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Neural Control of Energy Expenditure

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Abstract

The continuous rise in obesity is a major concern for future healthcare management. Many strategies to control body weight focus on a permanent modification of food intake with limited success in the long term. Metabolism or energy expenditure is the other side of the coin for the regulation of body weight, and strategies to enhance energy expenditure are a current focus for obesity treatment, especially since the (re)-discovery of the energy depleting brown adipose tissue in adult humans. Conversely, several human illnesses like neurodegenerative diseases, cancer, or autoimmune deficiency syndrome suffer from increased energy expenditure and severe weight loss. Thus, strategies to modulate energy expenditure to target weight gain or loss would improve life expectancies and quality of life in many human patients. The aim of this book chapter is to give an overview of our current understanding and recent progress in energy expenditure control with specific emphasis on central control mechanisms.

Keywords

Neuronal circuits; Hypothalamus; Hormones; Leptin; FGF21; Dorsomedial hypothalamus; Body weight

1 Introduction

The nervous system has evolved to regulate and coordinate bodily functions and behavior in a changing environment. The mammalian brain thus extensively communicates not only with the external world, but also with all aspects of internal physiology. While the neural controls of cardiovascular and gastrointestinal functions have been most intensively studied, the neural control of metabolism is less well understood and appreciated, probably owing to its complexity. Neural control of metabolism includes energy production, storage, mobilization, conversion, and utilization, as accomplished by the coordinated actions of the gastrointestinal tract, liver, pancreas, muscle, white adipose tissue (WAT), and brown adipose tissue (BAT).

The neural control of metabolism can be conceived as consisting of sensory inputs, central integrative circuits, and motor outputs (sympathetic and parasympathetic), allowing for

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typical feedback regulation of specific functions (Fig. 1). Sensory input to the brain is accomplished by primary afferents innervating and by humoral factors secreted from relevant peripheral organs (Cechetto 1987; Craig 2002; Fealey 2013; Janig 1996). In turn, the brain controls specific functions of these organs through the autonomic nervous system and endocrine outflow. Most of these sensory and motor neural pathways have been well documented since the inception of neural tract tracing methods some 40 years ago (Ricardo 1983) and particularly the ascent of trans-synaptic viral tracing techniques (Card and Enquist 2014; Loewy 1998). Much less is known about the organization of integrative circuits in the brain. This is probably due to the complexity of these circuits and lack of appropriate methodology to untangle them. However, the recent availability of neuron-specific stimulation and recording techniques in animals and functional neuroimaging techniques in humans is starting to provide exciting new insights (Rezai-Zadeh and Munzberg 2013; Williams and Elmquist 2012).

One of the first accounts demonstrating brain-evoked changes in a metabolic parameter can be traced back almost 150 years to Claude Bernard's "piqûre diabetique," in which he showed a slow rise in blood glucose following lesions in the caudal brainstem (Bernard 1957). More systematic investigations followed much later in the context of the classical studies on the hypothalamic control of energy balance and body weight of the mid-1900's (Brobeck 1946; Kennedy 1951; Mayer and Barrnett 1955). A key observation was the increase in body weight and adiposity in rats with ventromedial hypothalamic (VMH) lesions, even when food intake was restricted to sham-operated rats (Cox and Powley 1981); it is a clear evidence that the hypothalamus not only controls energy intake but also energy expenditure to achieve energy balance. This led to the discovery of BAT and its role in heat production and body weight regulation (Rothwell and Stock 1979). The discovery of leptin some 20 years ago provided the final push toward identification of neural circuitry in the hypothalamus and beyond, responsible for the regulation of energy balance and control of metabolism (Halaas et al. 1995). In this chapter, we review recent progress in the identification of brain circuits and pathways that control energy expenditure via peripheral organs.

2 Input and Output Systems for Energy Expenditure Control

Energy expenditure depends on several external and internal factors such as ambient temperature, nutritional or reproductive state, circadian rhythms, and levels of circulating hormones (Fig. 1). These external and internal modulators have sometimes opposing physiological effects and need to be integrated and translated via the brain to allow appropriate physiological changes and ensure homeostasis. Cold exposure is an excellent example that demonstrates the quick increase in energy expenditure within minutes after such an external challenge (Fig. 2a). Conversely, increased ambient temperature results in decreased energy expenditure (Fig. 2b).

Three components of whole-body energy expenditure can be distinguished: basal metabolic rate (BMR), adaptive thermogenesis, and physical activity (Fig. 3). BMR is the energy expenditure that is measured at thermoneutrality (no extra energy needed for cold- or warm-defensive adaptations), postprandially (after active meal digestion), and at rest (minimal

muscle movement) and defines the oxygen consumed for ATP production. The coupling of oxidative processes to ATP production is not perfect, and some energy is lost by proton leaks (basal leak) across the mitochondrial membrane (Brand et al. 1999). Thus, BMR also includes such basal leaks and is also called obligatory metabolism as it is required to maintain minimal bodily functions.

