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65 Abstract

The hypothalamus is a brain region in charge of many vital functions. Among them, BAT thermogenesis represents an essential physiological function to maintain body temperature. In the metabolic context, it has now been established that energy expenditure attributed to BAT function can contribute to the energy balance in a substantial extent. Thus, therapeutic interest in this regard has increased in the last years and some studies have shown that BAT function in humans can make a real contribution to improve diabetes and obesity-associated diseases. Nevertheless, how the hypothalamus controls BAT activity is still not fully understood. Despite the fact that much has been known about the mechanisms that regulate BAT activity in recent years, and that the central regulation of thermogenesis offers a very promising target, many questions remain still unsolved. Among them, the possible human application of knowledge obtained from rodent studies, and drug administration strategies able to specifically target the hypothalamus. Here, we review the current knowledge of homeostatic regulation of BAT, including the molecular insights of brown adipocytes, its central control, and its implication in the development of obesity.

66 Keywords separated by ' - '

Thermogenesis - Hypothalamus - Obesity - Brown adipose tissue - Browning - White adipose tissue

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REVIEW

Hypothesizing about central combat against obesity

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Abstract
The hypothalamus is a brain region in charge of many vital functions. Among them, BAT thermogenesis represents an essential physiological function to maintain body temperature. In the metabolic context, it has now been established that energy expenditure attributed to BAT function can contribute to the energy balance in a substantial extent. Thus, therapeutic interest in this regard has increased in the last years and some studies have shown that BAT function in humans can make a real contribution to improve diabetes and obesity-associated diseases. Nevertheless, how the hypothalamus controls BAT activity is still not fully understood. Despite the fact that much has been known about the mechanisms that regulate BAT activity in recent years, and that the central regulation of thermogenesis offers a very promising target, many questions remain still unsolved. Among them, the possible human application of knowledge obtained from rodent studies, and drug administration strategies able to specifically target the hypothalamus. Here, we review the current knowledge of homeostatic regulation of BAT, including the molecular insights of brown adipocytes, its central control, and its implication in the development of obesity.

Keywords Thermogenesis · Hypothalamus · Obesity · Brown adipose tissue · Browning · White adipose tissue

Introduction: brown adipose tissue through history

Firstly anatomically described by Konrad Gessner in 1551 in the inter-scapular region of marmots, the brown fat was originally termed "hibernating gland" due to its presumed role during the hibernation phase of these animals. However, it was only in 1961 that the brown adipose tissue (BAT) was really identified as a thermogenic organ responsible for non-shivering thermogenesis generating heat through several metabolic processes [1].

BAT differs from the white adipose tissue (WAT) in terms of function and morphology. While BAT adipocytes contain large number of small lipid droplets within their cytoplasm providing the required energy fuel for thermogenic processes, WAT adipocytes are composed of one single lipid droplet that accounts for more than 90% of their volume and are implicated mainly in the lipid storage and endocrine control [2–4]. Until recently, the widely held view was that BAT was only encountered in newborn infants [5–7] and that BAT was disappearing quickly over the first few years of postnatal life. However, some studies suggested that BAT could also be encountered in adults [8]. Indeed, 10 years ago, when research considerably focused on BAT therapeutic potential in several diseases, such as metabolic related ones, numerous studies—notably using fluoro-deoxyglucose positron emission tomography (FDG-PET; an approach usually employed to track cancer metastasis)—identified regions of high glucose uptake areas very similar to the presumed brown fat, confirming that active BAT could also be detected in adults subjects [9–12]. These first statements opened a wide avenue on the study of BAT therapeutic implication in humans.

Inside the brown adipocyte: thermogenesis

Brown fat is a high metabolically active tissue responsible for heat production, a process known as thermogenesis that uses

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lipids as energy fuel [13, 14]. Thermogenesis is mainly mediated by the inner mitochondrion membrane uncoupling protein 1 (UCP1) that dissipates the proton gradient by allowing them to be transported back to the mitochondrion, short-circuiting ATP synthase processes, generating heat, and overall activating thermogenesis [15].

Adrenergic stimulation is known to activate the thermogenic program in BAT through the binding of norepinephrine (NE) to ß3-adrenoreceptors (ß3-AR). ß3-AR are located on the brown adipocyte membrane and are coupled to excitatory G-protein, structurally formed by α, β, and ɣ subunits. Following the binding of norepinephrine to ß3-AR, the G-protein α-subunit is translocated to adenylate cyclase (AC) inducing AMPc synthesis activating protein kinase A (PKA) [16, 17]. PKA promotes thermogenesis in two independent manners. (i) Firstly, an acute effect, increasing the lipolytic activity through the activation of adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), and monoacylglycerol lipase (MGL) hydrolyzing triglycerides increasing free fatty acids (FFAs) levels, that will be later imported into the mitochondria by the carnitine palmitoyltransferase 1a (CPT1a) [17–21], where they will be used fuel to provide energy to thermogenic process. However, recent evidence suggests that lipolysis is not essential for the thermogenic process that can be produced by using circulating nutrients supply [22, 23]. UCP1 facilitates the transport of protons—expelled to the intermembrane space along the respiratory chain—back to the mitochondrial matrix leading to heat production avoiding ATP synthesis through the ATP-synthase [24–27]. Thus, UCP1 uses FFAs originating from BAT surrounding lipid droplets to generate heat through catabolic mechanisms [28]. Besides FFAs, glucose can also be used as energy supply for thermogenesis. Uptaken by the BAT glucose transporters 1 and 4 (GLUT 1/4), glucose will undergo glycolysis, generating metabolites involved in the formation of FFAs; these FFAs being used by mitochondria for the thermogenic process [28] (Fig. 1). (ii) Secondly, PKA can trigger a chronic activation of thermogenesis following longer sympathetic stimulations through the activation of p38-mitogen-activated protein kinase (MAPK), which is implicated in mitogenic effects, gene transcription, and protein synthesis, stimulating UCP1 synthesis and brown adipocytes proliferation and differentiation [29] .

Browning of WAT and whitening of BAT

More recently, a new type of adipocytes was described in WAT sections following sympathetic stimuli, as cold acclimation or stimulation with adrenergic agonists. Due to its brown-like profile exhibiting thermogenic properties, it was named beige or brite ("brown in white") adipose tissue. Interestingly, the process consisting in the enhancement of thermogenesis process within white adipocytes, namely browning of WAT (i.e., increased expression and activity of UCP1 in what are normally considered WAT depots) was described in both rodents and humans [13, 30–36]. Brown and white adipocytes originate from different lineages; while brown adipocytes are derived from a *Myf5*-precursor shared with myocytes, white adipose cells originate from *Myf5*-negative precursors [37, 38]. Numerous evidences have shown that Pr domain containing 16 (PRDM16) is an important transcriptional factor involved in the browning of WAT [39, 40]. Moreover, it has been demonstrated that ß-adrenergic stimulations could promote de novo productions of beige adipocytes [41] as well as "trans-differentiation" of preexisting mature white adipocytes in beige ones [38]. However, this last point remains unclear as some studies have suggested that some adipocytes could exhibit a morphologically white phenotype while originating from a beige lineage, thus bearing the potential to initiate the thermogenic program in response to thermogenic stimulus instead of the proposed ability of "trans-differentiation." Therefore, it is suggested that cold exposure could unmask the thermogenic properties of preexisting beige adipocytes [42, 43].

