Autonomic Neuroscience: Basic and Clinical 196 (2016) 14–24

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

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

Central neural control of thermoregulation and brown adipose tissue

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ARTICLE INFO

Article history:
Received 8 September 2015
Received in revised form 5 February 2016
Accepted 19 February 2016

Keywords:
Brown adipose tissue
Shiver
Cutaneous vasoconstriction
Thermogenesis
Fever
Sympathetic nerve activity
Preoptic hypothalamus
Rostral raphe pallidus
Dorsomedial hypothalamus

ABSTRACT

Central neural circuits orchestrate the homeostatic repertoire that maintains body temperature during environmental temperature challenges and alters body temperature during the inflammatory response. This review summarizes the experimental underpinnings of our current model of the CNS pathways controlling the principal thermoeffectors for body temperature regulation: cutaneous vasoconstriction controlling heat loss, and shivering and brown adipose tissue for thermogenesis. The activation of these effectors is regulated by parallel but distinct, effector-specific, core efferent pathways within the CNS that share a common peripheral thermal sensory input. Via the lateral parabrachial nucleus, skin thermal afferent input reaches the hypothalamic preoptic area to inhibit warm-sensitive, inhibitory output neurons which control heat production by inhibiting thermogenesis-promoting neurons in the dorsomedial hypothalamus that project to thermogenesis-controlling premotor neurons in the rostral ventromedial medulla, including the raphe pallidus, that descend to provide the excitation of spinal circuits necessary to drive thermogenic thermal effectors. A distinct population of warm-sensitive preoptic neurons controls heat loss through an inhibitory input to raphe pallidus sympathetic premotor neurons controlling cutaneous vasoconstriction. The model proposed for central thermoregulatory control provides a useful platform for further understanding of the functional organization of central thermoregulation and elucidating the hypothalamic circuitry and neurotransmitters involved in body temperature regulation.

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http://dx.doi.org/10.1016/j.autneu.2016.02.010
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1. Introduction

Central neural circuits orchestrate a homeostatic repertoire to maintain body temperature during thermal challenges, both from the ambient and the internal (e.g., exercise) environment, and to alter body temperature during specific behavioral states (e.g., sickness, sleep, stress, etc.). Body temperature regulation is effected primarily through dedicated pathways in the brain which function to produce an optimal thermal environment for neurons and for the many tissues on which the brain depends for survival. The effector mechanisms for cold defense, recruited in order of increasing energy costs, include thermoregulatory behavior to reduce heat loss; cutaneous vasoconstriction (CVC) to conserve heat in the body core and limit heat loss to the environment; piloerection to supplement CVC in reducing heat loss; heat production (thermogenesis), a by-product of the inefficiency of mitochondrial ATP production and of ATP utilization, in skeletal muscle (shivering) and brown adipose tissue (BAT), the principal sources of metabolic heat production beyond those contributing to basal metabolic rate. Effector mechanisms for heat defense include thermoregulatory behavior to increase heat loss; cutaneous vasodilation, including an active vasodilation that appears to be specific to humans (Smith and Johnson, 2016), that facilitates heat loss by conducting heat from the body core to the body surface; and evaporative cooling through sweating. The activation of these effectors is regulated by parallel but distinct, effector-specific, efferent pathways within the central nervous system that share common peripheral thermal sensory inputs. A wide variety of non-thermal physiological parameters, disease processes, neurochemicals and drugs can influence the central regulation of body temperature and their effects are hypothesized to result from an alteration of the activity within these core neural circuits for thermoregulation. For instance, since the high metabolic rate of BAT and shivering skeletal muscles during thermogenesis cannot be sustained without a dependable supply of metabolic fuels, particularly oxygen, lipolytic byproducts and glucose, the CNS network driving cold-defensive and behavioral BAT activation or shivering is exquisitely sensitive to signals reflecting the short- and long-term availability of the fuel molecules essential for BAT and skeletal muscle metabolism.

The core central thermoregulatory network (Fig. 1), involving thermal afferent pathways, hypothalamic sensorimotor integration and descending efferent pathways to spinal motor neurons, comprises the fundamental pathways through which cutaneous cold and warm sensation and/or reductions or elevations in brain temperature elicit changes in thermoregulatory effectors to counter or protect against deviations from a homeostatic temperature of the brain and other critical organs. Although the experimental basis for this model depends largely on studies in rodents (reviewed in (Morrison, 2011; Morrison and Nakamura, 2011; Nakamura, 2011; Morrison and Madden, 2014a; Morrison et al., 2014b)) and often under anesthetized conditions, the fundamental neural circuits elucidated through this work are expected to be relevant to human thermoregulation since rodents have, with the exceptions of sweating and thermoregulatory behaviors, a repertoire of thermal effectors and thermal reflex responses that is similar to those in humans. This review will summarize the results of the principal studies leading to our current model (Fig. 1) of the core thermoregulatory neural circuits controlling CVC, and shivering and BAT thermogenesis.