During external challenges such as cold exposure, additional systems are activated and increase energy expenditure beyond BMR. This can be conscious and voluntary exercise, and involuntary muscle shivering (Rowland et al. 2014). In addition, adaptive systems are activated – specifically during chronic cold exposure – that are known as cold-induced thermogenesis or adaptive thermogenesis. These processes use active uncoupling of the mitochondrial proton-motive force from ATP production or futile cycling to “waste” energy and to release energy as heat (Rowland et al. 2014). This active energy wasting is also known as facultative metabolism, because it is optional and not required to maintain minimal bodily functions under thermoneutral conditions. BAT is an invention of euthermic animals such as birds and mammals and is a heat-generating tissue that is specialized in adaptive thermogenesis.

2.1 BAT and Adaptive Thermogenesis

In rodents, the interscapular BAT is the largest depot, with smaller depots in the mediastinum, along the cervical and thoracic aorta, and around the kidney (Giordano et al. 2004). In humans, BAT is less centralized than in rodents, with significant depots in supraclavicular, neck, and paraspinal regions (Cypess et al. 2009; Lidell et al. 2013; Saito et al. 2009). Based on numerous experiments with denervation of the interscapular pads in rodents, as well as pharmacological studies using ß3-adrenergic agonists and blockers, the main driver of BAT thermogenesis seems to be its noradrenergic sympathetic innervation (Andrews et al. 1985; Bartness and Wade 1984; Himms-Hagen et al. 1990; Takahashi et al. 1992; Tsukazaki et al. 1995). Retrograde tracing and other studies in rats and Siberian hamsters have identified postganglionic perikarya innervating BAT in the stellate ganglia (Grkovic and Anderson 1997; Oldfield et al. 2002), known to receive input from preganglionic neurons in the intermediolateral cell column of the cervical and thoracic spinal cord (Nozdrachev et al. 2002; Tanche and Therminarias 1967) (Fig. 4).

BAT is also innervated by dorsal root sensory nerve fibers (De et al. 1998; Himms-Hagen et al. 1990; Vaughan et al. 2014), but based on the lack of cholinergic markers, BAT is not innervated by the parasympathetic nervous system (Norman et al. 1988). Sympathetic activation of BAT leads to the activation and gene expression of the uncoupling protein-1 (UCP1), which is well accepted as a true uncoupler with heat-producing properties (Shabalina and Nedergaard 2011). The idea to burn excess calories by activating BAT in the fight against obesity flared up 35 years ago (Rothwell and Stock 1979) and, after a long hiatus, returned only recently because the existence of functional and inducible BAT was convincingly demonstrated in adult humans (Cypess et al. 2009; Saito et al. 2009; van Marken Lichtenbelt et al. 2009; Virtanen et al. 2009).

2.2 Muscle, Energy Expenditure, and Thermogenesis

Physical activity greatly contributes to whole-body energy expenditure and can be distinguished into exercise and non-exercise activity thermogenesis (NEAT). NEAT involves occupational activities, walking, sitting, standing, fidgeting, talking, leisure activities, etc., but excluding voluntary exercise, sleeping, or eating (Levine 2004) and can substantially contribute to total energy expenditure (15–50%). Therefore, NEAT has been studied as a malleable variable for body weight regulation through increasing energy expenditure.

Physical activity is at least in part genetically encoded, because selective breeding for physical activity in rats resulted in the genetic distinction of high- and low-capacity runners (HCR, LCR, respectively) with low and high incidences of obesity, respectively (Wisloff et al. 2005). HCR had higher total energy expenditure, even though resting energy expenditure was similar between HCR and LCR, suggesting that increased locomotion largely accounts for changes in total energy expenditure. However, HCR rats had increased mitochondria content and increased sympathetic drive in their skeletal muscle, and the existence of skeletal muscle thermogenesis, not exercise per se, has been suggested as a contributing factor for weight gain resistance on high-fat diets (Gavini et al. 2014; Wisloff et al. 2005). HCR also have increased expression of uncoupling protein 2 and 3 (UCP2 and UCP3). However, in contrast to UCP1, UCP2 and UCP3 do not have true uncoupling functions (Brand and Esteves 2005; Shabalina and Nedergaard 2011). Another potential mechanism to mediate muscle non-shivering thermogenesis is sarco-/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) by uncoupling ATP hydrolysis from Ca^{2+} transport (Bal et al. 2012). Whether SERCA uncoupling is also controlled by sympathetic nerve activity (SNA) similar to UCP1 is unknown. Thus, muscle thermogenesis and its regulatory properties, e.g., during diet-induced obesity, remains ill defined and is an urgent future topic.