Although the role of beige fat on the modulation of energy balance has been questioned [44, 45], its presence and activity in humans has been widely demonstrated [31, 35, 46, 47], opening a new avenue in the development of anti-obesity drugs focusing on BAT thermogenesis and WAT browning to increase energy expenditure [48, 49].

Current evidences have also suggested that the opposite process to browning could also occur. Known as the "whitening of BAT", brown adipocytes, in response to elevated temperatures, can be differentiated in white adipocytes. However, a recent study using brown, beige, and white cell cultures exposed or not to cold, and subsequently re-warmed, has demonstrated that only beige adipocytes, but not brown, could reverse their phenotype toward a white one, suggesting a cellular plasticity in response to preexisting environmental signals and status [50]. Whitening process has been associated to BAT dysfunction in obesity and insulin resistance states in animal models [51, 52]. Indeed, the BAT of obese mice displays large lipid droplets with augmented amount of fatty acids associated to reduced ß-adrenergic signaling, as well as mitochondrial dysfunction, mirroring white fat [51]. Whitening of brown fat is also associated with peripheral loss of vascularity and development of hypoxia correlating with a significant reduction of vascular endothelial growth factor (VEGF) leading to endothelial dysfunction in BAT [53].

Therefore, WAT and BAT, in spite of their opposite functions, share the ability for reciprocal reversible trans-differentiation in response to physiologic needs. Thus, chronic positive energy balance and obesity are related with whitening induction, while chronic needs for thermogenesis, associated to lean and overstimulation of sympathetic activity, has been suggested to induce browning [54–56].

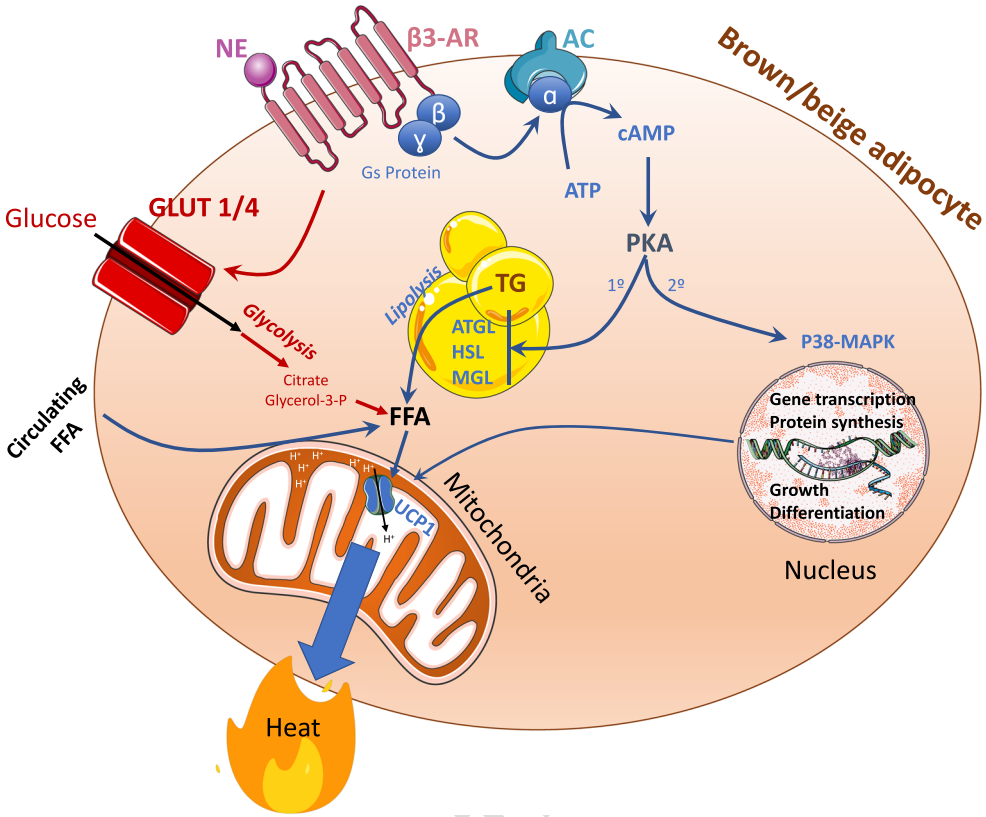

Fig. 1 The molecular events during the thermogenesis inside the brown and beige adipocyte. Sympathetic stimulus release norepinephrine (NE) that binds to β3 adrenoreceptor (β3-AR) in the brown/beige adipocyte. It is coupled to excitatory G protein (Gs), formed by subunits α, β, and γ. α subunit moves to activate adenilate cyclase (AC) which converts adenosintriphosphate (ATP) in cyclic adenosinmonophophate (cAMP) that activates protein kinase A (PKA). PKA has a dual effect: (1) Induces the triglycerides hydrolysis by the activation of lipases (adipose triglyceride lipase, ATGL; hormone-sensitive lipase, HSL; monoacylglycerol lipase, MGL) leading free fatty acids release (FFA). Of note, thermogenesis can be produced without lipolysis by circulating nutrients supply. FFA activates the thermogenic uncoupling protein 1 (UCP1). UCP1, located in the inner mitochondrial membrane, re-introduces the protons (H+) broken out the mitochondria by the respiratory chain. This process generates heat instead of ATP and is namely thermogenesis. (2) PKA activates p38-mitogen activated kinase (p38-MAPK) inducing transcriptional effects in the nucleus for UCP1 synthesis. Glucose transporter 1 or 4 (GLUT 1/4) takes up glucose which can be hydrolyzed in the glycolysis whose metabolic products as citrate and glycerol-3-phosphate may be introduced in the lipogenic pathways to generate triacylglycerols used to thermogenic process.

Thermogenesis inducers

Numerous crucial transcriptional factors playing a key role in the thermogenic capacity of the adipocyte have been described. Peroxisome proliferator-activated receptor ɣ (PPAR ɣ) is a nuclear factor essential for the activation of *UCP1* gene transcription and other thermogenic markers of brown phenotype, as well for the differentiation of brown/beige adipocytes [57, 58]. Conversely, PPARα is only expressed in BAT, not in WAT, and is considered to be a specific BAT-phenotype marker due to its involvement in the induction of lipid catabolism and mitochondrial uncoupling [59, 60]. PRDM16 and the peroxisome proliferator-activated receptor γ coactivator 1α (PGC1α) are shared by both brown and beige adipocytes, and are implicated in mitochondrial biogenesis and strongly associated to brown-like phenotype, and not to the white one. All of these transcriptional factors are considered as the main thermogenic markers along with UCP1 [61–63].

