Cell Metabolism
Review

Central Neural Regulation of Brown Adipose Tissue Thermogenesis and Energy Expenditure

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Thermogenesis, the production of heat energy, is the specific, neurally regulated, metabolic function of brown adipose tissue (BAT) and contributes to the maintenance of body temperature during cold exposure and to the elevated core temperature during several behavioral states, including wakefulness, the acute phase response (fever), and stress. BAT energy expenditure requires metabolic fuel availability and contributes to energy balance. This review summarizes the functional organization and neurochemical influences within the CNS networks governing the level of BAT sympathetic nerve activity to produce the thermoregulatory and metabolically driven alterations in BAT thermogenesis and energy expenditure that contribute to overall energy homeostasis.

Introduction

Thermogenesis, the production of heat energy, occurs to a greater or lesser extent in all tissues, since heat generation is an unavoidable consequence of the inefficiency of both mitochondrial adenosine triphosphate (ATP) production and cellular ATP utilization. However, thermogenesis is the specific metabolic function of beige and brown adipose tissue (BAT) in many species from mouse to man and is accomplished by the heat-generating capacity of a "proton leak" across the extensive mitochondrial membranes of the beige and brown adipocytes, facilitated by the high expression of uncoupling protein-1 (UCP1) in BAT mitochondria (Cannon and Nedergaard, 2004). BAT thermogenesis is an essential component of the homeostatic repertoire to maintain body temperature during the challenge of low environmental temperature. The heat generated during pyrogen (i.e., fever-producing substances)-stimulated thermogenesis in BAT also contributes to fever, a controlled elevation in body temperature that reduces pathogen viability and stimulates immune cell responses. However, since energy consumption during BAT thermogenesis involves oxidation of lipid and glucose fuel molecules, not only is BAT thermogenesis potently influenced in a permissive manner by signals related to fuel substrate and oxygen availability, but also, the level of BAT thermogenesis can contribute to energy balance, regulation of body adipose stores, and glucose utilization. Indeed, with the recent confirmation of metabolically active BAT in adult humans (Cypess et al., 2009; van Marken Lichtenbelt et al., 2009), there is increasing interest in devising pharmacological approaches to activate BAT as a metabolic furnace to burn the excess calories stored in the white adipose tissue of the obese. This will require not only therapeutic strategies to augment BAT depots, but also those to increase the CNS sympathetic drive to BAT, the latter requiring an improved understanding of the CNS mechanisms integrating the wide array of signals that influence BAT energy expenditure and overall energy homeostasis. This review will summarize our understanding of the functional organization and neurochemical influences specifically within the CNS networks that modulate BAT thermogenesis and BAT energy expenditure by altering the level of BAT sympathetic nerve activity (SNA) and thus the norepinephrine (NE) release onto β3-adrenergic receptors in brown adipocyte membranes.

The level of BAT sympathetic outflow is determined primarily by three factors. BAT is principally a thermoeffector and the core thermoregulatory network in the CNS (Figure 1; reviewed in Morrison et al., 2012) comprises the fundamental pathways through which cutaneous and visceral cold and warm sensation and/or reductions or elevations in brain temperature elicit changes in BAT thermogenesis to protect against or to counter changes in the temperature of the brain and other critical tissues. This circuit, involving thermal afferent pathways, hypothalamic sensorimotor integration, and descending efferent pathways to the spinal BAT sympathetic preganglionic neurons (SPNs), provides an important framework for understanding the overall regulation of BAT thermogenesis by the CNS. Second, a variety of behavioral states, including wakefulness, immunologic responses, and stress, are characterized by elevations in body temperature to which central command-driven BAT activation makes a significant contribution. Although the neural circuitry and transmitters underlying behavioral state modulations of BAT are poorly understood, it is likely that at least some of the neurochemical influences (e.g., histamine and orexin) and modulatory brain regions depicted in Figure 1 are related to such behavioral-state controls on BAT thermogenesis. Third, since the high metabolic rate of BAT 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 is strongly influenced by signals reflecting the short- and long-term availability of the fuel molecules essential for BAT metabolism. Synaptic and hormonal signals related to metabolic substrates can influence the sympathetic outflow to BAT in several ways. Signals that increase as the availability of a metabolic substrate falls can produce a potent inhibition of BAT sympathoexcitatory neurons, as is the case with arterial chemoreceptor inputs during systemic hypoxia (Madden and Morrison, 2005). In contrast, a tonically active signal such as leptin, indicating the