2.3 Sensory System

The skin is a very important sensory organ for thermoregulatory control of energy expenditure. It works as a feed-forward system, so that ambient temperature changes are communicated to the brain for temperature defensive adaptations, even though core temperature is not immediately compromised. Temperature-sensing receptors (superfamily of transient receptor potential (TRP) channels) are located in the nerve endings of sensory cells throughout the skin. The cell bodies of these bipolar sensory neurons are found in trigeminal and dorsal root ganglia from where they further communicate with central structures in the spinal cord (dorsal horn lamina) and brain (Damann et al. 2008; Julius and Nathans 2012). Temperature changes in the skin cause the opening of TRP channels and promote the activation of sensory neurons (Voets 2014). This is further communicated to the CNS to modulate SNA in peripheral tissues (e.g., BAT, WAT), which is further addressed in Sect. 3.

BAT and WAT also send feedback information to the CNS via sensory nerves that connect adipocytes via dorsal root ganglia with the brain (Bartness et al. 2010a; b; De et al. 1998; Himms-Hagen et al. 1990; Vaughan et al. 2014). Incoming (afferent) sympathetic nerves can be distinguished from outgoing (efferent) sensory nerves with multisynaptic anterograde (Herpes virus) and retrograde (pseudorabies virus) viral tracers that are injected into BAT or

WAT. Surprisingly, many CNS sites showed both sympathetic and sensory connectivity, so that an extensive feedback system for incoming and outgoing signals is likely (Ryu et al. 2015; Ryu and Bartness 2014). Adipose tissue sensory nerves are responsive to metabolic changes (e.g., lipolysis) (Song et al. 2009) and the adipokine leptin (Murphy et al. 2013). In the BAT, sensory input may specifically influence the trophic adaptations to changes in ambient temperature (Himms-Hagen et al. 1990). However, we still do not have a firm understanding of the extent and how sensory feedback loops influence physiological function.

2.4 Endocrine Systems and Energy Expenditure Regulation

The modulation of energy expenditure in response to external and internal challenges involves neuronal input to and outputs from the brain to perform energy expenditure changes in peripheral tissues (e.g., BAT). In addition to this neural loop, various endocrine hormones are important communicators between peripheral tissues and the central sites to regulate energy expenditure.

2.4.1 Cold-Induced Endocrine Hormones—The thyroid hormone is perhaps the most important humoral regulator of metabolism and energy expenditure. Its production is regulated by the brain via the hypothalamic-pituitary-thyroid (HPT) axis, in which the activation of thyrotropin-releasing hormone (TRH) neurons within the hypothalamus ultimately leads to increased thyroid hormone (T4/T3) signaling at peripheral tissues (for review, see Fekete and Lechan 2014; Joseph-Bravo et al. 2015). Thyroid hormone acts on many tissues to promote cellular metabolism and energy expenditure, including effects on heart function, skeletal muscle, and BAT, and as such thyroid hormone is a critical positive regulator of BMR. Changes in ambient temperature or nutritional state influence the activity of TRH neurons within the paraventricular hypothalamus (PVH), resulting in increased release of thyroid hormone from the thyroid gland (Bianco et al. 2002; Zoeller et al. 1990). Leptin also directly stimulates TRH neurons while fasting inhibits these neurons (Huo et al. 2004; Legradi et al. 1997, 1998). Thus, TRH neurons and the HPT axis are critically involved in the regulation of whole-body energy expenditure in response to changes in the external and internal milieu. The thyroid axis may also modulate BAT thermogenesis via central thermoregulatory circuits as discussed in Sect. 3.

Ongoing efforts aim to discover additional “peripheral” endocrine modulators of energy expenditure that could promote weight loss. The muscle-derived hormone irisin (produced by the *fndc5* gene) has received considerable attention. Irisin is increased by exercise to promote the transition of lipid-storing WAT to energy expending BAT-like properties, also known as “browning” of WAT, and is also induced by cold exposure (Bostrom et al. 2012; Lee et al. 2014). Another notable metabolic hormone is fibroblast growth factor 21(FGF21) (Lee et al. 2014). FGF21 is mainly secreted from the liver (Markan et al. 2014) but is also robustly induced by cold exposure in the BAT (Chartoumpekis et al. 2011). Whether FGF21 in BAT is solely induced by cold exposure or instead requires additional metabolic stressors as observed in UCP1-deficient mice (Keipert et al. 2015) remains to be clarified. Also, it is unclear if cold-induced production and secretion of irisin (from muscle) or FGF21 (e.g., BAT) depends on increased sympathetic outflow to skeletal muscle and BAT, respectively.