Apart from transcription factors, cold exposure is considered as one of the main factor in the increase of thermogenesis, in the recruitment of BAT and in the induction of browning, and overall in the increase of energy expenditure associated to lipid catabolism to finally induce a reduction of body weight [64–66]. Newborns are exposed to a reduced ambient temperature just after birth, requiring non-shivering thermogenesis processes to adapt to the new conditions. This adaptation process is mediated by metabolic hormones such as thyroid hormones (THs), cortisol, leptin, or insulin, all involved in the induction of thermogenic mechanisms. Thus, cold exposure plays a key role as a main inducer of BAT. In response to low temperature, NE is released by sympathetic fibers, binds to ß3-AR inducing lipolysis and thermogenesis. More recent data show that cold exposure during winter also induces browning of WAT, inducing the expression of UCP1 and PGC1 mRNA in subcutaneous white fat [67].

Moreover, THs play a key role in the energy balance regulation being a powerful activator of cell metabolism in several tissues such as skeletal muscle, brain, heart, liver, pancreas, and adipose tissues (WAT and BAT) [68]. High THs levels (i.e., hyperthyroidism) are known to increase feeding, to activate ATP and oxygen consumption, and to increase both body temperature and basal metabolic rate. Furthermore, THs promote catabolic processes such as glucose uptake, glycogenosis, gluconeogenesis, and lipolysis. Thus, being implicated in all these metabolic rate increases, THs have also a demonstrated role on decreasing body weight [69–72]. BAT and WAT widely express deodinase type 2 and nuclear TH receptors (TR), contributing to the activation of thermogenesis among the adrenergic stimulus [68, 72, 73]. The different isoforms of TR, TRα and ß, have been described to be involved in the thermogenesis regulation at different levels. Acting synergistically, TRα ensures a correct adrenergic response, while TRß stimulates *UCP1* expression [74, 75]. However, the most recent evidence associating THs to BAT and WAT thermogenesis via a central hypothalamic action will be later developed in this review [71, 76, 77].

Furthermore, recent studies have also described other new factors able to induce thermogenesis independently of adrenergic stimulation [78]. Many of them are hormones or circulating factors involved in the differentiation of brown and beige adipocytes [79–81]. Bone morphogenetic proteins (BMP), a family of growth factors, are involved in the brown fat differentiation, as well as in the browning induction of WAT. Indeed, BMP7 induces brown adipocyte differentiation [79], while a lack of BMP receptor type 1A induces BAT shortage associated to increased browning to compensate reduced thermogenesis [81]. Conversely, BMP4 seems to be a pivotal factor in WAT browning since it is correlated with lean phenotype and thermogenesis in white fat [80], similar to the growth differentiation factor 5, that activates BMP receptors, protecting against obesity [82]. On the other hand, BMP8b acts as a brown fat regulator promoting BAT sensitization to sympathetic activity [83].

The inflammatory mediators prostaglandins (PG) activate thermogenesis through sympathetic-dependent and independent pathways [84, 85]. Thereby, genetic and pharmacological approaches have demonstrated that prostaglandin E_1 (PGE_1) is essential to maintain a normal UCP1 expression and to promote thermogenesis in brown adipocytes and browning of white ones, which is mediated by ciclooxigenase-2 (COX-2), a key enzyme involved in PG formation [84–86].

Furthermore, vitamin A derivatives, named retinoids, were also described to be involved in *UCP1* gene expression modulation mainly via nuclear receptors. Retinoids are usually described to be implicated in several metabolic functions and energy homeostasis. However recent evidences have demonstrated that the chronic administration of retinoic acid (RA) induced thermogenesis in BAT and browning of WAT in mice [87–89], independently of any sympathetic stimulations. Interestingly, RA treatment improved insulin sensitivity by enhancing fat mobilization and energy utilization inducing body weight loss associated with an increase in brown specific genes including *UCP1* [90, 91]. An essential factor in the retinoid-dependent activation of thermogenesis is the intracellular conversion of retinol into active forms, retinal and RA [87]. The activation of RA receptor (RAR) and PPARδ has been suggested to be involved in the RA-induced thermogenesis leading to increased BAT activation, browning, and FA oxidation [87–89, 92].

In addition, transient receptor potential (TRP), an ion channel family implicated in temperature sensing, was also described to induce thermogenesis. Each TRP is activated at different temperature ranges. As an example, TRP-vanilloid-8 (TRPV8) is activated when the temperature is lower than 27 °C, and TRP-ankyrin-A1 (TRPA1) when lower than 17 °C. Interestingly, a lack of these low-temperature-induced TRPs was described to impair the cold adaptation [93–95]. Conversely, TRP-vanilloid-1 (TRPV1) is activated when the temperature is higher than 43 °C [96]. Furthermore, some TRPs are located in adipose tissues, such as TRP-melastin-8 (TRPM8) which is expressed in BAT and induces UCP1 expression. Moreover, TRPM8 pharmacological activation has been demonstrated to increase BAT activity in rodents [97, 98]. TRPM8 has been described to be expressed in human adipose tissue and acting as an UCP1 inducer [98]. Conversely, other ion channels have been described to be involved in the repression of thermogenesis, such as TRPV4 channel whose inhibition promotes WAT browning and BAT thermogenesis [99, 100].

Natriuretic (NP), atrial (ANP), and ventricular peptides (VNP) are also involved in the control of thermogenesis and browning [101]. All of them are vasodilator peptides secreted by the myocardium in response to high blood pressure. Interestingly, brown adipocytes express NP receptors (NPRs), which, when activated, induce an increase of the expression of thermogenic markers promoting BAT activation through MAPK pathway [101]. Furthermore, chronic treatment with NP activates browning of WAT [101].

Fibroblast growth factor 21 (FGF21) is an important hepatic-released regulator of glucose and ketone homeostasis [102–104]. FGF21 improves dyslipidemia and protects against obesity by enhancing energy expenditure, mainly through the activation of thermogenesis and browning [105, 106]. Some evidences have also suggested that brown adipocytes can release FGF21 in response to sympathetic stimulation, acting as an autocrine factor enhancing the thermogenic process [29, 107]. Notably, FGF21 can induce *UCP1* gene expression and uncoupling in brown adipocytes through the activation of p38-MAPK [29]. Novel findings demonstrate that FGF21 favors BAT thermogenesis and also browning of

WAT through G-protein receptor 120 (GPR120) that binds unsaturated long-chain fatty acids and contribute to the anti-inflammatory response protecting against obesity and type II diabetes [108]. Interestingly, data in rodents and humans have demonstrated that obese subjects exhibit high circulating levels of FGF21, suggesting a FGF21 resistance during obesity [109, 110]. Therefore, FGF21 has emerged as a potent inducer of thermogenesis; however, the complete underlying molecular mechanism through which FGF21 exerts its effects remains unclear.

