Neuroendocrine Control of Brown Adipocytes: Functions, Beiging, Whitening and Autophagy

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Abstract

Adipose tissue has emerged as a fundamental player in metabolic and energy processes. Beyond its fat storage capacity, it displays adaptive mechanisms to react to metabolic challenges throughout life. Three types of adipocytes, white, brown and beige, share common and yet fundamentally different roles and molecular regulation.

This review focuses on brain and endocrine control of the function and plasticity of brown and beige adipocytes. The involvement of brain circuits controlling brown adipocytes and thermogenesis via the sympathetic nervous system is described. This autonomic control is mainly exerted by the hypothalamus and brainstem, and noradrenaline released from sympathetic efferent postganglionic fibers interacts with brown or beige b3 adrenoreceptors (b3Adr) to trigger a cascade of events favorable to thermogenesis.

Metabolic plasticity in response to environmental or hormonal cues, such as high fat diets, temperature, or hormones and aging, has been identified as a hallmark feature of brown/beige adipocytes. Besides the plastic response of WAT beiging, which is the generation of brown-like adipocytes within white adipose depots, diet-induced obesity and other cues evoke vascular remodeling and functional hypoxia in BAT leading to a whitening phenotype, characterized by mitochondrial dysfunction and loss, lipid droplet accumulation, and decreased thermogenesis. A detailed analysis of the participation of autophagy, and the endocrine signals relied by prolactin and growth hormone uncovers potential avenues of intervention to improve the metabolic function of BAT. Because BAT dysfunction in rodents is linked to fat gain, and glucose and lipid disorders, targeting BAT function and WAT beiging holds promise for obesity prevention and metabolic improvement.

Introduction

Adipose tissue has emerged as a fundamental player in the regulation of metabolic and energetic processes. Beyond its fat storage capacity, it displays adaptive mechanisms or plasticity to react to metabolic challenges throughout life. Three types of adipocytes, white, brown and beige, share common and yet fundamentally different roles and molecular regulation. White adipocytes have a large unilocular lipid compartment, store excess energy as triglycerides, and in times of caloric scarcity release free fatty acids (FFA) to support energy metabolism. In addition, white adipose tissue (WAT) is an endocrine organ which produces and secretes adipokines such as leptin, adiponectin and resistin, among other endocrine signals which participate in the regulation of food intake and energetic metabolism.

Brown adipose tissue (BAT), on the other hand, is composed of adipocytes with numerous small lipid droplets and large number of mitochondria. It provides protection against hypothermia and obesity, due to its capacity to oxidize FFAs and glucose to produce heat, actively participating in thermogenesis. This mechanism relies on the presence of the proton transporter uncoupling protein 1 (UCP1) found in the inner membrane of the adipocyte mitochondria, which uncouples electron transport in the respiratory chain, from ATP synthesis. Several batokines, such as protein peptides, metabolites, or miRNAs have

been identified in BAT, though their action as secreted factors has not been completely settled (Nishio and Saeki, 2020).

Thermogenic brown-like adipocytes named brite/beige adipocytes in rodents and humans are interspersed within WAT, in rodents mainly in the inguinal, but also in other fat depots (Cannon and Nedergaard, 2004;Giordano *et al.*, 2004;Gouon-Evans and Pollard, 2002;Lizcano, 2019). Both brown and beige adipocytes participate in thermoregulatory processes and have been put forward as potential targets in obesity control.

This review focuses on brain and endocrine control of the function and plasticity of brown and beige adipocytes. It has become clear that BAT dysfunction in rodents is linked to obesity, and glucose and lipid disorders. Therefore, understanding BAT physiology and WAT beiging is paramount in obesity prevention and metabolic improvement. On the other hand, it has to be kept in mind that hyperactivation of BAT may be linked to adverse effects in atherosclerosis prone conditions (Dong *et al.*, 2013;Nishio and Saeki, 2020) or in the development of cancer cachexia (Beijer *et al.*, 2012;Petruzzelli and Wagner, 2016) pointing to the necessity of an equilibrium of function for the beneficial effects of BAT activation to override the unfavorable ones.

Bat Location And Function

Location

The fact that BAT is present not only in rodents but also in infantile and adult humans (Cypess *et al.*, 2009;Marken Lichtenbelt *et al.*, 2009;Nishio and Saeki, 2020;Ouellet *et al.*, 2012;Virtanen *et al.*, 2009) has fueled an increasing interest for its role in energy balance regulation.

In rodents, BAT is found mainly in the interscapular and subscapular regions, but also in cervical, axillary, perirenal, and pericardic regions and mammary gland (Cannon and Nedergaard, 2004;Giordano *et al.*, 2004;Gouon-Evans and Pollard, 2002); while in humans, it is mainly located in supraclavicular and cervical regions, but also in paravertebral, mediastinal, pericardial and periadrenal regions (Cannon and Nedergaard, 2004;Lidell *et al.*, 2014;Nishio and Saeki, 2020;Virtanen *et al.*, 2009). BAT is more abundantly found in new born babies, and markedly decreases with age (Ponrartana *et al.*, 2013); nevertheless, some adults have traceable BAT, and in some individuals with very low BAT, cold acclimation induces its mass increase and the related non shivering thermogenesis (Marken Lichtenbelt *et al.*, 2009), suggesting that BAT is recruitable. Adult human BAT contains both brown and beige cells (Wu *et al.*, 2012).

Function

BAT is involved in thermoregulatory processes, including non-shivering cold-induced thermogenesis, diet-induced thermogenesis, and as part of the febrile response (Cannon *et al.*, 1998;Morrison *et al.*, 2012;Nakamura and Morrison, 2011). Thermogenesis is activated in cold environments allowing protection against hypothermia, and depends mainly on the presence of UCP1 (Carre and Binart, 2014).

For this purpose, brown adipocytes utilize fatty acids liberated by intracellular lipolysis which activate UCP1, and consequently lead to heat production (Townsend and Tseng, 2014). Studies in rodents further reveal that cell death-inducing DFFA-like effector A (*Cidea*), peroxisome proliferator activated receptor γ coactivator 1α (*Pgc1a*), CCAAT/enhancer-binding protein alpha (*C/Ebpa*), peroxisome proliferator-activated receptor (*Ppar*), PR/SET Domain 16 (*Prdm16*) and other genes expressed in brown and beige adipocytes, are also critical regulators of BAT activity in response to environmental stimuli (Sharma *et al.*, 2014;Townsend and Tseng, 2014).