2.4.2 Endocrine Signals and Adaptive Responses to Energy Restriction— Changes in energy availability (e.g., during fasting) also induce adaptive changes in energy expenditure. This process of energy homeostasis requires the CNS to detect and respond to endocrine hormones (and possibly sensory inputs from peripheral tissues) that are triggered by negative or positive energy balances (Morrison and Berthoud 2007). Such a decrease in energy expenditure typically accompanies fasting and starvation (Dulloo and Jacquet 1998; Leibel et al. 1995), even though acute fasting may initially rather trigger an increased sympathetic tone to mobilize fat stores in WAT (Goodner et al. 1973; Havel 1968; Koerker et al. 1975). Fasting-induced hypometabolism involves a variety of circulating hormones with central actions, including the adipose-derived hormone leptin. Circulating leptin levels rapidly fall with negative energy balance, and the resulting hypometabolism can be prevented by restoring serum or central leptin levels (Ahima et al. 1996; Rosenbaum et al. 2002, 2005). Taken together, falling leptin levels during starvation are detected by the CNS to change the motivation to eat and to reduce energy expenditure.

The gut hormone ghrelin also contributes to starvation-induced adaptive responses. Ghrelin release is increased during starvation and suppresses energy expenditure (Muller et al. 2015). Also insulin and glucagon are highly regulated by energy intake and contribute substantially to the starvation response, e.g., induction of lipolysis. Considering the variety of hormones that act in the brain to suppress food intake and energy expenditure simultaneously, it is suggested that a precise interaction of feeding and thermoregulatory neuronal circuits exist. However, comprehensive knowledge of how these systems are coordinated is missing and a key goal for the future.

2.4.3 Overfeeding and Energy Expenditure: Diet-Induced Thermogenesis—A negative energy balance (e.g., during fasting) is associated with a reduction in energy expenditure, while increased food intake (e.g., during high-fat feeding) induces thermogenic responses, also known as diet-induced thermogenesis (DIT) (Rothwell et al. 1983). Rothwell and Stock also demonstrated that low-protein diet increased energy expenditure, suggesting that both overfeeding and protein restriction triggered DIT (Rothwell et al. 1983). The circulating hormone FGF21 is well known to increase energy expenditure and promote the browning of WAT (Douris et al. 2015; Fisher et al. 2012), but only recent work showed that FGF21 is required for the low protein-induced energy expenditure (Laeger et al. 2014; Morrison and Laeger 2015). Whether FGF21 promotes these effects within the periphery and/or through the brain remains unclear (Kharitonenkov and Adams 2014; Owen et al. 2015).

In summary, the maintenance of body weight and thermoregulation in response changes in external temperature and food availability are mediated by an intricate neural and endocrine network.

3 Neural Circuits That Modulate Energy Expenditure

The brain network that regulates adaptive thermogenesis receives inputs from temperature- and energy-sensing neurons through hypothalamic and brain stem areas such as the preoptic area (POA), arcuate nucleus (ARC), and nucleus of the solitary tract (NTS) (Morrison et al.

2014). Naturally, many physiological states such as fever, stress-induced hyperthermia, and diurnal fluctuation of body temperature require attention from these central thermoregulatory circuits. Some physiological states may require opposing adaptations of energy expenditure, e.g., cold exposure increases energy expenditure, but fasting requires energy preservation and decreased energy expenditure. Thus, if cold exposure and fasting challenges are combined, this conflict needs to be solved by the brain for an appropriate modulation of energy expenditure, manifested in a change of SNA and secretion of neurohormones.

The anatomical location of BAT-related CNS neurons that control BAT thermogenesis stems from multisynaptic, retrograde tracing studies with PRV infections of the BAT (Cano et al. 2003). Another tool to identify thermoregulatory neurons is to track which neurons are activated by changes in ambient temperature. The early response gene cFos is rapidly induced by neuronal firing and is a reliable and efficient marker for neurons that are activated in response to temperature changes. (Bamshad et al. 1999; Cano et al. 2003; Oldfield et al. 2002). However, molecular identities and synaptic connections of these neurons are not entirely understood. In this section, we focus on central circuits that govern BAT SNA. We also briefly discuss neural circuits that modulate the release of neurohormones that affect adaptive thermogenesis.

3.1 Hypothalamus

Much of the literature that defines central sites that control BAT thermogenesis stems from research on pyrogenic stimuli and cold-defense behavior. The POA has received specific attention in the control of such thermoregulatory processes (Nakamura 2011). Thermoregulatory neurons in the POA receive thermosensory neuronal inputs from the skin, but many POA neurons are internally temperature sensitive. They change their firing activity with local temperature changes, thus enabling the POA to detect both peripheral and brain temperature changes (Boulant and Dean 1986; Nakamura and Morrison 2008, 2010). These neurons are proposed to be mostly warm-sensitive GABAergic (inhibitory) neurons that directly inhibit BAT sympathetic premotor neurons in the rostral medullary raphe (RMR) or indirectly through the dorsomedial hypothalamus/dorsal hypothalamic area (DMH/DHA) (Yoshida et al. 2009). Therefore, during a cold exposure, warm-sensitive POA neurons are inhibited and enable thermogenic neurons in the DMH/DHA and RMR to increase BAT SNA.