Human thermogenesis

As mentioned above, the first studies demonstrating the existence of BAT in human patients were performed using FDG-PET technique 10 years ago, a method usually used for the detection of carcinogen cells due their high glucose uptake. They have revealed that brown fat in adult humans was located in the neck and in supraclavicular, mediastinum, peri-aortic, paravertebral, and suprarenal areas, and that BAT regions were inactivated in response to ß3-AR antagonist [11]. They have also shown that BAT activity was higher in women than in man, in lean than in obese, and in young than in elderly people; and importantly, these fat depots widely expressed UCP1, an unequivocal marker of brown adipocytes [10, 12]. However, further studies have demonstrated that the thermogenic markers present in the neck and supraclavicular fat matched better with beige selective genes than brown ones, suggesting that thermogenic adipose tissue in humans rather corresponds to beige adipocytes than to classical brown ones [31, 35, 111]. Subsequent studies pointed that both brown and beige adipocytes were coexisting in humans [31, 33, 112, 113]. Browning process of human WAT has been reported in patients undergoing severe burns, as a model of prolonged adrenergic stress, whom also exhibited increased metabolic rate [47]. The same observations were made in patients with pheochromocytoma, a neuroendocrine tumor secreting large amounts of catecholamines, in which several thermogenic markers and hypermetabolism in omental and mesenteric adipose tissue were observed [114–116]. Cancer-associated cachexia is characterized by high lipolysis and fat catabolism, which have been related to deep browning process in both human patients and rodent models [117, 118]. Interestingly, human subcutaneous fat expresses thermogenic markers as UCP1 or PGC1α seasonally in winter, and also under acute cold exposure [67]. All these studies indicate an activation of browning under different states with increased sympathetic rate in humans.

Curiously, human beige adipose tissue transplantation in rodents improves glucose tolerance and insulin sensitivity [119] suggesting a key role of browning in metabolic homeostasis. However, the exact molecular mechanisms regulating thermogenesis in humans remain unknown. Therefore, promoting thermogenesis in humans appears as a promising therapeutic strategy to counter obesity, diabetes, and hyperlipidemias, by enhancing energy expenditure as well as decreasing glucose and lipid circulating levels.

Central regulation of thermogenesis

In addition to its peripheral control, energy homeostasis is also regulated at a central level, mainly in the hypothalamus, a region located bellow the thalamus and composed of several hypothalamic nuclei widely interconnected between each other. The hypothalamus is involved in the physiological control of many evolutionarily conserved functions. Among them, the hypothalamus regulates the hormonal axes, the autonomic nervous system activity, and the metabolic homeostasis. Regarding this last function, the different hypothalamic nuclei play an important role in the sensing of peripheral signals informing on the energy status, such as hormones and nutrients, integrating them and generating an appropriated response in terms of food intake and energy expenditure [2, 120–122]. Due its implication in numerous metabolic processes, the hypothalamus is considered as the master regulator of energy balance.

On the one hand, the hypothalamus controls food intake through the regulation of neuropeptide expression: orexigenic neuropeptides, such as agouti-related peptide (AgRP), neuropeptide Y (NPY), and orexins (OX) that increase food intake, while anorexigenic neuropeptides, such as proopiomelanocortin (POMC) and amphetamine-regulated transcript (CART) promote satiety [123–127]. Furthermore, the hypothalamus is involved in the regulation of energy metabolism in peripheral tissues such as liver, skeletal muscle, pancreas, and both adipose tissues, brown and white, through the autonomic nervous system, sympathetic and parasympathetic. Accordingly, many studies have demonstrated that BAT and WAT thermogenesis are modulated by the hypothalamus that strictly regulates thermogenesis as a main component of the energy expenditure [2, 128–130].

As mentioned above, the hypothalamus is composed of several neural groups namely hypothalamic nuclei, widely interconnected through axonal projections. It is known for a long time that some of these hypothalamic nuclei are involved in the regulation of energy balance, such as the arcuate nucleus of the hypothalamus (ARC), the dorsomedial nucleus of the hypothalamus (DMH), the ventromedial nucleus of the hypothalamus (VMH), the lateral hypothalamic area (LHA), and the paraventricular nucleus of the hypothalamus (PVH) (Fig. 2) [2, 130, 131]. Recently, many molecular mechanisms regulating the thermogenesis in these nuclei have been described.