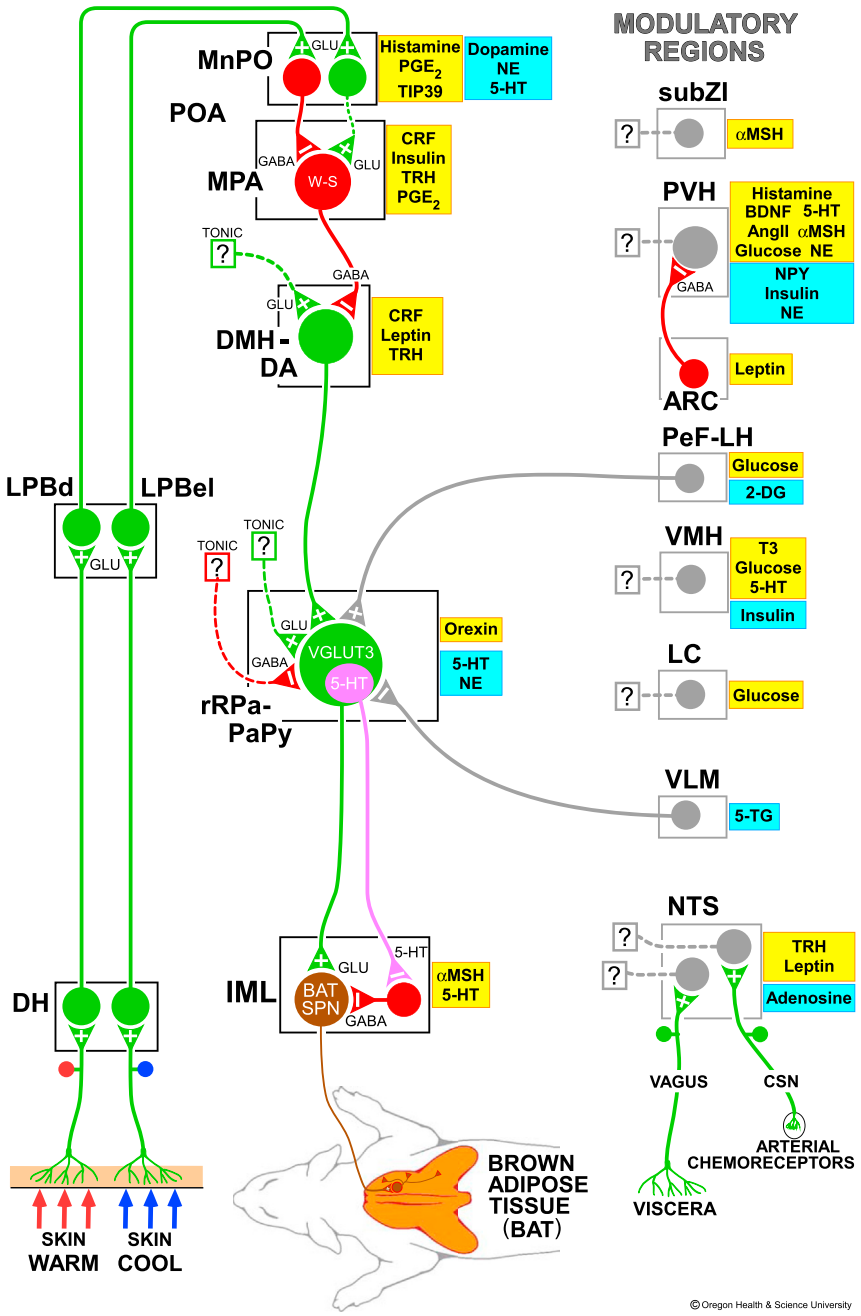

Figure 1. Model for the Neuroanatomical and Neurotransmitter/Hormonal Organization of the Core Thermoregulatory Network and Other CNS Sites Controlling and Modulating Brown Adipose Tissue Thermogenesis