Some warm-sensitive GABAergic POA neurons express prostaglandin E receptor subtype EP3 and mediate febrile responses by using the same POA > DMH/DHA > RMR circuits to BAT (Lazarus et al. 2007; Nakamura et al. 2009; Scammell et al. 1996; Ushikubi et al. 1998). However, stimulatory glutamatergic inputs to the DMH/DHA have been proposed as well (Madden and Morrison 2004), and cold-sensitive glutamatergic POA neurons may provide these inputs (Dimitrov et al. 2011). Because there are also warm-activated cholinergic neurons in the DMH that directly inhibit thermogenic RMR neurons (Jeong et al. 2015), the POA is very likely to contain warm-sensitive glutamatergic neurons that directly innervate these DMH neurons.

Other lines of research that are more concerned with body weight regulation have focused on additional neuronal sites and their effect on energy expenditure and body weight regulation. These energy homeostatic sites have not been well characterized for their responsiveness to thermal inputs, but clearly modulate BAT SNA. The ARC is highly responsive to changes in energy/nutritional state (e.g., fasting) and mediates changes in BAT SNA. Pro-opiomelanocortin (POMC)-expressing neurons in the ARC are anorexigenic neurons that increase BAT thermogenesis. The secretion of ∝-melanocyte-stimulating hormone, a byproduct of POMC, or melanotan II (MTII), an MC4R agonist, activates melanocortin 4 receptors (MC4R) to increase energy expenditure and UCP1 expression via BAT SNA, while loss of MC4R decreases energy expenditure and promotes weight gain (Chen et al. 2000; Haynes et al. 1999; Ste Marie et al. 2000). Although the exact sites of MC4R-mediated BAT activation is not completely understood, MC4Rs in the PVH are not involved in the regulation of energy expenditure, while cholinergic neurons in the intermediolateral nucleus (IML) within the spinal cord are sufficient to restore energy expenditure in whole-body MC4R-deficient mice (Berglund et al. 2014; Rossi et al. 2011; Sohn et al. 2013).

GABAergic ARC neurons agouti-related peptide/neuropeptide Y (AgRP/NPY) neurons and RIP-Cre neurons both affect BAT SNA. NPY derived from ARC AgRP/NPY neurons inhibits BAT SNA via activation of Y1 receptor in unknown target neurons (Shi et al. 2013). Similarly, DMH NPY neurons also inhibit BAT sympathetic control (Bi et al. 2003; Chao et al. 2011), and the central administration of NPY induces torpor-like hypothermia (Dark and Pelz 2008), suggesting overall sympathoinhibitory NPY function in the brain. Another set of sympathoinhibitory neurons exist in the DMH that are warm-activated neurons and project to the RMR (Jeong et al. 2015). RIP-Cre neurons are a distinct population of GABAergic neurons within the ARC that inhibit PVH neurons to enhance BAT activation (Kong et al. 2012).

Interestingly, several central thermoregulatory and energy homeostatic neurons express leptin receptors or are controlled by LepRb neurons (Bachman et al. 2002). Leptin action within the DMH has a clear sympathostimulatory effect on BAT thermogenesis and associated cardiovascular responses, which are largely independent of anorexic leptin effects (Enriori et al. 2011; Rezai-Zadeh et al. 2014). Some of these leptin-mediated effects on energy expenditure requires glutamate signaling (Xu et al. 2013), even though leptin likely exerts its effects via complex inhibition and stimulation of several neuronal populations, including its interaction with insulin via POMC neurons to promote browning of WAT (Dodd et al. 2015).

The PVH is an essential output center for neuronal and humoral signals and has been rediscovered as an important thermoregulatory site. General PVH activation prevents cold- and prostaglandin E2-increased BAT SNA by increasing GABAergic inputs to the RMR (Madden and Morrison 2009). Because the PVH consists of mainly glutamatergic neurons, this may involve multisynaptic circuits, possibly involving identified PVH > NTS > RMR circuits that are modulated by ARC RIP-Cre neurons (Kong et al. 2012). With the use of the modern genetic toolbox, some thermoregulatory PVH subpopulations have been further identified as nitric oxide synthase 1 (NOS1), oxytocin (OXT), or brain-derived neurotrophic

factor (BDNF)-expressing neurons that project directly to sympathetic preganglionic neurons in the spinal cord to increase BAT activity (An et al. 2015; Sutton et al. 2014).