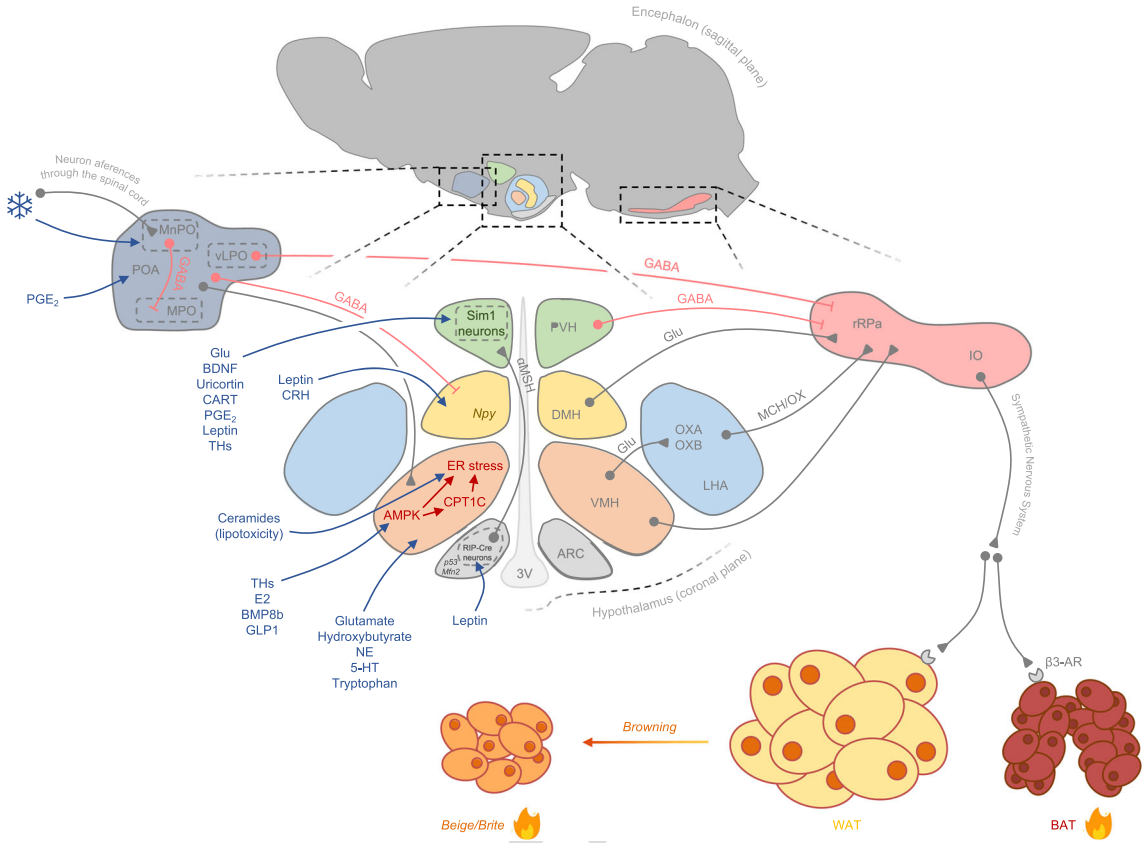

Fig. 2 Central nervous system neuroendocrine connectivity involved in BAT thermogenesis and WAT browning regulation. Together with physical stimulus (i.e., cold and heat) peripheral signals reach the central nervous system where interact with their particular receptors. Hypothalamic nuclei will integrate those signals in order to regulate brown adipose tissue (BAT) thermogenesis. Heat-sensitive neurons in the preoptic area (POA) detect cold and prostaglandin E_1 (PGE_1) to promote BAT thermogenesis through projections to the dorsomedial hypothalamus (DMH), the rostral raphe pallidus nucleus (rRPa), and the ventromedial nucleus of the hypothalamus (VMH). Moreover, additional signals from periphery are integrated in the hypothalamus regulating the sympathetic tone to BAT. In particular, thyroid hormones (THs), estradiol (E2), glucagon-like peptide-1 (GLP-1), and bone morphogenetic protein-8b (BMP8b) modulates AMP-activated protein kinase (AMPK) activity in the VMH. Together with this, endoplasmic reticulum (ER) stress levels and carnitine palmitoyltransferase 1C (CPT1C) in the VMH as well as orexin (OX) signalling in the lateral hypothalamus (LHA) are part of the signalling mediated by AMPK. Neuropeptide Y (NPY) expression in DMH neurons, p53 and mitofusin 2 (Mfn2) expression in the arcuate nucleus of hypothalamus (ARC) are also contributing to the regulation of BAT activity. Brown fat and beige/brite cells in the white adipose tissue (WAT) are under the control of sympathetic nervous system activity. Blue arrow lines indicate signal local action, grey lines indicate active/stimulatory neuronal pathways, and red lines indicate inactive/inhibitory pathways, respectively. Third ventricle: 3V, serotonin or 5-hydroxytryptamine: 5-HT, α-melanocyte-stimulating hormone: α-MSH, β3-adrenergic receptor: β3-AR, brain-derived neurotrophic factor: BDNF, cocaine and amphetamine related transcript: CART, corticotropin-releasing hormone: CRH, gamma-aminobutyric acid: GABA, glutamate: Glu, inferior olive: IO, lateral hypothalamus: LHA, lateral preoptic area: vLPO, medial POA: MPO, median POA: MnPO, melanin-concentrating hormone: MCH, norepinephrine: NE, orexin A: OXA, orexin B: OXB, single-minded homolog 1: Sim1

The preoptic area

The preoptic area (POA), anatomically located on the anterior hypothalamic nucleus, is one of the primary brain areas associated with the body temperature homeostasis [132–135]. In the POA, peripheral as well as central signals are integrated to initiate a physiological response to maintain the body temperature within a physiological range. The POA displays a double capacity to sense temperature changes. Firstly, cold and heat-sensitive neurons in situ are able to respond to a direct thermal stimulus. For example, direct cooling of POA neurons triggers sympathetic nervous system activation of BAT together with an increase of shivering thermogenesis [134, 136, 137], whereas the heat-sensitive neurons are able to increase their activity when locally heated [138]. In parallel, the direct electric stimulation of POA increases BAT activity [139, 140]. Secondly, POA neurons receive information from the thermosensitive peripheral afferent nerves. At a cutaneous level, the TRP family previously introduced can detect both cold (TRPA1 and TRPM8) and heat stimuli (TRPV3 and TRPV4) [141]. These receptors located in the primary somatosensory neurons of the skin detect the temperature variations before spreading the nervous signal to the POA through the spinal cord [142, 143]. In addition to these cutaneous nerve endings, other thermoreceptor afferent nerves located in the abdomen

viscera and in the spinal cord (where somatosensory nerves detect the temperature of internal regions) participate in the thermoregulation process [144]. After being sensed and integrated, the two kinds of afferences—superficial and internal—are transferred through splanchnic and vagus nerves to the CNS. As internal temperatures are less incline to fluctuate than skin-surrounding ones, abdomen viscera and spinal cord afferent signals are primary used in the enhancement of cutaneous thermal information [143]. As mentioned above, POA-located neuronal populations are also susceptible to be modulated by peripheral signals through the decrease of their tonic discharge and the increase of their local thermosensitivity after skin cooling [138]. More specifically, neuronal populations located in the median part of POA (MnPO) were described to integrate cold stimuli originating from the periphery. Thus, due to the neuronal functional specificity and connectivity, the administration of a glutamatergic agonist, *N*-mehyl-D-aspartate (NMDA) within the MnPO induces a cold-defensive response [142] while its injection in the medial POA (MPO) or lateral POA (LPO) does not induce any effect. However, MPO neurons seem to act as downstream effectors of MnPO neurons through direct GABAergic projections from MnPO to MPO [142]. Moreover, neurons in the ventral part of the lateral preoptic area (vLPO) are also required for the warm ambient-evoked inhibition of BAT thermogenesis, mediated in this case by GABAergic inputs from vLPO to the raphe pallidus nucleus (rRPa) [145].

Additionally, POA has a key role on fever regulation. Fever, or pyrexia, is an increase of body temperature set point as response to a potential damage. Usually, under a bacterial or viral infection, the increase in temperature generated by fever provides an optimal environment to the action of immune system as well as a decrease of pathogen survival [146]. In this mechanism, peripheral pyrogens released in the plasma, such as PG, reach central regions, in particular the POA, and trigger the febrile response. The direct administration of PG in the POA stimulates BAT thermogenesis [147]. It has been observed that PGE_2-induced fever is reduced by the phosphodiesterase inhibitor aminophylline and that a decrease in cAMP and cGMP levels in the POA induced fever [148]. Interestingly, within the POA, neurons expressing a subtype of prostaglandin E receptor (EP3) project directly to the DMH and to the rRPa. Those different neuronal populations independently control the febrile responses to the BAT and to the cutaneous vessels (i.e., PGE_2 pyrogenic signalling projections from POA neurons to the DMH activate BAT thermogenesis while POA to rRPa projections increase cutaneous vasoconstriction [149]).

In terms of connectivity, neuronal populations of POA project to other regions such as DMH, rRPa, and VMH [150–152]. Among those, the VMH projections mediate BAT activation after peripheral cooling [150, 151].

The dorsomedial nucleus of the hypothalamus

The DMH is located on both sides of the third ventricle and dorsally from the VMH. Seminal anatomic lesion studies of the DMH have demonstrated its implication in feeding modulation. Interestingly, food intake was inhibited when the area containing the DMH was electrically injured [153, 154]; evidence later confirmed by others [155] [156, 157]. The DMH is also involved in the regulation of BAT thermogenesis. Indeed, chemical stimulations of DMH neuronal populations have been described to modulate BAT thermogenic capacity through the SNS [158]. These stimulations relied on the administration of $GABA_A$ receptor antagonists in the DMH, implying that the DMH receives inhibitory GABAergic projections decreasing BAT activation [158]. Interestingly, those inhibitory afferences originate from GABAergic neurons located in the POA (mentioned above) providing an inhibitory feedback to the sympatho-excitatory neurons of the DMH [159, 160].

