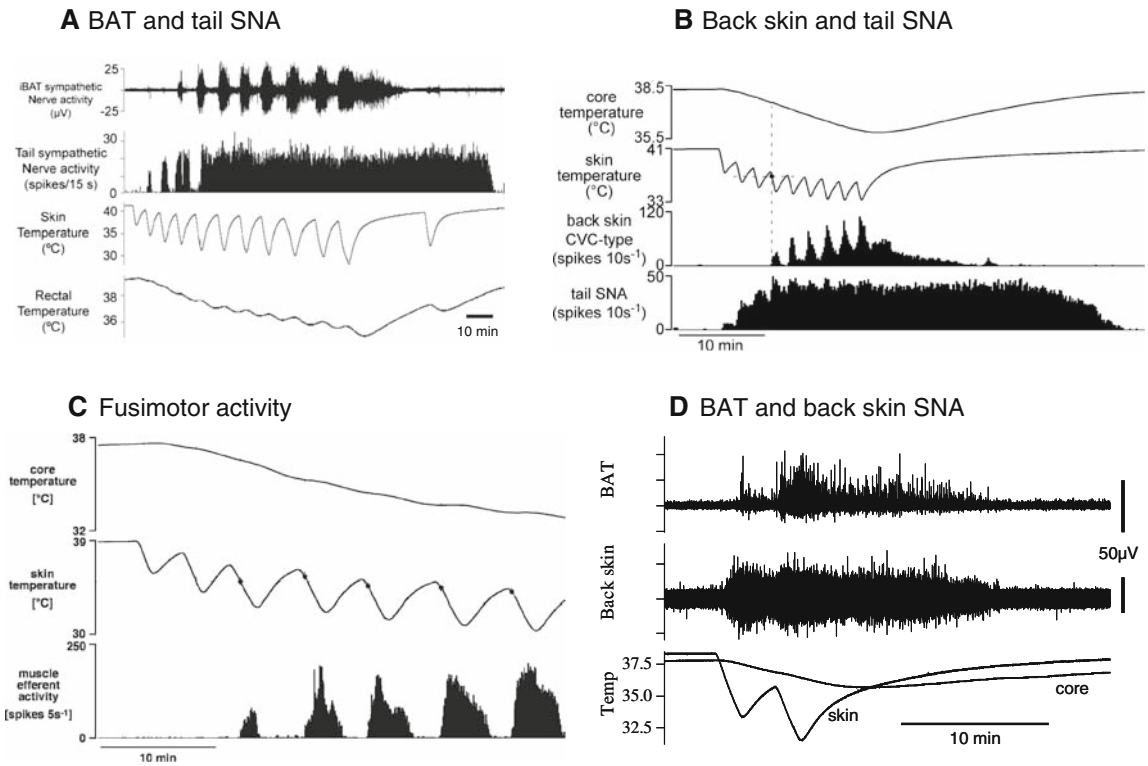


**Fig. 1** Representative chart recordings of sympathetic nerve activity (SNA) supplying several thermoregulatory effector organs in the rat showing responses to repeated brief episodes of skin cooling, whilst core temperature was allowed to fall. **a** Comparison of SNA supplying brown adipose tissue (BAT) with that supplying tail vessels. Note the different thresholds to skin and core cooling, as well as the much stronger response to core cooling by tail than by BAT SNA (Ootsuka and McAllen 2006). **b** Comparison of SNA supplying back skin versus that to tail vessels. Note the different thresholds and the lesser response to core cooling by back skin SNA compared with tail SNA (Tanaka et al. 2007). **c** Fusimotor fibre activity supplying the gastrocnemius muscle. Note how these fibres are activated by skin cooling, but not by core cooling, even when it fell to 33°C (From reference Tanaka et al. 2006). **d** Comparison of SNA supplying BAT and back skin. Note that the back skin SNA is activated earlier by skin cooling, and shows a proportionately greater response to core temperature than does BAT SNA (MT, MMcK and RMcA, unpublished data)

different between proximal CVC and tail fibre activity (Fig. 1b). Finally, there was a lack of coherence between the activity spectra of the two nerves in the frequency domain (Tanaka et al. 2007).

Although both back skin CVC and tail fibre activity may be silenced by inhibiting raphé neurons (Tanaka et al. 2007), it appears that their central drive pathways must be different.

### Case 3: fusimotor fibre activity

A further 'unconscious' cold-defence response was recently reported: activation of fusimotor fibres to the limb muscles (Tanaka et al. 2006). The significance of this response may be twofold: first, it could underlie the increased muscle tone that precedes overt shivering in the cold (Meigal et al. 2003); second, it would enhance the stretch reflex, on which shivering is heavily dependent (Perkins 1945) and may thereby facilitate shivering.

As shown in Fig. 1c, fusimotor fibres were silent in anaesthetized rats until activated by skin cooling. The remarkable feature that we wish to emphasise is that whilst repeated skin cooling episodes reliably activated fusimotor fibres, they always fell silent when the skin was rewarmed; no component of activity was attributable to core cooling, even when core temperature fell as low as 33°C (Fig. 1c). There was, however, evidence for a minor inhibitory action of warm core temperature on the fusimotor response to skin cooling (Tanaka et al. 2006). This effect may be mediated by preoptic temperature-sensitive neurons (Von Euler and Soderberg 1957). Like BAT and tail and back skin CVC fibre activity, fusimotor activation by cold skin was abolished by inhibiting medullary raphé neurons (Tanaka et al. 2006).