2. Afferents influencing thermoeffector activity

2.1. Cutaneous thermoreceptor afferent pathway

The central thermoregulatory system receives signals related to changes in the external environmental temperature through cutaneous thermoreceptors (primary sensory nerve endings distributed in the skin) and signals related to changes in the temperature of various tissues in the body core through local thermoreceptors, including intrinsically thermally-sensitive neurons in the brain (Boulant and Dean, 1986; Tabarean et al., 2004; Boulant, 2006; Lundius et al., 2010). Relatively little is known about visceral thermoreceptors; but, species and body location differences notwithstanding, many of the cutaneous thermoreceptors are cool thermoreceptors (Darian-Smith et al., 1973) that drive cold-defensive CVC and thermogenesis. The membranes of thermal afferent neurons contain transient receptor potential (TRP) cation channels whose temperature-dependent conductances transduce skin temperature into primary thermoreceptor afferent neuronal activity. The TRPM8 channel, activated by menthol and cooling, is the primary candidate for the cutaneous cold receptor TRP channel. Some non-thermal, unmyelinated afferents expressing TRP channels (Andresen et al., 2012) also have access to central thermoregulatory circuits: endogenous ligand-stimulated TRPV1 channels inhibit BAT thermogenesis (Steiner et al., 2007) and TRPV1 agonist infusion reduces thermogenesis and lowers body temperature (Feketa et al., 2013).

In addition to cutaneous thermoreception (reviewed in (Romanovsky, 2014)), thermoreceptive mechanisms exist in body core structures including the brain, spinal cord and abdomen. The afferent fibers from cold and warm receptors in the abdominal viscera are included among the splanchnic and vagus nerve afferent fibers and their responses to temperature changes are similar to those of cutaneous thermoreceptors (Riedel, 1976; Gupta et al., 1979). Temperature changes in the spinal cord can affect the activity of thermoregulatory neurons in more rostral areas of the brain (Guieu and Hardy, 1970). TRP channels that are located in the central endings of primary somatosensory fibers in the spinal dorsal horn (Tominaga et al., 1998; Bautista et al., 2007) may sense spinal temperature and could underlie an integration of spinal thermal signals with cutaneous thermal signals at the spinal cord level. These could function to enhance thermoregulatory responses in extreme thermal environments when the feedforward thermoregulatory responses driven by changes in skin temperature prove inadequate to prevent changes in brain, spinal cord or body core temperatures.

Primary thermoreceptor dorsal root ganglion neurons synapse on thermoreceptive-specific, lamina I spinal (or trigeminal) dorsal horn cells that respond linearly to graded, innocuous cooling or warming stimuli, but are not activated further in the noxious temperature range (Craig, 2002). The TRP channels in the thermoreceptor central endings may also provide a substrate for spinal cord or trigeminal nucleus temperature to influence the level of thermal effector activity. In turn, spinal and trigeminal lamina I neurons collateralize and innervate the thalamus, providing the neural substrate for cutaneous thermosensory perception and localization (Craig et al., 1994; Craig, 2002), and the pontine lateral parabrachial nucleus (LPB) (Hylden et al., 1989; Li et al., 2006) (Fig. 1), responsible for triggering involuntary (e.g., autonomic, shivering and respiratory) thermoregulatory responses.

Spinal lamina I cold thermal responsive neurons provide a glutamatergic excitation to neurons in the external lateral subdivision of the lateral parabrachial nucleus (LPBel), which, in turn, project principally to the median preoptic subnucleus (MnPO) of the preoptic area (POA) (Nakamura and Morrison, 2008b). In parallel, glutamatergic excitation of POA-projecting neurons in the dorsal subnucleus of the LPB (LPBd) (Nakamura and Morrison, 2010) is necessary for the skin warming-evoked inhibition of CVC and BAT thermogenesis (Nakamura and Morrison, 2010). The discharge rate of single, MnPO-projecting LPBel neurons recorded in vivo increased markedly in response to skin cooling in a manner paralleling the skin cooling-evoked increases in BAT sympathetic nerve activity (SNA) (Nakamura and Morrison, 2008b). In contrast, single, MnPO-projecting LPBd neurons were excited by skin warming in parallel with the simultaneous inhibition of BAT SNA (Nakamura and Morrison, 2010). Activation of LPBd or LPBel neurons evokes decreases or increases, respectively, in CVC, and in BAT and shivering thermogenesis that mimic respective skin warming-evoked or skin cooling-evoked physiological responses. The critical role of LPB neurons in transmitting cutaneous, and possibly visceral, thermal sensory information to the hypothalamus to drive thermoregulatory

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