Anatomically, the DMH and the BAT seem to be connected by projections through the rRPa and it has been shown that the inhibition of DMH neurons or the blockade of DMH glutamate receptors could revert the cold and febrile activation of the SNS and of the BAT thermogenesis [158, 161]. In addition, the inferior olive (IO) has also been suggested to participate in DMH-BAT connections by hosting neuronal intermediate projections. Recently, it has been described that both leptin and corticotropin-releasing hormone (CRH) could act on DMH neurons, triggering the stimulation of the rRPa and the BAT sympathetic innervation of BAT [162, 163].

A recent study has shown that the expression of NPY in DMH neurons could play an important role in the regulation of BAT thermogenesis. Indeed, a DMH NPY-specific knockdown induced an increase of UCP1 expression in both inguinal white fat and BAT associated to an increase of energy expenditure and to an enhancement of thermogenic response to a cold environment [164].

The paraventricular nucleus of the hypothalamus

The PVH is the most dorsal hypothalamic nucleus and is located on both sides of the top of the third ventricle. PVH is an integrative nucleus that receives projections from ARC neuronal populations, as well as from extrahypothalamic regions such as the nucleus of the solitary tract (NTS) [165, 166]. Lesions in the PVH induce hyperphagia and eventually obesity in animal models [167, 168]. Moreover, it has been described that the PVH was implicated in the modulation of BAT thermogenesis in the febrile response. Indeed, PVH neurons projecting to preganglionic sympathetic cells are activated during fever and lesions in the PVH blunt this process [169, 170]. Pseudorabies retro-infection data also support the

functional implication of PVH in BAT thermogenesis [171–173]. However, the PVH action on BAT activity seems more related to a modulatory role, whereas a direct control remains unclear. In this sense, it has been reported that direct stimulations of PVH do not induce effects on BAT activity [174, 175], whereas the inhibitory projections from the PVH to the rRPa could be implicated in the decrease of the sympathetic activity of the BAT [175, 176].

However, a direct functional connection associating PVH and BAT thermogenesis has been described through several lines of evidence. In this regard, direct administration of glutamate, BDNF, urocortin, CART, PGE2, leptin, and thyroid hormones within the PVH have been shown to activate brown fat thermogenesis [177–183]. The single-minded homolog 1 (Sim1) neuronal population, mostly restricted to the PVH, has also been described to be an important contributor of brown fat regulation. For instance, mice with neuronal ablation of Sim1 display reduced BAT temperature and decreased UCP1 expression suggesting an impairment of thermogenesis [184]. Together with this, the specific leptin receptor (LepRb) deletion in Sim1 neurons induced cold-induced adaptive (non-shivering) thermogenesis disruption with defective cold-induced up-regulation of BAT UCP1 [185]. In contrary, when cannabinoid type 1 (CB1) is specifically knocked out in Sim1 neuronal population, animals develop an increased thermogenesis, based on increased expression of β3-adrenergic receptor and BAT thermogenic markers [186].

The ventromedial nucleus of the hypothalamus

Located just above the arcuate nucleus (ARC), the VMH nucleus was initially described as a centre of satiety as early injury studies induced hyperphagia and obesity in animal models [187, 188]. Nowadays, it is known that VMH has a huge relevance on the energy balance modulation that goes far beyond its only implication on food intake, especially regarding its influence on energy expenditure [4]. The VMH was the first described hypothalamic nucleus to be involved in the regulation of thermogenesis. Its electrical stimulation induced an increase in BAT temperature [189], an effect that disappeared through sympathetic ganglia blockade or sympathetic denervation [190]. Subsequently, VMH-specific injections of glutamate, hydroxybutyrate, norepinephrine, serotonin, and tryptophan activate BAT thermogenesis [178, 191–193]. Genetic evidences, more recently published, also link the VMH to the BAT thermogenesis. In this sense, the specific deletion of steroidogenic factor 1 (SF1) in VMH neuronal populations triggers a decrease in the energy expenditure and in the expression of UCP1 in the BAT [194, 195]. Recently, it has also been shown that the VMH was involved in the thermogenic response of multiple hormonal signals (thyroid hormones, estrogens, BMP8b) [83, 196–199] as well as to pharmacological agents (nicotine, liraglutide) [200–202]. Interestingly, it seems that these mechanisms could be dependent of an inhibition of AMP-activated protein kinase (AMPK) in VMH neurons triggering a sympathetic activation of BAT thermogenesis. Specifically, it seems that AMPKα1 in SF1 neurons could be the molecular entity mediating the SNS-driven BAT thermogenesis [203]. These actions on BAT activity can modulate body temperature and energy expenditure, significantly affecting energy balance and metabolism [204]. The neuron-specific isoform of carnitine palmitoyltransferase 1C (CPT1C) enzyme has also been described to be involved in the AMPK-brown fat axis to regulate thermogenic program in the VMH [205]. The CPT1C knockout mice displayed impaired leptin-induced thermogenesis promoting an early obesogenic phenotype. The genetic activation of AMPK within the VMH of CPT1C knockout mice was unable to activate BAT thermogenesis, indicating that CPT1C was likely an AMPK downstream event. Even if the exact mechanism remains unclear, CPT1C is able to bind malonyl-CoA, suggesting that CPT1C could act as a sensor of this canonical lipid signalling pathway informing on the hypothalamic energy status.

Another mechanism described to be involved in BAT thermogenesis modulation is the lipotoxic action of ceramides within the VMH. Ceramides are a family of sphingolipids involved in several cell functions such as cellular signalling and protection and formation of cell membranes. However, under some metabolic conditions, these lipids trend to accumulate in the VMH, inducing lipotoxicity (toxicity induced by abnormal lipid content) and endoplasmic reticulum (ER) stress, leading to a decrease in the BAT sympathetic tone [206]. The ER stress modulation through the overexpression of the glucose-related protein 78 (GRP78) chaperone in the VMH can restore BAT thermogenesis in animal models inducing feeding-independent weight loss [207–209]. Interestingly, this mechanism is shared by THs and estradiol (E2) to exert their thermogenic actions on BAT [71, 210].

Although the neuronal pathways transmitting information from the VMH to the BAT remain unclear, it has been proposed that glutamatergic projections toward the orexigenic neurons of the LHA could be responsible for mediating the sympathetic activation of brown fat [211]. However, the VMH-BAT connection remains controversial due to the absence of trans-synaptic retro-infection with pseudovirus after BAT inoculations [172, 212]. Nevertheless, indirect evidence have shown how VMH neurons project their axons to different control centers of the autonomic nervous system and to brainstem areas such as RPa and IO, the latter being clearly associated with BAT thermogenic activity [213–215].