The thermogenic capacity of BAT is engaged not only during cold exposure, but also in response to stress or energetically rich diets. Forced immobilization stress (Shibata and Nagasaka, 1982), or psychosocial stress (Kataoka *et al.*, 2014) increase heat production by BAT, effect which relies on the sympathetic innervation of BAT. On the other hand, BAT has also an important role in lipid and glucose regulation (Maliszewska and Kretowski, 2021), and therefore its function is triggered by energetically rich diets (Bachman *et al.*, 2002). Importantly, clearance of 50% of ingested triglycerides and 75% of ingested glucose can be attributed to BAT (Bartelt *et al.*, 2011). In this context, subcutaneous transplant of embryonic BAT reversed type I diabetes in mice (Gunawardana and Piston, 2012). Therefore, considering that transplant of BAT or human pluripotent stem cell derived brown adipocytes (Nishio *et al.*, 2012;Stanford *et al.*, 2013) improve lipid and glucose metabolism in experimental settings, and that energy expenditure is associated to the thermogenic process, targeting BAT function can be envisaged as an anti-obesity strategy.

Brain Control Of Bat Function

The involvement of brain neuronal circuits controlling brown adipocytes and thermogenesis via the sympathetic nervous system (SNS) has been conclusively demonstrated (Bartness *et al.*, 2010;Bartness and Ryu, 2015;Chechi *et al.*, 2013;Labbe *et al.*, 2015). Brain centers, mainly the hypothalamus and brainstem, participate in this autonomic control of BAT (Cannon and Nedergaard, 2004;Labbe *et al.*, 2015) and denervation causes atrophy of BAT and decreased thermogenic capacity.

Brown adipocytes are richly innervated with strong immunopositivity for tyrosine hydroxylase (Murano *et al.*, 2009) and beta adrenoceptors (bAdr), the main receptors involved in BAT thermogenesis, in particular b3Adr (Bartness *et al.*, 2010;Cannon and Nedergaard, 2004). The release of noradrenaline from SNS efferent postganglionic fibers, activates the b3Adr in brown adipocytes and leads to substrate oxidation and heat production (Bachman *et al.*, 2002;Jimenez *et al.*, 2002). The cascade of events is initiated by increased cyclic adenosine monophosphate levels, activation of protein kinase A (PKA), phosphorylation of hormone sensitive lipase, and finally lipolysis of triglycerides into FFA which are energy substrates for beta oxidation in mitochondria, and UCP1 substrates for H + transport across the membrane with the generation of heat in the process (Cannon and Nedergaard, 2004). Simultaneously the number of brown adipocytes increase, there is mitochondrial biogenesis, and thermogenic proteins are upregulated.

Hypothalamic centers participating in BAT thermogenic activity

Using pseudorabies virus as polysynaptic retrograde tracers, brain areas which modulate the sympathetic innervation of BAT and WAT have been delineated. Injection of pseudo rabies virus in BAT mapped the distribution and neurochemical characteristics of viral infected neurons in the hypothalamus, mainly in the para ventricular hypothalamus (PVH), arcuate nucleus (ARC), dorsomedial hypothalamus (DMH), lateral hypothalamus (LH) and preoptic area (POA) (Bamshad *et al.*, 1999;Oldfield *et al.*, 2002;Ryu *et al.*, 2015).

Hypothalamic components of cold activated pathways, which shape the thermoregulatory pathway, mainly include the POA, DMH, the rostral raphe pallidus (rPA) and also VMH and PVH. The **POA** is considered a major coordinator, receiving inputs from the brain and skin thermoreceptors (Morrison *et al.*, 2014;Nakamura and Morrison, 2008;Nakamura and Morrison, 2011). Skin or POA cooling (Imai-Matsumura *et al.*, 1984;Martelli *et al.*, 2014;Osaka, 2004) activates BAT through the SNS. Activated POA neurons relay information mainly in the DMH, preventing GABA inhibition of DMH neurons, and ultimately facilitating thermogenesis (Morrison *et al.*, 2014). Concordantly, desinhibition of DMH neurons using a GABA antagonist increases BAT and body temperature (Zaretskaia *et al.*, 2002). DMH neurons do not directly stimulate BAT, but project to the rPA, which is a main site of BAT SNS premotor neurons, (Nakamura *et al.*, 2005). Desinhibition of DMH neurons, activates glutamatergic descending signaling to the rPA and subsequently sympathetic activity in BAT is increased (Zhang and Bi, 2015). POA also projects to the VMH and PVH, which may participate in the thermogenic response to cold.

Diet induced thermogenesis is a metabolic response for the management of ingested lipid and glucose. It activates energy homeostasis regulatory pathways which include the ARC, POA, DMH, PVH, LH and VMH (Chechi *et al.*, 2013;Richard, 2015;Stefanidis *et al.*, 2014). These hypothalamic centers sense energy balance oscillations and could act independently of the thermoregulatory circuit (POA-DMH-rPa) (Labbe *et al.*, 2015). Melanocortin and endocannabinoid systems, and SF1 neurons of the VMH are key factors in homeostatic regulation of thermogenesis. MC4R neurons are connected to BAT (Song *et al.*, 2008), and injection of melanocortin agonists in the PVH or medial POA (Labbe *et al.*, 2015;Monge-Roffarello *et al.*, 2014;Song *et al.*, 2008) increases BAT thermogenesis and FFA uptake. Furthermore, obese hyperphagic *Pomc*-/- and Mc4rKO mice have decreased thermogenic response to cold exposure indicating that the melanocortin systems is important in cold as well as in diet induced thermogenesis (Butler *et al.*, 2001;Voss-Andreae *et al.*, 2007).