PVH OXT neurons are a subpopulation of NOS1 neurons, and activation of either population activates BAT thermogenesis. Interestingly, simple-minded homolog 1 expressing PVH neurons, which marks most PVH neurons, also increase BAT thermogenesis when activated (Sutton et al. 2014), contradicting earlier findings mentioned above. Similarly, posterior PVH BDNF neurons seem to regulate BAT thermogenesis because PVH-specific BDNF deletion reduced energy expenditure and increased body weight (An et al. 2015). Whether PVH BDNF neurons also express NOS1 is not known. These findings are in line with earlier studies showing that cFos in the PVH is induced by both cold and warm exposures (Cano et al. 2003; Yoshida et al. 2002). Taken together, the PVH seems to be involved in both directional controls of BAT sympathetic activity, and future research needs to identify the neurochemical properties of sympathoinhibitory PVH neurons.

In addition to the neural control of sympathetic BAT inputs, the PVH also modulates humoral effectors of BAT thermogenesis. Cold exposure increases while warm exposure decreases thyroid hormone levels via TRH neurons to stimulate BAT activity and BMR (Andersson et al. 1963; Eastman et al. 1974; Kim 2008). Interestingly, in addition to the intensely studied peripheral effects of thyroid hormone, more recent data also indicate a central function of thyroid hormone to increase BAT SNA (Coppola et al. 2007; Lopez et al. 2010). Furthermore, TRH neurons are found outside the PVH in important thermoregulatory sites like the DMH and RMR (based on Allen Brain Atlas data, http://mouse.brain-map.org/), and compelling functional data support thermoregulatory synergistic effects of TRH and leptin via brainstem circuits (Hermann et al. 2006; Rogers et al. 2009, 2011).

Another thermoregulatory PVH neurohormone is corticotropin-releasing hormone (CRH), which is increased by low glucose levels or other stressor. CRH increased pituitary adrenocorticotropic hormone release to induce stress hormones like glucocorticoids that upon other functions inhibit BAT activity peripherally (Moriscot et al. 1993). Like TRH neurons, CRH neurons are also found outside the PVH (based on Allen Brain Atlas data) and may function within thermoregulatory central circuitries, e.g., central CRH infusions into the POA and other hypothalamic sites stimulate BAT SNA output (Egawa et al. 1990a,b).

The VMH has long been implicated in the control of BAT SNA and energy expenditure even though the pathways leading to BAT sympathetic neurons have not been identified (Perkins et al. 1981), due to the typical lack of PRV labeling. Nonetheless, insulin, thyroid hormone, and estrogen affect BAT SNA through the VMH (Klockener et al. 2011; Lopez et al. 2010; Musatov et al. 2007). Estrogen signals via its receptor ER$\propto$ and promotes different aspects of thermogenesis via distinct ER$\propto$-expressing VMH neurons (Correa et al. 2015; Xu et al. 2011). Future studies are needed to explore the involved downstream targets within these thermoregulatory circuitries.

Finally, a subpopulation of orexin/hypocretin neurons in the lateral hypothalamic area (LHA) project to BAT sympathetic premotor neurons in the RMR, and the secretion of

orexin seems to potentiate already existing BAT sympathostimulatory signals onto the RMR (Berthoud et al. 2005; Tupone et al. 2011). Interestingly, LHA orexin neurons are not involved in cold- or pyrogen-induced BAT thermogenesis (Nakamura et al. 2005) but are rather critical for stress-induced BAT thermogenesis (Zhang et al. 2010), even though the DMH may be more dominantly involved in stress-induced thermogenesis (Kataoka et al. 2014).

3.2 Brainstem

Hypothalamic areas that receive BAT-related inputs send efferent fibers to sympathetic premotor neurons in the RMR or project directly to spinal preganglionic neurons as mentioned above for the PVH. The RMR includes the rostral raphe pallidus (rRPa), raphe magnus, parapyramidal area, and ventrolateral medulla (VLM) and contains main sympathetic premotor neurons for BAT, vasculature, and heart (Nakamura 2011). The rRPa is especially important for BAT thermogenesis and innervated by many excitatory and inhibitory neuronal fibers that are originated from the hypothalamus and brainstem. rRPa neurons receive tonic inhibitory inputs at neutral conditions, most notably by warm-sensitive GABAergic POA neurons, and disinhibition of rRPa neurons by various thermogenic signals increases BAT SNA. Catecholaminergic neurons in the VLM including the A1/C1 neurons inhibit rRPa BAT premotor neurons through the activation of $\alpha 2$ adrenergic receptor, possibly explaining the systemic $\alpha 2$ adrenergic agonist-mediated hypothermia (Cao et al. 2010; Madden et al. 2013). C1 neurons have been proposed to respond to emergencies such as hypoxia and glucoprivation (Guyenet et al. 2013), and this VLM > rRPa pathway may account for inhibition of BAT during those situations (Madden 2012; Madden and Morrison 2005).

Neurons in the NTS receive viscerosensory information and inhibit BAT SNA when activated (Cao et al. 2010). The NTS also regulates BAT activity independent of hypothalamic inputs via hindbrain leptin/TRH signaling (Rogers et al. 2009) and ARC RIP-Cre neurons (Kong et al. 2012), implying it as a potential integrative site of viscerosensory and metabolic signals.