The lateral hypothalamic area

The LHA is located laterally to the VMH in the opposite area of the third ventricle. In contrast to the “satiety center”

referring to the VMH, Anand and Brobeck proposed in 1951 the term "feeding center" to firstly describe the LHA [216]. In this study, anatomic lesions in the LHA of rats and cats triggered aphagia and weight loss. Subsequently, it has been shown that LHA was involved in the regulation of hypothalamic-pituitary axes, thirst, glucose homeostasis, sleep-wake cycles, and in the hedonic aspects of food intake [120, 217–221]. In relation to BAT thermogenesis, identification studies using neurotropic virus pseudorabies inoculated in the BAT have found different neuronal populations labeled on the LHA. Immunocytochemical characterization of those populations have identified them in melanin-concentrating hormone (MCH) and orexin (hypocretins) neurons [172], meaning that MCH and orexin neurons from the LHA projected to the BAT. Particularly, it has been described that LHA orexin neurons are involved in fever-induced thermogenesis and in the stress response [222, 223]. Moreover, as previously mentioned, numerous evidences are indicating that VMH axons project to the orexin neurons of the LHA where the overexpression of OXs activates BAT thermogenesis [211]. This VMH-OX neuronal connection is essential for BMP8b induction of BAT activity [211]. In agreement, OX-null mice and knocked-down glutamate vesicular transporter 2 (VGLUT2) do not respond to the thermogenic effect of BMP8b. Overall, the AMPK(VMH)-glutamatergic-OX(LHA)-SNS-BAT pathway appears as a key axis of BAT thermogenesis modulation.

The arcuate nucleus of the hypothalamus

Located on both sides of the third ventricle and immediately dorsal to the median eminence, the ARC is defined by two distinct neuronal populations: those expressing AgRP and NPY and, those expressing POMC and CART [224]. The fundamental role of ARC in the regulation of feeding is deeply established since the late 60s when anatomic-specific ARC lesions were described to induce hyperphagia and obesity phenotype in animal models [225]. However, beyond its role in the control of feeding, the ARC also participates in the regulation of BAT thermogenesis. In this sense, it seems that orexigenic populations inhibit thermogenesis based on the evidence that the partial loss of AgRP neurons induces a sympathetic activation of BAT [226]. The action is apparently mediated by the melanocortin system in the PVH as the MC4R deficiency prevents the thermogenic action of leptin [227]. The thermogenic action of leptin is in turn mediated by its receptors in the ARC where its genetic deletion blunts the mechanism [228]. Together with this, GABAergic RIP-Cre neurons in the ARC contribute to the thermogenic actions of leptin [229]. In this context, ER stress plays an important role in leptin resistance in POMC neurons. ER stress improvement through the overexpression of Mitofusin 2 is associated with an increase in BAT temperature [230]. Moreover, ER stress in AgRP neurons was also recently associated with BAT thermogenesis. In this case, the AgRP-specific deletion of p53 promotes obesity on mice, whereas the overexpression of p53 in the ARC or specifically in AgRP neurons of obese mice attenuated DIO-induced hypothalamic ER stress stimulating BAT thermogenesis and reducing body weight [229, 231].

Central regulation of browning

As described for BAT, WAT receives sympathetic innervation which controls lipolysis and browning. Neuroanatomical knowledge about axonal projections to WAT was firstly established more than 20 years ago [232]. The use of anterograde tracers has allowed to identify sympathetic inputs in the fat pads, exhibiting difference in the postganglionary projections between the inguinal and epididymal fat depots [232]. The sympathetic neuro-adipose junction has been described in vivo as a direct "enveloping" of the terminal nerves by the adipocytes. The functional activation of those sympathetic outputs using optogenetic techniques induced lipolysis in WAT, suggesting the existence of a nervous component modulating WAT functions [233]. Some studies were able to describe an extended autonomic neural axis connecting the fat tissue with central areas, mainly the hypothalamus and POA [171]. Interestingly, labeled viral particles infected downstream of the sympathetic preganglionic neurons were later observed in the medulla (rostroventrolateral medulla (RVLM), rostroventromedial medulla (RVMM), rRPa pallidus, and raphe magnus), as well as in the hypothalamus (PVN, LHA, ARC), the suprachiasmatic nucleus (SCN), the retrochiasmatic area (RCA), and the medial POA. Moreover, it has also been described that neuronal populations located in the regions of the medulla and midbrain including the NTS, area postrema, locus coeruleus (LC), parabrachial nuclei (PBN), and the periaqueductal gray were involved in WAT regulation [234, 235]. Interestingly, it has been described that males had a higher proportion of neurons in the abdominal fat, whereas females exhibited high neuronal proportion in the subcutaneous fat, suggesting that the neural regulation of the different fat depots is sexually dependent and dimorphic [234]. A recent study has also characterized the central neural projections to the beige adipose tissue providing precious information on how the different brain regions were involved in the browning mechanism. Oldfield and colleagues have described how under cold exposure, the central neural circuits in hypothalamic (PVH and LHA) and brainstem (rRPa and LC) regions could reorganized themselves with higher proportions of command neurons projecting to both brown fat and beige WAT. These data provide strong evidences indicating a probable reorganization of the nervous system connectivity following WAT browning [236].

Together with the neurochemical characterization, functional evidences have connected specific brain areas to the WAT browning. NPY-specific knockdown in the DMH promotes the development of brown adipocytes in the inguinal WAT through the local SNS [164]. Accordingly, NPY signalling in DMH is also essential to mediate the MPO browning regulation. Thus, MC4R signalling and hence, the melanocortin system in the MPO were described to modulate WAT metabolism and, possibly, the brown adipocyte development in the inguinal fat depot [237]. Another neuronal population known to be involved in the WAT browning is the PVH. The $p22^{phox}$ genetic ablation in the PVH is associated to an increase of subcutaneous WAT browning in diet-induced obese (DIO) mice [238]. Specifically, this study suggests that NADPH oxidase-derived ROS are associated with the metabolic alterations induced by HFD. As the membrane protein $p22^{phox}$ is an essential factor for NADPH functioning, its deletion reduces NADPH oxidase-dependent oxidative stress in the PVN elevating metabolic activity in subcutaneous WAT during diet-induced obesity [238]. Furthermore, another piece of evidence has shown how CART administration in the PVN induces an increase in the WAT thermogenic marker, UCP2 [181].

As mentioned above, AMPK is the master regulator of many hormonal signals in the VMH. Different studies have shown how thyroid hormones [71], E2 [199], GLP1 [201], uroguanylin [239], and BMP8b [211] could reach the VMH to decrease AMPK phosphorylation to induce WAT browning. The genetic inactivation of AMPK specifically in the VMH prevented the WAT browning effect of these signals. Additionally, an increase of ER stress in the VMH, previously described to induce BAT thermogenesis, could also be associated with white fat browning. In this regard, high-fat diet feeding promotes unfolding protein response in the hypothalamus, a highly conserved pathway which is triggered in response to ER stress. When genetically overexpressed within the VMH, the chaperone GRP78 ameliorates the ER stress leading to the activation of sympathetic β3-AR signalling and to increased WAT browning leading to a weight loss, which is able to revert the obese and metabolic phenotype [208, 209].