The **DMH** is a key nucleus in thermogenesis. Besides DMH-GABAergic involvement in this process, there is an inverse relationship of NPY expression in the DMH, and BAT thermogenesis. Overexpression of NPY in the DMH leads not only to hyperphagia and obesity, but also to decreased BAT activity and BAT-*Ucp1* expression (Lopez-Vicchi *et al.*, 2020a;Yang *et al.*, 2009). Conversely, DMH-NPY deletion safeguards against high fat diet (HFD)-induced obesity (Chao *et al.*, 2011), in association with increments in BAT

UCP1 as well basal and cold induced thermogenesis (Chao *et al.*, 2011). Furthermore, during cold exposure there is a decrease in DMH-*Npy* expression (Park *et al.*, 2007).

The **VMH** also participates in the SNS control of BAT activity increasing thermogenesis, as indicated by electrical stimulation or lesion of this nucleus (Holt *et al.*, 1987;Monda *et al.*, 1997;Perkins *et al.*, 1981;Yoshida and Bray, 1984). Importantly, deletion of SF1 which is specifically expressed in the VMH evoked a decrease in BAT UCP1 (Kim *et al.*, 2011a). Even though retrograde viral studies did not point to the VMH as a main hypothalamic center in the connection of BAT to the brain (Bamshad *et al.*, 1999), a participation of rPA and the inferior olive has been suggested in VMH modulation of SNS outflow to BAT (Morrison 1999). GLP1 and BMP8R activation of VMH may also mediate the action of VMH on BAT function (Beiroa *et al.*, 2014;Whittle *et al.*, 2012).

Neurons in **ARC, LH and PVN** also serve as important mediators in BAT regulation (Zhang and Bi, 2015). NPY and AGRP in the ARC suppress the sympathetic outflow to BAT, lowering thermogenesis (Ruan *et al.*, 2014;Shi *et al.*, 2013), the PVN being involved in this effect (Shi *et al.*, 2013). Orexin and melanin concentrating hormone (MCH) neurons in the LH are implicated in thermoregulation. MCHKO mice have increased BAT UCP1 levels and energy expenditure (Segal-Lieberman *et al.*, 2003), while orexin null mice have impaired BAT differentiation and activity (Sellayah *et al.*, 2011).

Bat Plasticity

Metabolic plasticity in response to environmental or hormonal cues, such as high fat diets or changes in temperature, or hormones, has been identified as a hallmark feature of brown adipose tissue (Galic *et al.*, 2010). Besides the plastic response of WAT beiging, which is the generation of brown-like adipocytes in white adipose depots, diet-induced obesity in mice evokes vascular remodeling and functional hypoxia in BAT leading to a whitening phenotype, characterized by mitochondrial dysfunction and loss, lipid droplet accumulation, and decreased expression of thermogenic markers (Shimizu *et al.*, 2014b). BAT whitening is associated to decreased thermogenic capacity and impaired energy balance of this tissue, while WAT beiging increases thermogenesis in this depot.

Beiging

Though beiging in rodents is classically studied in subcutaneous depots, it may also occur, depending on mouse strain, in visceral depots such as mesenteric, periaortic, mediastinal or perirrenal depots (Vitali *et al.*, 2012). Brown but not white or beige adipocytes derive from myogenic factor 5 (*Myf5)*-expressing precursors and therefore share a common lineage with skeletal myocytes (Crisan *et al.*, 2008;Kajimura and Saito, 2014). Beige adipocytes, on the other hand, originate from the lineage of *Myf5*-negative cells, and are conceived as inducible or recruitable brown adipocytes within WAT.

Beige adipocytes may derive *de novo* from endothelial and perivascular cells (Lee *et al.*, 2012;Tran *et al.*, 2012), but are mainly originated by transdifferentiation of white *Myf5*-negative adipocytes (Barbatelli *et al.*, 2010). Beiging of WAT is under the control of various key transcription factors, such as PGC-1α,

C/EBPa, PPARg, and PRDM16 (Seale *et al.*, 2009), and the central nervous system is paramount in fat beiging (Bi and Li, 2013;McGlashon *et al.*, 2015).

The recruitment of brown-like adipocytes within subcutaneous depots induced by cold, stress or HFD (Garcia-Ruiz *et al.*, 2015;Kurylowicz and Puzianowska-Kuznicka, 2020;Wu *et al.*, 2012) favors resistance to HFD-induced obesity due to enhanced energy expenditure and increased metabolic rate at the expense of smaller WAT depots (Kajimura *et al.*, 2015) (Kurylowicz and Puzianowska-Kuznicka, 2020), and has therefore garnered particular interest in obesity studies for its calorie burning potential.

SNS and beiging

The central nervous system is key to the development of white fat beiging (Bi and Li, 2013;McGlashon *et al.*, 2015). Experiments using pseudorabies virus as retrograde tracers indicate that descending signals from hypothalamic areas modulate the sympathetic innervation of WAT, and therefore likely participate in beiging (Bamshad *et al.*, 1999).

Several nervous components have been delineated in this process. B adrenergic agonism, driven by cold or drugs, promotes the beiging of white fat. DMH NPY knockdown not only increases BAT thermogenesis but also induces beiging of subcutaneous inguinal fat in rats, and protects from diet induced obesity (Chao *et al.*, 2011). Inactivation of ARC-*AgRP* promotes beiging in retroperitoneal WAT, also protecting mice from diet induced obesity and insulin resistance (Ruan *et al.*, 2014). Similar results were described for the combined action of leptin and insulin on POMC neurons (Dodd *et al.*, 2014). Therefore, both the ARC and DMH participate in WAT beiging, conveying information through the sympathetic neurons, and final activation of adrenergic input in WAT.

Whitening

In contrast to beiging which occurs in WAT, whitening is a phenomenon evidenced mainly in BAT, though it also may occur in beige adipocytes. Physiological inactivation of brown/beige adipose tissues by the whitening process is observed during obesity, aging, lactation, or increased environmental temperature, playing autophagy a central role in this process (Altshuler-Keylin *et al.*, 2016;Bartke *et al.*, 2021;Cairo *et al.*, 2019;Darcy and Tseng, 2019;Gospodarska *et al.*, 2015). The shift from cold to thermoneutral temperature in mice triggers massive loss of protein content in brown and beige adipocytes due to an adaptive decrease in thermogenic activity (Gospodarska *et al.*, 2015). Beige adipocytes within WAT “disappear” when returning to thermoneutrality: they lose their multilocular phenotype and UCP1 expression. Conversely, BAT inactivation includes protein degradation, protein synthesis inhibition, and lipid accumulation, even though brown adipocytes do not disappear. In obese subjects, or HFD-fed rodents, an increase in BAT weight may be found, explained by higher lipid content, and a reduction in the thermogenic function of the tissue. In this sense, heavier BAT depots do not necessarily indicate a greater thermogenic capacity but are associated with a defective tissue, as triglycerides are stored instead of being used for heat production (Shimizu *et al.*, 2014b).