Cool and warm cutaneous thermal sensory receptors transmit signals to respective primary sensory neurons in the dorsal root ganglia, which relay this thermal information to second-order thermal sensory neurons in the dorsal horn (DH). Cool sensory DH neurons glutamatergically activate third-order sensory neurons in the external lateral subnucleus of the lateral parabrachial nucleus (LPBel), while warm sensory DH neurons project to third-order sensory neurons in the dorsal subnucleus of the lateral parabrachial nucleus (LPBd). Thermosensory signals for thermoregulatory responses are transmitted from the LPB to the preoptic area (POA), where GABAergic interneurons in the median preoptic (MnPO) subnucleus are activated by glutamatergic inputs from cool-activated neurons in LPBel and inhibit a BAT-regulating population of warm-sensitive (W-S) neurons in the medial preoptic area (MPA). In contrast, glutamatergic interneurons in the MnPO, postulated to be excited by glutamatergic inputs from warm-activated neurons in LPBd, excite W-S neurons in MPA. Prostaglandin (PG) E_2 binds to EP3 receptors to inhibit the activity of W-S neurons in the POA. Preoptic W-S neurons providing thermoregulatory control of BAT thermogenesis inhibit BAT sympathoexcitatory neurons in the dorsomedial hypothalamus and dorsal hypothalamic area (DMH/DA), which, when disinhibited during skin cooling, excite BAT sympathetic premotor neurons in the rostral ventromedial medulla, including the rostral raphe pallidus (rRPa) and parapyramidal area (PaPy), that project to BAT sympathetic preganglionic neurons (SPN) in the spinal intermediolateral nucleus (IML). Some BAT premotor neurons can release glutamate (GLU) to excite BAT SPNs and increase BAT sympathetic nerve activity, while others can release serotonin (5-HT) to interact with 5-HT_{1A} receptors, potentially on inhibitory interneurons in the IML, to increase the BAT sympathetic outflow. Orexinergic neurons in the perifornical lateral hypothalamus (PeF-LH) project to the rRPa to increase the excitability of BAT sympathetic premotor neurons. Activation of neurons in the ventrolateral medulla (VLM) produces an inhibition of BAT thermogenesis, at least in part by noradrenergic activation of α2 receptors on rRPa neurons. Neurochemicals/hormones in yellow boxes activate and those in blue boxes reduce BAT activity. 2-DG, 2-deoxyglucose; 5-HT, 5-hydroxytryptamine; 5-TG, 5-thioglucose; αMSH, alpha melanocyte-stimulating hormone; AngII, angiotensin II; BDNF, brain-derived neurotrophic factor; CRF, corticotrophin releasing factor; CSN, carotid sinus nerve; NE, norepinephrine; NPY, neuropeptide Y; PGE_2, prostaglandin E2; T3, triiodothyronine; TIP39, tuberoinfundibular peptide of 39 residues; TRH, thyrotropin-releasing hormone; VGLUT3, vesicular glutamate transporter 3.

availability of a lipid fuel store in positive balance, may act within the CNS network for BAT activation in a "permissive" manner by reducing a tonic inhibition of BAT activity (Kong et al., 2012) or by facilitating the discharge of BAT sympathoexcitatory neurons (Zhang et al., 2011a). Although several of these modulatory influences on the CNS network for BAT activation are recognized, in most cases little is known about the pathways and neurochemical mediators through which they influence BAT activity. Thus, they are likely included in the modulatory (i.e., nonthermoregulatory) influences on BAT activity summarized in Figure 1, which indicate not only the complexity of the central control of this highly metabolic organ but also the many central mechanisms determining BAT sympathetic outflow that remain to be explored.

Sensory Pathways Affecting BAT Thermogenesis

The membranes of thermal afferent neurons contain transient receptor potential (TRP) cation channels whose temperature-dependent conductances transduce skin temperature into