Another important area implicated in WAT browning is the ARC. Both leptin and insulin can act directly on POMC neurons to promote white fat browning. This effect is counteracted by tyrosine phosphatases 1B (PTP1B) and tyrosine-protein phosphatase non-receptor type 2 (TCPTP), whose deletions enhance insulin and leptin signalling pathways in POMC neurons increasing WAT browning and energy expenditure [240]. In an analogous way to BAT thermogenesis, ER stress in ARC neurons has also been associated to the browning mechanism. In this regard, the transcription factor X-box-binding protein 1 (Xbp1), a key component of the UPR, has been used to restore ER stress levels in POMC ARC neurons, inducing an increase of WAT browning [241]. Moreover, AgRP neurons, the other neuronal population composing ARC, were also associated to browning modulation. Specifically, the fasting activation of AgRP neurons as well as their chemogenetic activation suppresses the browning of white fat. Interestingly, the O-linked β-*N*-acetylglucosamine (O-GlcNAc) acylation dynamic has been described to play a key role in the modulation of this phenomenon [242]. This protein modification is regulated by the O-GlcNAc transferase (OGT) enzyme which levels are coupled to the feeding status. Thus, under fasting conditions (or ghrelin stimulation), OGT levels and O-GlcNAcylations are increased in AgRP neurons. The ablation of *Ogt* in AgRP neurons inhibits neuronal activity, promotes WAT browning, and protects mice against diet-induced obesity.

Thermogenesis and obesity

The World Health Organization (WHO) estimates that more than 1.9 billion adults are in overweight, and of these, over 650 million are obese. The worldwide prevalence of obesity has nearly tripled in the last 40 years, and among children, has risen dramatically from 4 to 18%, becoming a true pandemic. Obesity is a major risk factor for non-communicable diseases such as cardiovascular diseases (first leading cause of death), diabetes, musculoskeletal disorders, and some types of cancers. Therefore, obesity is responsible for more deaths worldwide than underweight [243]. Recently, many studies have demonstrated that a stimulation of thermogenesis could increase the energy expenditure, favoring lipid and glucose clearance from circulation, and overall having a positive impact in the total energy balance leading to body weight loss [244–246]. Most of these studies have attempted to elucidate the exact molecular mechanisms underlying the peripheral and central control of brown fat thermogenesis in order to discover new therapeutic targets against obesity and related disorders, such as hyperlipidemia, hyperglycemia, hypertension, hepatic steatosis, endothelial dysfunction, etc.

Obesity is the consequence of a positive energy balance due to an increase in food intake exceeding energy expenditure. Undeniably, the obesogenic environment of the current industrialized societies defined by the combination of hypercaloric overnutrition and sedentary habits can explain partially these startling obesity trends. As thermogenesis has the ability to increase energy expenditure using large amounts of glucose and lipids avoiding lipid accumulation in WAT, it has become an attractive target to prevent obesity and its related-metabolic alterations, especially since that BAT was described in human adults [9, 12, 44, 45, 247].

Human data have shown that the thermogenic activity was inversely correlated with the body mass index, being lower in obese than in lean subjects [10, 248, 249]. Many other

evidences have highlighted that BAT thermogenesis and WAT browning were decreased during obesity and overweight, especially in rodent models [207–210]. From a therapeutic point of view, genetic and pharmacological manipulations of molecular targets to activate thermogenesis in BAT and WAT could induce a body weight and adiposity decrease, independently of food intake, associated to an improvement of associated metabolic disorders such as hyperglycemia, insulin resistance, hepatic steatosis, leptin resistance, and hyperlipidemia. However, the current developed drugs known to activate thermogenesis are hampered by non-specific extensive sympathetic activation inducing side effects. Thus, growing research effort has been made by the scientific community to find a way to activate specifically the thermogenesis avoiding the secondary complications. Promising results were obtained targeting upstream hypothalamic molecular actors implicated in the regulation of the thermogenic process. Interestingly, the inactivation, genetically or using pharmacological inhibitors, of AMPK within the VMH had demonstrated effects on increasing BAT thermogenesis and WAT browning through an increase of sympathetic firing resulting in significant body weight loss [71, 77, 83, 199–201, 203, 210, 250]. Furthermore, the hypothalamic reduction of ER stress could also be used as an innovative strategy to reduce body weight, insulin and leptin resistance, hepatic steatosis, and other metabolic disorders, through the activation of SNS to BAT and WAT [207, 208, 210]. Further work will be needed in the coming years to address these questions and finding new question marks. For example, much attention need to be focused on the interrelationship of BAT and WAT physiology with other whole-organism functions, such as how immune cells control thermogenesis, browning, and sympathetic control [251–255]. The role of browning and BAT in cachexia [118] will be also of interest as it will provide not only alternative to cancer patients but also the knowledge of mechanism that can induce negative energy balance to treat obesity.

Conclusion

In summary, the role of BAT (and browned WAT) has change in the last decade from a "residual perspective" to a key organ/tissue that seems critical to understand how energy balance is modulated. Key to our current understanding was the characterization of the different adipocytes cell types (white, brown, and browned). Studies emerging from different groups had contributed to understand the homeostatic regulation of BAT activity pointing to the central nervous system, in particular the hypothalamus, as the main actor. In many studies, the thermogenic activity of BAT and browning was assessed using UCP1 as biomarker. Recent evidences showing the existence of thermogenic activity via a UCP1-independent mechanism highlight the need for additional studies dissecting out the regulatory mechanisms and signaling pathways which can mediate in a specific way canonical vs. non-canonical (UCP1-independent). For many years, the key question in the field was whether the amount of BAT tissue in humans and the browning capacity of WAT was enough to have a relevant impact on human well-being and disease development. Although the issue is not yet fully solved, numerous evidences support its relevance in the development of metabolic maladies, such as obesity and diabetes. Thus, this link has raised a strong interest for its therapeutic intervention. However, some flaws and limitations had also been pointed as well. One of the most often claimed is the likely difference between rodents and humans in terms of functional relevance. Despite of that, current data support its human role showing that there is room for exploration and even for a potential development of new approaches and rational therapies [256]. Data obtained in rodents indicates that chronic AMPK activation protects against high-fat diet-induced obesity through both UCP1 dependent and independent mechanisms. Although some of the therapies used in humans, such as GLP-1-agonists, may act at least in part through a similar mechanism, there is not yet an AMPK-based therapy for obesity. One of the main focus currently is the assessment of nutritional regulation of adaptive thermogenesis as a nutrient-based therapy to improve human health. However, despite the large number of studies reported, there are not conclusive evidences in humans among other reason because of the inherent difficulties to assess BAT-activity and browning. Development of specific biomarkers for monitoring these aspects in humans are eagerly awaited as do the ones related to explain the gender-related differences and the mechanisms involved in the decrease of energy expenditure in aged subjects. The exciting endeavor of understanding BAT physiology has not finished yet and future research will be needed to achieve the required knowledge to combat against obesity.

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