During BAT whitening, cells with multilocular lipid droplets evolve to unilocular cells, resembling white adipocytes. There is a proneness to tissue inflammation and adipocyte death (Kotzbeck *et al.*, 2018). Tissue inflammation leads to macrophage infiltration, and the appearance of crown like structure formations, enlarged endoplasmic reticulum, cholesterol crystals, degenerating or dysfunctional mitochondria, decreased lipid oxidation and increased collagen fibrils (Kotzbeck *et al.*, 2018). Importantly, reduced insulin stimulated glucose uptake by BAT can be found, suggesting insulin resistance of the tissue (Kuipers *et al.*, 2019;Roberts-Toler *et al.*, 2015). A reduced uptake of triglycerides derived from FFA, and marked reduction of thermogenic biomarkers are also key features of whitening. As a result, thermogenesis is compromised and the ability to maintain body temperature when exposed to cold is impaired.

The whitened brown adipocytes still retain some brown like typical mitochondria, and weak UCP1 expression, suggesting a conversion of brown to white in stressful conditions such as lipid overload, or inhibition of oxidation (Cinti, 2009;Giordano *et al.*, 2014). Even so, *de novo* white adipocyte formation, and infiltration of adjacent white adipocytes, usually found in the periphery of BAT lobules, have been suggested as contributing factors.

Multiple causes contribute to the whitening of brown adipocytes, and in some mouse models the phenotype can be even evidenced macroscopically at necropsy. Among these factors are long and short term HFD (Kuipers *et al.*, 2019;Roberts-Toler *et al.*, 2015;Shimizu *et al.*, 2014b), high ambient temperature (Kotzbeck *et al.*, 2018), leptin receptor deficiency (Kotzbeck *et al.*, 2018), impairment of adrenergic signaling (Kotzbeck *et al.*, 2018), lipase deficiency (Kotzbeck *et al.*, 2018), deficient BAT vascularization (Shimizu *et al.*, 2014a), and increased autophagy (Deng *et al.*, 2020).

Genetic ablation or overexpression of different genes yield important information to unravel the participating mechanisms. For example, BAT whitening is found in different transgenic mice such as the adipose triglyceride lipase knockout mouse (*Atgl*-/-) (Kotzbeck *et al.*, 2018), mice lacking beta-adrenergic receptors (beta-less) (Kotzbeck *et al.*, 2018), the obese *db/db* (Kotzbeck *et al.*, 2018), the adipose *Vegf* knockout mouse (Shimizu *et al.*, 2014a), mice with adipocyte specific loss of scaffold protein p62 (Muller *et al.*, 2013), and mice overexpressing the Carbohydrate response element-binding protein b (*Chrebpb)* in BAT tissue (Wei *et al.*, 2020). It can be therefore inferred that adipose *Atgl* expression and its normal lipolytic action are needed to provide fatty acids as initial fuel for thermogenesis, preventing whitening. Furthermore, correct B-adrenergic signaling, and Vegf induced vascularization (Kotzbeck *et al.*, 2018;Shimizu *et al.*, 2014a) are paramount in shaping a healthy brown adipocyte. The scaffold protein p62 is necessary for adequate mitochondrial biogenesis and function (Muller *et al.*, 2013), and adequate levels of Chrebpb (Wei *et al.*, 2020), a key transcription factor regulating *de novo* lipogenesis, prevents whitening (Deng *et al.*, 2020). Finally, in the lacDrdKO mouse which is hyperprolactinemic (Luque *et al.*, 2016), massive whitening and decreased *Ucp1* expression in BAT point to an action of this hormone on BAT plasticity (Lopez-Vicchi *et al.*, 2020b).

The occurrence of whitening in response to exogenous compounds may be involved in their capacity to induce obesity. And therefore the inhibition of this process is a promising target in the treatment or prevention of obesity. For example, glucocorticoids which induce obesity, decrease BAT UCP1 expression and hinder thermogenesis in rodents (Deng *et al.*, 2020;Mousovich-Neto *et al.*, 2019). In humans they acutely increase or chronically suppress BAT activity (Ryu *et al.*, 2015). In this respect, it has been shown that dexamethasone induces BAT whitening *in vivo* and *in vitro* (Deng *et al.*, 2020) decreasing thermogenic markers, and increasing the expression of WAT markers within brown adipocytes. This effect has been related to whitening due to enhanced autophagy, mediated by the antiproliferative gene B cell translocation gene 1 (*Btg1*). Therefore, knocking down either *Btg1* or the autophagy related gene *Atg7* prevented the whitening effect induced by dexamethasone (Deng *et al.*, 2020).

Whitening may also add to the deleterious effects of organic contaminants. Such is the case of Dechloran Plus (DP) a polychlorinated organic molecule, used in cable coating, electrical wires, computer connectors and plastic roofing materials (Zheng *et al.*, 2014), which promotes BAT whitening, reduces UCP1 expression and induces BAT dysfunction (Peshdary *et al.*, 2020).

On the other hand, fenofibrate, an agonist of peroxisome proliferator-activated receptor a (PPARa), countered the whitening induced in BAT by HFD, improving thermogenesis, increasing UCP1, inducing mitochondrial biogenesis, and stimulating the SNS and its downstream effectors (Miranda *et al.*, 2020), positioning the PPARa pathway as a therapeutic target to decrease whitening and enhance BAT function.