Other brainstem areas such as the lateral parabrachial nucleus, periaqueductal gray, and locus coeruleus have been associated with BAT sympathetic control as sensory afferent or effector efferent relay stations, but more studies are required to precisely identify their involvement in specific conditions (Almeida et al. 2004; Chen et al. 2002; Nakamura and Morrison 2008, 2010; Rathner and Morrison 2006; Yoshida et al. 2005).

Overall, many central sites possess a mixture of sympathostimulatory and sympathoinhibitory sets of neurons that may interact with the RMR as a master modulator for sympathetic BAT inputs. The hypothalamus is central for regulation of adaptive thermogenesis. Recent technical advancements of various neural mapping, recording, and manipulation tools at a spatially, genetically, and temporally controlled manner have accelerated our understanding of how brain works. The next step of understanding how the brain regulates energy expenditure would be deciphering where and how various environmental and internal signals are integrated and ramified to different thermoeffectors.

4 Remaining Questions and Conclusion

Metabolic diseases like obesity and diabetes are still increasing and remain a serious healthcare problem. Despite considerable efforts to treat obesity, it has been widely recognized that any treatment is flawed by the powerful ability of the body to adapt to dietary changes. A considerable part of the population is affected by the opposite problem: the failure to maintain healthy body weight and excessive weight loss due to enhanced energy expenditure in cachexic patients. This state is observed in neurodegenerative diseases and cancer and in patients with progressing acquired immune deficiency syndrome (AIDS) (Argiles et al. 2015; Dupuis et al. 2011; Salomon et al. 2002). Thus, targeting the central or peripheral nervous system to modulate energy expenditure is a realistic goal that would benefit many human patients and is currently under intense investigation.

One major roadblock is that the molecular basis of defended homeostatic levels (e.g., body weight and body temperature) remains unclear. Also, how changes in the defended levels (e.g., during obesity) are realized at the molecular level. Specifically, the interplay of energy expenditure and food intake is important to defend homeostatic levels. The reviewed work in this chapter compiles research from the thermoregulation and body weight regulation fields. However, more studies are required with emphasis on the interaction of thermoregulatory and food intake regulating neuronal circuits. Only if we are able to modulate the defended homeostatic body weight, we a will be able to achieve sustainable corrections in body weight.

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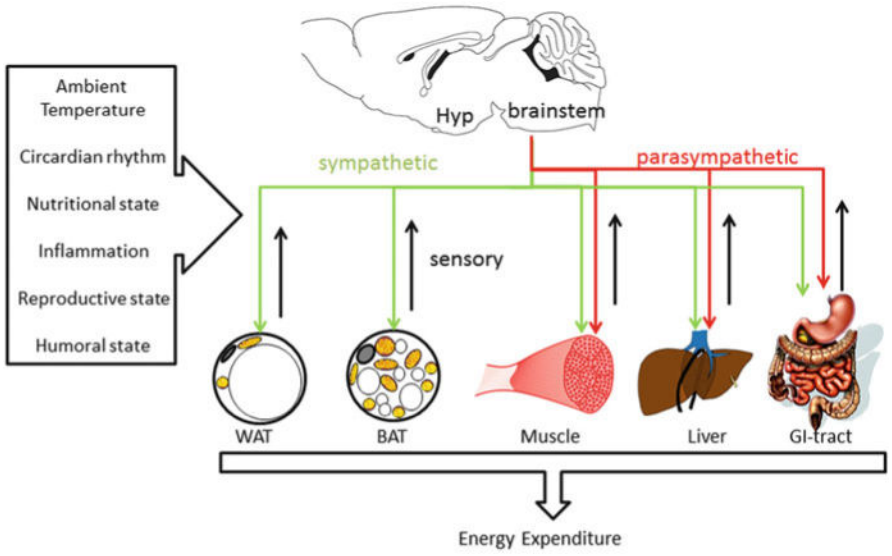

Fig. 1.

Schematic view of the complex interaction of brain, peripheral tissues, and environment

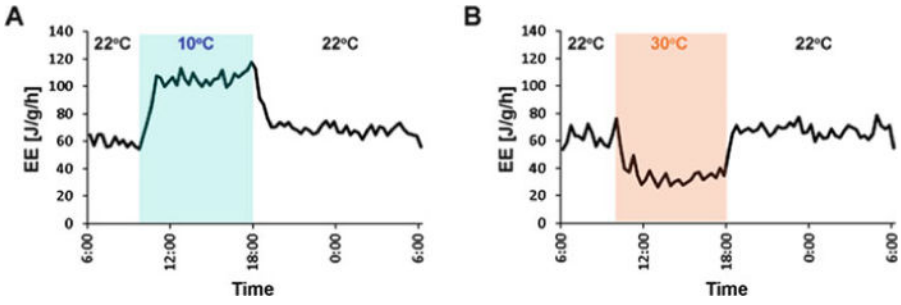

Fig. 2.