### Case 4: comparison of BAT and back skin CVC activity

Both BAT and back skin CVC activity occupy an intermediate position between tail and fusimotor fibres, with respect to their thermal thresholds and their relative responsiveness to skin versus core temperature (Fig. 2a). Their

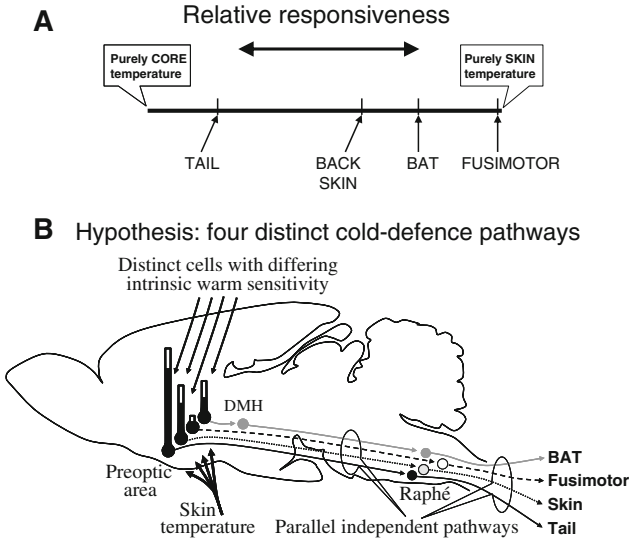


**Fig. 2** **a** The relative responsiveness to skin and core temperatures of four cold-activated neural outflows: tail vessels, back skin vessels, brown adipose tissue (BAT) and fusimotor fibres. **b** Inferred neural pathways driving those four neural outflows. The hypothesis is that each is driven by independent neural pathways regulated by distinct preoptic neurons with different intrinsic thermosensitivity (indicated by the length of the thermometer shaft)

preganglionic axons both emerge from a similar level of the thoracic spinal cord. Could they perhaps be receiving copies of the same neural drive signals? To answer this question, simultaneous recordings from the two nerves were made in two rats (M. Tanaka, M.J. McKinley and R.M. McAllen, unpublished data). As may be seen from the record excerpt shown in Fig. 1d, their response patterns were distinct. Back skin CVC fibres were activated earlier during skin cooling and showed a greater relative response to core temperature than did BAT nerve activity.

## Discussion

Our hypothesis for how these four neural outflows receive their temperature-sensitive drives is illustrated diagrammatically in Fig. 2b. The key point (cf. Nagashima et al. 2000) is that these efferent pathways are entirely separate from the preoptic area downwards. Whilst it has not been formally shown that back skin CVC and fusimotor activity are regulated by preoptic neurons, we consider it most probable that they are. A further unknown point is whether back skin CVC or fusimotor pathways involve a relay in the dorsomedial hypothalamus (DMH), or indeed elsewhere.

What we can infer is that the preoptic neurons regulating tail fibre activity must be much more sensitive to core temperature than those regulating other outflows. In contrast, the neurons regulating the fusimotor outflow evidently possess minimal intrinsic core temperature sensitivity (the relative sensitivity to core temperature in each pathway is represented in Fig. 2b by the length of the thermometer shaft). It seems likely that similar afferent pathways, via lamina 1 of the spinal cord dorsal horn and the parabrachial nuclei, convey skin temperature signals to all of these effector mechanisms (Nakamura and Morrison 2008a). Again, it is assumed by analogy with the BAT pathway (Nakamura and Morrison 2008a; Osaka 2004; Nakamura and Morrison 2008b) that the main input from skin temperature signals to each of these other cold-defence pathways is relayed via preoptic neurons. These points await direct confirmation.

The significance of the obligatory synaptic relay in the medullary raphé for all four pathways considered here, as well as others (Tache et al. 1995; Zaretsky et al. 2003), remains an enigma. The idea that this synapse might be a subsidiary site, where humoral factors such as prostaglandin $E_2$ might act on several pathways at once to cause fever, received no experimental support (Tanaka and McAllen 2005). A further point that deserves consideration is that the abundant serotonergic neurons in this region, whilst they may not constitute the primary drive pathway for thermogenesis or vasoconstriction (Nakamura et al. 2004), nevertheless, could play a modulatory role that reinforces several cold-defence responses at a spinal level (Madden and Morrison 2008; Marina et al. 2006). Serotonergic neurons in this region are activated by cold exposure (Yang et al. 2000; Nakamura et al. 2004) and may receive their temperature-related signals directly or indirectly from the preoptic area. Alternatively or additionally, they might receive signals from cold skin by more direct pathways that are contained within the midbrain and brain stem. This possibility should be considered because in decerebrate rats, cold exposure is still able to increase BAT norepinephrine turnover (indicating sympathetic activation) (Nautiyal et al. 2008) and neurons responding to skin temperature may still be recorded in the medullary raphé (Dickenson 1977).

## Conclusions

The four thermoeffector outflows considered here are regulated by parallel efferent pathways; they all relay synaptically in the medullary raphé, but do so without any apparent neural cross talk. We infer that distinct preoptic neurons with differing intrinsic temperature sensitivity regulate each effector. The task remains to link individual effectors with their own central thermoregulatory control neurons.

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