Autophagy

The autophagic process. Role of autophagy in BAT physiology

Autophagy is an evolutionary conserved catabolic process through which a cell degrades cytoplasmic substrates (misfolded or aggregated proteins, damaged organelles and intracellular pathogens) by delivering them inside lysosomes. The resulting small molecules are then exported to the cytoplasm and used as energy source or precursors for the synthesis of new macromolecules (Levine and Kroemer, 2008;Mizushima *et al.*, 2008). Adipocytes evidence three types of autophagy: macroautophagy, microautophagy, and chaperone-mediated autophagy (Choi *et al.*, 2013). In macroautophagy, hereafter referred to as “autophagy”, the cytoplasmic cargo is engulfed by a double-membrane vesicle (autophagosome), which fuses to a lysosome to form an autolysosome; this process has been extensively reviewed (Bento *et al.*, 2016).

Autophagy may participate in BAT plasticity dynamically turning on or off, depending on the thermogenic status of adipocytes, in order to respond to different cues, adapting not only intracellular processes (i.e. mitochondrial biogenesis/degradation) but also tissue remodeling (i.e. hypertrophy/hyperplasia) (Gospodarska *et al.*, 2015).

Autophagy and the noradrenergic-dependent regulation of thermogenesis

During thermogenic activation autophagic activity is decreased in brown adipocytes (Altshuler-Keylin *et al.*, 2016;Cairo *et al.*, 2016;Cairo *et al.*, 2019). Both processes are regulated by PKA, which activates the thermogenic program and inhibits autophagy (Altshuler-Keylin *et al.*, 2016;Cairo *et al.*, 2016). Although yet unclear, transcriptional repression of autophagy genes by PKA could be mediated by mTOR, which controls cell growth and metabolism in response to various environmental inputs, and is considered the main repressor of autophagy (Mavrakis *et al.*, 2007). Furthermore, the participation of melanocyte-inducing transcription factor (MITF), forkhead box O3 (FOXO3) (Altshuler-Keylin *et al.*, 2016), and transcription factor EB (TFEB) has also been suggested (Cairo *et al.*, 2016;Lee *et al.*, 2014;Namkoong *et al.*, 2015;Seok *et al.*, 2014). In addition, PKA can inhibit autophagy directly by phosphorylating the autophagy protein LC3 (Cherra, III *et al.*, 2010).

In this context, b3-adrenergic stimulation of brown and beige adipocytes triggers activation of mTORC1 by PKA (Liu *et al.*, 2016), leading to autophagy inhibition. In addition, induction of the thermogenic program upon short-term cold exposure, and expansion of the BAT and beige tissues during long-term cold adaptation require activation of mTORC1 (Labbe *et al.*, 2016;Liu *et al.*, 2016;Shan *et al.*, 2016;Tran *et al.*, 2016). Thus, as both kinases (PKA and mTORC1) are necessary for cold-induced thermogenesis and are also known repressors of autophagy, it is possible that induction of thermogenesis autophagy inhibition are related events.

Autophagy, lipophagy and mitophagy participation in the thermogenic activation of BAT, and WAT beiging

Lipophagy is a specific form of autophagy which consists in the selective removal of lipid droplets in autophagosomes by lysosomes (Singh and Cuervo, 2012;Ward *et al.*, 2016). In brown adipocytes cold exposure regulates lipophagy, and this effect may be dependent on the length of the stimulus. Whereas chronic cold exposure inhibits lipophagy through the cAMP-PKA signaling pathway (Cairo *et al.*, 2016), acute cold exposure activates autophagy-mediated lipid degradation involving the specific surface protein of lipid droplets, adipose triglyceride lipase (ATGL), and LC3 association (Martinez-Lopez *et al.*, 2016). Interestingly, adipose-specific *Atg7* knockout mice evidence white adipocyte beiging (Singh *et al.*, 2009;Zhang *et al.*, 2009), further suggesting that inhibition of autophagy is needed for induction of thermogenesis. Thus, although evidence suggests that lipophagy occurs in brown adipocytes, the main lipid break-down mechanism upon thermogenic activation relies on cytosolic lipases downstream of PKA (Peirce *et al.*, 2014).

Mitophagy, on the other hand, is the process of actively removing excess of mitochondria through during differentiation or in response to increase damage by oxidative stress such as ROS (Ashrafi and Schwarz, 2013;Zhang *et al.*, 2012)(Li *et al.*, 2015;Taylor and Gottlieb, 2017). The association between mitochondria

and autophagosomes is mediated by the ubiquitin-dependent PINK1-Parkin pathway (Bingol and Sheng, 2016;Narendra *et al.*, 2010;Vincow *et al.*, 2013). PTEN-induced putative kinase 1 (PINK1)/Parkin-mediated mitophagy is triggered in response to a drop in the mitochondrial membrane potential (usually a sign of mitochondrial dysfunction (reviewed in (Nguyen *et al.*, 2016;Pickles *et al.*, 2018)).

The PINK1/Parkin system seems to be important for maintaining the mitochondrial pool in thermogenically activated brown/beige adipocytes. Similar to other autophagic proteins, Parkin is induced during brown/beige adipocyte differentiation (in parallel to the increase in the mitochondrial content) and is required to maintain beige adipocytes in WAT (Cairo *et al.*, 2019;Lu *et al.*, 2018a;Taylor and Gottlieb, 2017), but PINK1 undergoes mainly post-transcriptional regulation and its stationary levels are usually very low. Parkin KO mice show enhanced BAT thermogenesis, increased beiging, reduced beige-to-white transition after β-adrenergic stimuli withdrawal (Cairo *et al.*, 2019)(Lu *et al.*, 2018a;Taylor and Gottlieb, 2017), and protection against HFD-induced obesity and obesity-associated metabolic diseases (Cairo *et al.*, 2019;Kim *et al.*, 2011b). Accordingly, overexpression of Parkin significantly impairs beiging in adipocytes (Taylor and Gottlieb, 2017).