Temperature changes induce robust adaptations in energy expenditure. (**a**) Acute decreases in ambient temperature quickly and robustly increase energy expenditure. (**b**) Acute increase in ambient temperature results in adaptive decrease in energy expenditure

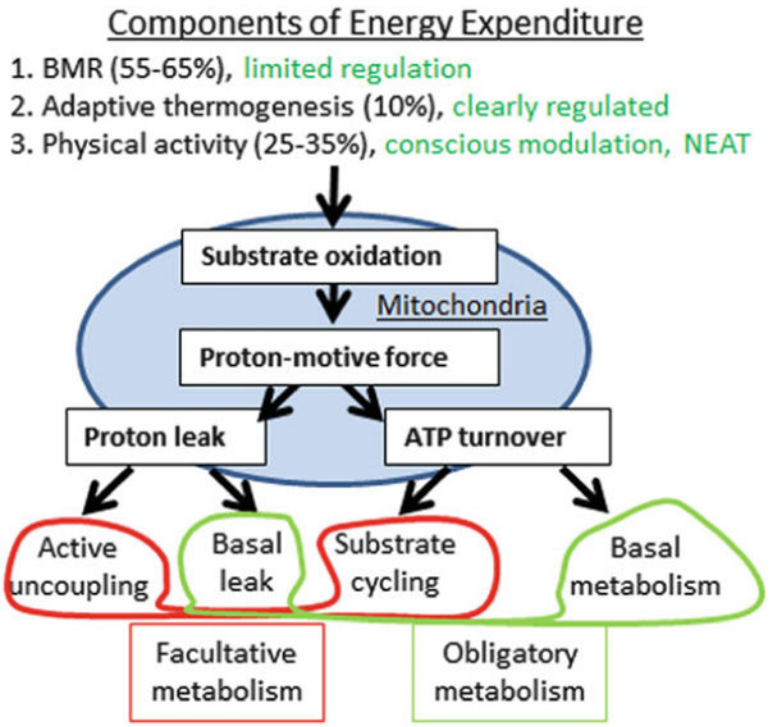

Fig. 3.

Components of energy expenditure. Oxidative processes result in a proton-motive force in the mitochondrion used to generate ATP, even though basal proton leaks are observed that "wastes" energy. ATP production and basal proton leaks together account for obligatory metabolism, required for minimal bodily functions. The active uncoupling of proton-motive force from ATP production is used to generate heat, e.g., in the brown adipose tissue. And uncoupling protein 1 (UCP1) is a well-studied example for active uncoupling. Substrate cycling also actively contributes to heat production. Together these mechanisms account for facultative metabolism, which is optional and not used for baseline maintenance of bodily functions, e.g., at thermoneutral conditions

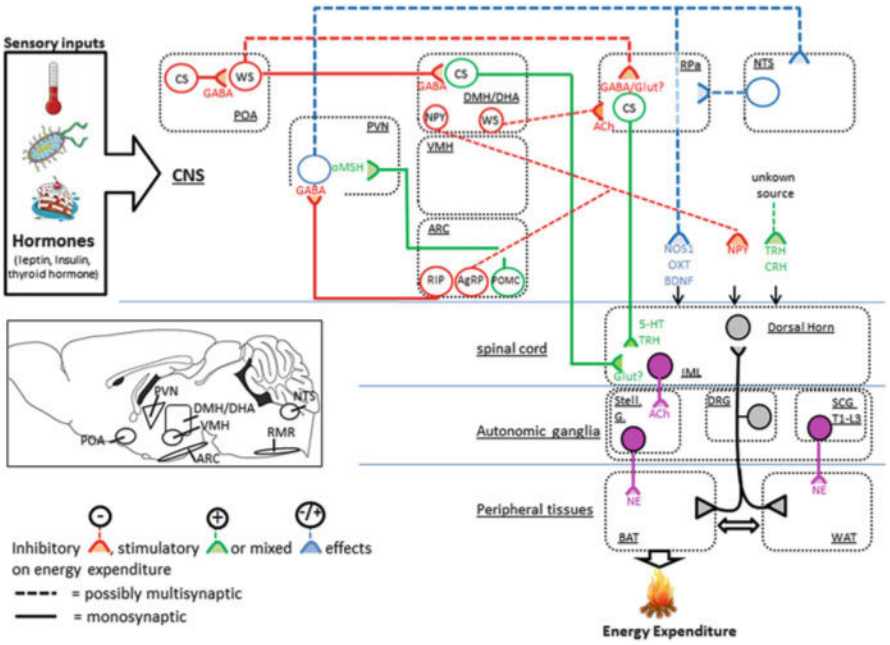

Fig. 4.

Schematic overview of central circuits that modulate energy expenditure