The thermogenic activity in BAT, which implies the depolarization of mitochondrial membrane triggered by UCP1-mediated proton conductance (Wikstrom *et al.*, 2014), could influence PINK/Parkin mitophagy. In this sense, acute cold-induced thermogenesis stabilizes PINK1 at the surface of depolarized (but healthy) mitochondria, but strongly represses Parkin at transcriptional level through a PPARa-dependent mechanisms and inhibits its translocation by PKA (Cairo *et al.*, 2019). This mechanism allows active mitochondria to avoid degradation even when physiological depolarization stabilizes PINK1. Nevertheless, and in contrast with the previous affirmations, cultured brown adipocytes with acute thermogenic activation and mice chronically exposed to cold showed increased mitophagy (Lu *et al.*, 2018b). These discrepant results could imply that despite thermogenic stimulation some mitochondria escape the “protective” role of Parkin downregulation, and have unfailingly the destiny to undergo mitophagy.

In general, lowering the expression of adipocyte Parkin or other autophagy mediators, can be envisaged as probable targets in obesity treatment, by preventing mitochondrial degradation and enhancing thermogenesis.

Autophagy and the adaptive inactivation of BAT by whitening

During the plastic process of whitening, autophagy is required for the mitochondrial protein degradation promoting the transition from beige and brown to white adipose tissue. This requirement was evidenced using mice with specific deletion of the autophagic genes *Atg5* and *Atg12* in brown and beige adipocytes, as well as Parkin KO mice, in which whitening was inhibited (Altshuler-Keylin *et al.*, 2016;Lu *et al.*, 2018a).

However, a recent study in mice with adipose tissue-specific ablation of Parkin did not reproduce this observation (Corsa *et al.*, 2019), further pointing to the complexity of the process.

Interestingly, in short-term adaptive inhibition of BAT activity during re-acclimation to a thermoneutral temperature, accumulation of defective mitochondria in BAT was found, while long-term inactivation of BAT elicited normalization in mitochondria degradation probably through Parkin-independent mitophagic mechanisms (Cairo *et al.*, 2019).

In summary, autophagy has a key role in regulating body lipid accumulation by controlling the thermogenic capacity of brown adipocytes, which is enhanced when autophagy or mitophagy is inhibited, allowing the net increase in mitochondrial mass and the consequent enhancement in beta oxidation.

Autophagy in human adipose tissue: a role in the pathophysiology of obesity?

Autophagy is increased in adipocytes from patients with obesity (Jansen *et al.*, 2012;Kovsan *et al.*, 2011;Ost *et al.*, 2010). More precisely, increased levels of transcripts of autophagy-related proteins and autophagosomes in the subcutaneous and, especially, in visceral fat depots of obese patients has been found (Haim *et al.*, 2015;Kosacka *et al.*, 2015;Kovsan *et al.*, 2011), even though some reports failed to reproduce these observations. In this sense, isolated white adipocytes from subcutaneous fat of patients with obesity evidenced less autophagic activity than those isolated from lean subjects (Soussi *et al.*, 2015). These discrepancies might be explained by differences of the cell composition of samples. Analyzing whole-tissue biopsies involves the presence of non-adipocyte cells including infiltrating immune cells with their own autophagy levels, therefore comparison between biopsies and cultured cells are somehow difficult (Koga *et al.*, 2010).

With regard to autophagy and BAT in humans there is yet a need to unravel the differential roles of autophagy in white versus brown/beige adipocytes. The validation of the knowledge obtained in mice require human brown and beige adipose tissue biopsy collection and analysis, and cellular models of human brown (Shamsi and Tseng, 2017) and beige adipocytes (Yeo *et al.*, 2017) have only been recently developed. Recent data found mitophagy occurrence in human masked adipocytes with thermogenic response to adrenergic stimuli, and mature beige adipocytes (Szatmari-Toth *et al.*, 2020). These cells underwent an immediate repression of mitophagy in response to a thermogenic stimulus, suggesting the ability to respond to cold or other browning stimuli by a fast adaptive mechanism.

Nevertheless, the relation of autophagy in brown and beige human adipocytes is far from being resolved.

Endocrine Regulation Of Bat Function

Several homeostatic hormones affect BAT thermogenesis, by acting directly at the tissue or modulating regulatory systems and pathways which intervene in the process.

a) Prolactin

Prolactin is a pituitary-derived hormone whose main function is to facilitate lactation, but that has multiple metabolic roles, associated to the widespread location of its receptors. *Prlr* mRNA has been documented in both white and brown adipocytes (Ling *et al.*, 2003;Royster *et al.*, 1995;Wittmann *et al.*, 2002). In WAT prolactin participates in adipogenesis and adipocyte differentiation (Fleenor *et al.*, 2006;Grattan, 2015), and the net effects are highly dependent on concentration, metabolic state, and species (Carre and Binart, 2014;Lopez-Vicchi *et al.*, 2020a). Furthermore, Prlr are detected in most hypothalamic nuclei involved in brain control of BAT function (Lopez-Vicchi *et al.*, 2020a) suggesting a central as well as a direct tissue action of prolactin in thermogenesis. Furthermore, neurons which encode a prolactin-releasing peptide in the DMH, participate in the thermogenic action attributed to leptin (Dodd *et al.*, 2014).

Prolactin and BAT

Prolactin receptors are key mediators of BAT differentiation, and participate in the thermogenic action of the tissue. Indeed, prolactin actions in this tissue are dependent on the developmental stage of animals. *Prlr-/-* neonate mice have hypotrophic BAT depots, and low levels of UCP1, PPARG2, PGC1a, and b3Adr, making them vulnerable to cold stress. *In vitro*, immortalized *Prlr-/-* preadipocyes have an inadequate differentiation to brown adipocytes, a phenotype which can be reversed by the ectopic expression of *Prlr*, an effect which is partly attributable to the prolactin induction of Insulin like growth factor 2 (Igf2) (Viengchareun *et al.*, 2008). Furthermore, greater *PRLR* abundance in late gestation in fetal sheep is associated with an increase in BAT UCP1 activity (Pearce *et al.*, 2003b); and in rats, prolactin administration during gestation increases BAT UCP1 in late gestation fetuses and neonatal animals (Budge *et al.*, 2002). These data clearly highlight a role for prolactin in the development and differentiation of BAT tissue, probably being involved in the protection of newborns against hypothermia.

Nonetheless, the action of this hormone shifts during lifespan to a negative control of BAT UCP1 expression, in accordance with the different needs for active thermogenesis in newborns and adult animals. Prolactin administration in 35 and 60, but not in 15 day-old female rats, and high prolactin levels induced by metoclopramide treatment in adult rats, reduce BAT UCP1 content (Chan and Swaminathan, 1990;Pearce *et al.*, 2003a). During lactation when prolactin levels are high, the expression levels of thermogenic genes in BAT are decreased in the lactating dams (Chan and Swaminathan, 1990;Krol *et al.*, 2011); and in hamsters BAT weight and activity decreases throughout pregnancy (Wade *et al.*, 1986). These data suggest a negative association between high prolactin and the thermogenic capacity of BAT during pregnancy and lactation, when glucose and triglycerides should not be burned to produce heat because they are needed for the pregnant and lactating mother, and glucose for the developing fetus. Furthermore, lactation performance is influenced by the capacity to dissipate body heat, and prolactin may participate in this process limiting thermogenesis by the downregulation of BAT UCP1 (Krol *et al.*, 2011).

Of note, larger depots of intrascapular BAT related to BW with higher UCP1 content are found in female compared to male rats as adults (Quevedo *et al.*, 1998;Rodriguez *et al.*, 2001), and it has been postulated that this sex difference might arise from sex differences in serum prolactin levels during development (Becu-Villalobos *et al.*, 1992). On the other hand, prolactin-induced UCP1 decrease in female adult rats was not evidenced in male rats (Pearce *et al.*, 2003a).

Prolactin and WAT beiging

Prolactin may also be involved in the process of beiging of WAT. *Prlr-/-* mice have reduced white fat mass, but increased emergence of massive brown like adipocytes which express *Ucp1* and *Pgc1a* in perirenal depots under HFD, indicating that prolactin may decrease beiging favoring obesity (Auffret *et al.*, 2012).

Prolactin and BAT whitening

In accordance with a negative action of prolactin on BAT UCP1, in the hyperprolactinemic lacDrd2KO mouse *Ucp1* mRNA levels were downregulated in BAT and a marked whitening of the tissue was evidenced (Lopez-Vicchi *et al.*, 2020a). Interestingly, prolactin increased NPY in the DMH to favor food intake, and simultaneously this increase may be related to the decrease of BAT *Ucp1*, given the negative correlation of BAT UCP1 and DMH NPY already described.

b) Growth hormone

Growth hormone (GH) action in mammalian species is a major determinant of growth, health span and in some cases longevity. It is well known for its anti-lipogenic and lipolytic effects on adipose tissue. But a diversity of other metabolic effects are exerted by GH, such as inhibition of insulin action in adipose tissue, decrease of glucose uptake, and the promotion of gluconeogenesis in the liver. As a result, in humans with excess GH, such as patients with acromegaly, decreased adiposity can be found, both in visceral and subcutaneous WAT (Berryman and List, 2017;Olarescu and Bollerslev, 2016). On the contrary, humans with GH hyposecretion, such as patients with GH deficiency or insensitivity have increased body fat compared to normal subjects (Beshyah *et al.*, 1995;Laron *et al.*, 2006;Murray *et al.*, 2004).

The GH receptor (GHR), a class 1 cytokine receptor, is expressed in many tissues including brown and white adipocytes, and pre-adipocytes (Vikman *et al.*, 1991;Zou *et al.*, 1997). But even though the effects of GH on WAT have been well studied, its impact on BAT function or in the process of WAT beiging is not yet a settled matter. In particular, there are only few clinical data on BAT activity in patients with acromegaly or GH deficiency. Nevertheless, increasing data using mouse models unravel the intricate and sometimes contradictory role of GH on BAT function and WAT beiging.

GH impact on brown and beige adipocytes

The role of GH on BAT function has been studied using several mouse models. Namely the Ames and Snell dwarfs, the GHRKO, the GHA, the FaGHRKO, and the AdGHRKO mice. The Ames dwarfs harbor a recessive Prophet of Pituitary Factor 1 (Prop1) loss-of-function mutation, and the Snell dwarfs have a point mutation within the Pit1 gene, therefore both mice have deficiencies of GH, thyroid stimulating

hormone and prolactin levels. The GHRHKO mouse harbors a disruption in the GH receptor/GH binding protein gene, and is resistant to the action of GH (Liang *et al.*, 2003). GH receptor antagonist (GHA) transgenic mice express a GH analog which competes with GH for binding to the GHR, thus decreasing, but not entirely eliminating, GH signaling (Coschigano *et al.*, 2003). In addition to studies using these global knockouts, mouse models with tissue specific deletion of GHR have also provided insightful data on the role of GH in BAT function (Li *et al.*, 2020;List *et al.*, 2013;List *et al.*, 2019;Nelson *et al.*, 2018;Ran *et al.*, 2019). The FaGHRKO and the AdGHRKO have a selectively disrupted GHR in adipose tissue using CreLoxP technology, the first model using the adipocyte protein-2 (aP2) promoter driving Cre expression (List *et al.*, 2013), and the second a more specific deletion to adipose tissue, using adiponectin promoter/enhancer to drive Cre expression (List *et al.*, 2019).

GH and BAT

A negative control of GH on BAT mass or function is mostly inferred from mouse studies. In the GHRKO mouse increased BAT mass, *Ucp1* expression, decreased droplet size in brown adipocytes, and increased expression of genes related to mitochondrial function and metabolism have been described (Darcy and Bartke, 2017;Li *et al.*, 2020;Li *et al.*, 2003;Stout *et al.*, 2015). Similar upregulation of *Ucp1* expression in BAT was found in GHA mice (Li *et al.*, 2003), and in Snell and Ames dwarfs (Darcy and Bartke, 2017;Li *et al.*, 2020). In this last model, *Pgc1a PParg*, and *b3Adr* mRNA expression levels were also increased, in correlation with increased metabolic rate, heat production and oxygen consumption (Darcy *et al.*, 2016;Darcy and Bartke, 2017). On the other side, mice overexpressing bovine GH showed decreased or similar BAT *Ucp1* expression (Li *et al.*, 2003;Olsson *et al.*, 2005), as well as decreased expression of transcripts involved in fatty acid oxidation, in particular peroxisomal oxidation (Nelson *et al.*, 2018). In contradiction to the negative role of GH on BAT function suggested by most mouse models with GH excess or deficiency, GH replacement increased BAT *Ucp1* in KK-Ay obese but not in lean mice (Hioki *et al.*, 2004), and pasireotide, a somatostatin analogue, decreased BAT mass in hamsters (Dumbell *et al.*, 2015).

Studies using adipocyte specific deletion of GHR are aimed at teasing apart the exact role of GH acting directly on adipocytes. Increased BAT mass was described in FaGHRKO and AdGHRKO mice (List *et al.*, 2013;List *et al.*, 2019), with no changes in UCP1 expression in the FaGHRKO mouse (Li *et al.*, 2020). On the other hand, a more detailed analysis in the AdGHRKO mouse revealed unchanged BAT mass, but decreased *Ucp1* and *Pgc1a* expression, and lipid droplet accumulation suggesting a whitening of the adipose depot (Ran *et al.*, 2019). The whitening process is sometimes evidenced in heavier BATs, and could explain the former results. Therefore, the lack of total concordance of the global and specific GHR knockouts implies that several other factors altered by global disruption of GH signaling may interact with a direct effect of GH on brown adipocytes.

GH and beiging within WAT

Studies using dwarf mouse models, global GHRKO, and GH overexpressing, as well as adipose tissue specific GHR knockout mice yield conflicting results on GH action on WAT beiging.

Some data favor a positive action of GH on WAT beiging. For example, in transgenic mice in which GH is unable to activate STAT5 (the GHR-391 mouse) a marked deficiency of beta oxidation was described in inguinal WAT, associated to a decrease in beiging transcripts including *Ucp1, Cidea, Pgca1, Ppara, and Prdm16* (Nelson *et al.*, 2018). Besides, in the GHR-391 mouse as well as in GHRKO mice there was a marked decrease in the transcript and protein levels of b3Adr, a receptor required for beiging of inguinal WAT, preventing beiging induced by a beta adrenergic specific agonist in WAT from both mouse models, unlike the robust response found in wildtype mice (Nelson *et al.*, 2018). Furthermore, a transcriptome study comparing WAT of wildtype and GHRKO mice featured a decreased expression of mitochondrial genes in response to the loss of GH signaling, in a divergent manner to the signature found in BAT (Stout *et al.*, 2015). In addition, increased GH action in the bovine GH transgenic mice showed the expected opposite pattern in WAT beiging, there was an increase in transcripts involved in fatty acid oxidation, as well as increments in protein expression of UCP1 and PRDM16 (Nelson *et al.*, 2018). These studies coalesce to demonstrate that intact GH signaling may be supportive to the beiging process in WAT. Nevertheless, opposite data have also been published. In a recent report Ucp1 mRNA and protein expression was increased in WAT of GHRKO compared to wildtype mice (Li *et al.*, 2020), and this finding was replicated in Snell mice (Li *et al.*, 2020). Results showcase the complexity of analyzing different mouse models and assays (transcriptome, protein, mRNA, heat production, etc).

Studies using adipocyte specific deletion of GHR yield concordant results in some though not all aspects of the WAT beiging response to the loss of adipocyte GHR. The FaGHRKO mouse showed decreased expression of genes associated with beige adipocyte differentiation, such as *Ucp1, Prdm16, CYp1b*, and *b3Adr*, in inguinal WAT (Nelson *et al.*, 2018), and similarly in the AdGHRKO mouse there was decreased beiging, adaptive thermogenesis response to cold exposure, and lack of *Ucp1* or *Pgc1a* upregulation by cold (Ran *et al.*, 2019). These data suggest a positive action of adipocyte GHR in WAT beiging, as also described above using the global knockouts. But on the other hand, in FaGHRKO mice an increase in UCP1 in inguinal WAT has been described in males, and not in females (Li *et al.*, 2020), further adding to the controversy of the exact role played by GH on WAT beiging.

Even so, a positive action of GH on WAT beiging, and a negative or restraining effect on BAT thermogenic function is in accordance with whole-genome microarrays which demonstrate divergent response patterns of BAT and WAT to the loss of GH signaling (Stout *et al.*, 2015).

Conclusions

Brain control is fundamental in the function of brown adipose tissue, and specific brain centers within the hypothalamus and brainstem participate in thermogenic and metabolic pathways which activate BAT function and WAT beiging. Furthermore, adequate autophagy promotes a healthy tissue; a decrease in autophagy is generally needed for BAT activation, and impaired authophagy is associated to BAT whitening and dysfunction. Whitening of BAT is a plastic response to stressful conditions such as chronic over nutrition, or increase in environmental temperature, among other stimuli. During this process

BAT weight may be increased, but its thermogenic function decreased, implying that organ weight may not a good readout of thermogenic capacity, and the need of assessing thermogenic markers.

Beiging or browning of white adipocytes within WAT is also a plastic response which opposes adipose accretion, by enhancing thermogenesis. This reveals an outstanding reaction of the organism to combat obesity by enhancing energy dissipation in an energy storing depot. Therefore, efforts have been channeled into the development of genetic or pharmacological tools to improve the recruitment of beiging in WAT, in an attempt to ameliorate overweight.

Finally, several endocrine mediators are involved in BAT control, such as leptin, insulin, prolactin and GH. In the present review, we focused on GH and prolactin actions, and, overall, chronic high prolactin levels are associated with BAT whitening, and loss of function, while GH has a negative action on BAT thermogenesis. Nevertheless, several contradictory data have been published which hints the use of caution when forwarding a hypothesis, as endocrine control of BAT may differ among species, transgenic mouse models, and metabolic status.

Since the description of an active and recruitable brown adipose tissue in humans, increasing interest in its physiology and pathology has positioned this tissue in a new hierarchy, as a possible target to tackle metabolic dysfunction. Within the genetic causes to obesity predisposition, UCP1 polymorphisms have been pointed (Murray *et al.*, 2004), as UCP1 has a secondary fat and calorie burning capacity which provides a useful advantage in a high calorie nutritional environment. BAT has turned out to be more dynamic and complex than once thought. Therefore unraveling the complexities of brown adipocytes may yield valuable tools in the effort to curtail obesity or accelerate weight loss.

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