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Switching on the furnace: Regulation of heat production in brown adipose tissue

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ABSTRACT

Endothermy requires a source of endogenous heat production. In birds, this is derived primarily from shivering, but in mammals it is mostly non-shivering thermogenesis (NST). Brown adipose tissue (BAT) is a specialized tissue found in Eutherian mammals that is the source of most NST. Heat production in BAT depends primarily on the activity of uncoupling protein 1 (UCP1), which decouples transport of protons across the inner mitochondrial membrane from synthesis of ATP. UCP1 and hence heat production of BAT is regulated by many factors. In this paper we discuss the main factors activating UCP1 and increasing heat production. Probably the most well-known activator is the catecholamine norepinephrine (NE) which is released from sympathetic nerve endings and binds to adrenergic receptors that are abundantly expressed on BAT. NE stimulates release of free-fatty acids. It was previously thought that such FFAs were essential for activation of UCP1. However recent work has suggested intracellular lipolysis is not essential and FFAs can be derived from extracellular sources. Thyroid hormones also exert impacts on metabolic rate via effects on brown adipocytes which express type 2 deiodinase. Knocking out DIO2 makes mice cold intolerant. Parathyroid hormone appears to also be a potent regulator of BAT activity and may be an important mediator of elevated expenditure during cancer cachexia, although this is disputed by observations that cachexia wasting is not blunted in UCP1 KO mice. Cardiac natriuretic peptides have also been implicated in regulating BAT thermogenesis and the interconversion of beige adipocytes from their white to brown form. Activation of BAT thermogenesis may be an important component of the post-ingestion rise in heat production. Recent work suggests the gut derived hormone secretin may play a key role in this effect, directly linking BAT activation to the alimentary tract. Not only gut hormones but also metabolites derived from gut microbiota such as butyrate may be an important activator of BAT during cold exposure. Additional regulatory factors include bone morphogenic proteins, fibroblast growth factor 21, Vascular endothelial growth factors and transient receptor potential vanilloid receptors which are important components of thermal sensing and hence how brown adipose tissue responds to the cold. In the future the main challenge is to understand how these regulatory factors combine with each other and with inhibitory factors to control heat production from BAT, and what their relative importance is in differing circumstances. Knocking out UCP1 has revealed other sources of heat production in BAT including creatine-dependent cycles and a futile cycle of Ca^{2+} shuttling into and out of the endoplasmic reticulum via the SERCA and ryanodine receptors.

1. Introduction

The evolution of endothermy, primarily restricted to the birds and mammals, required the ability to generate endogenous heat independent of the environment. Such heat generation allows endothermic animals to sustain a relatively stable body temperature (homeothermy) independent of changes in environmental temperature, and other drivers of heat loss. Ectothermic animals can also sustain

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homeothermy for prolonged periods, but they do this primarily by managing their heat uptake and heat loss. Hence when deprived of a source of external heat (like solar radiation) their body temperatures decline towards, and track, the ambient temperature. Gigantic dinosaurs may have been functionally homeothermic because their large size led to thermal inertia, even if they were not endotherms (Gillooly et al., 2006). Birds and mammals found different evolutionary solutions to the problem of how to generate endogenous heat that supports their endothermy (Mezentseva et al., 2008; Gaudry et al 2018, 2019). Birds primarily generate heat for thermoregulation by shivering – asymmetrical contractions of skeletal muscle that produce heat but not work (Hohtola, 1981). Mammals can also shiver to produce heat and tend to do so as an immediate response to unanticipated acute cold exposure. However, it was discovered almost 70 years ago that this shivering phase in many Eutherian mammals, following acute cold exposure, is relatively short lived. Thereafter they appear able to sustain their body temperature without shivering, and so must have a source of heat production independent of shivering that was called 'non-shivering thermogenesis' or NST.

The source of this NST appears to involve a large amount of heat generated by a specialized tissue called brown adipose tissue (BAT) that is absent in birds (and ectotherms). BAT was first described in marmots (*Marmota marmota*) in the 16th century (Gesner, 1551) and is found in large deposits particularly in smaller mammals where the energy demands of thermoregulation are relatively high because of their unfavorable surface to volume ratio (Cannon and Nedergaard, 2004). Hibernating animals like the marmot have particularly large depots of BAT and it has been called as a result the 'hibernating organ' (Smith, 1964; Smith and Hock, 1963). Large depots of BAT in hibernators may appear paradoxical because during hibernation these animals regulate their body temperatures at levels barely above ambient and hence require minimal thermogenic heat production (e.g. Humphries et al., 2002). However, most small hibernating mammals oscillate between torpid periods, when regulating their body temperature near to ambient, and 'arousal' bouts where their body temperature returns for a short period (less than 24 h) to the normal euthermic level (Lee et al., 2009; Barnes and Buck, 2000). Moving between these states where body temperature rises by over 30 °C in a period of tens of minutes requires prodigious amounts of heat production, which thermal imaging cameras clearly demonstrate originates mostly in the large subscapular BAT depots (Fig. 1).

Although shivering is a primary response to unanticipated cold exposure, animals in the wild can largely anticipate when their exposure to cold conditions is more likely, because of the progression of the seasons. Many studies have shown that capacity for NST in small temperate and arctic zone rodents is increased during winter (Feist and Rosenmann, 1976; Jansky, 1973; Rosenmann et al., 1975). Hypertrophy of BAT, elevated NST capacity and elevated basal metabolism occurs in response to a suite of environmental stimuli including reduced temperatures (Ashwell et al., 1983; Cannon and Nedergaard, 1983; Girardier, 1983; Heldmaier and Buchberger, 1985; Himms-Hagen, 1986; Lean et al., 1983; McDevitt and Speakman, 1994a; Trayhurn et al., 1987) a reduction in photoperiod (Haim, 1982; Haim and Yahav, 1982; Heldmaier et al., 1981, 1989) or a combination of both (Klaus et al., 1988; Klingenspor et al., 1989). Increased photoperiod, however, seems to an insufficient stimulus to de-acclimate animals from cold acclimation (McDevitt and Speakman, 1994b).

BAT is also highly abundant in neonates that must navigate the transition from living inside the highly regulated thermal environment of the uterus to the harsh thermal reality of the outside world, over a relatively short period. Switching on NST prior to birth would potentially lead to overheating within the uterus, yet delaying it would potentially lead to fatal hyperthermia after birth. Vaginal birth appears key to appropriately timed activation of BAT in the neonate since in sheep (*Ovis aeries*) offspring born by Caesarian section have reduced capacity for thermoregulation (Clarke et al., 1997). Neonates of many larger animals, including humans (Heaton, 1972) have abundant BAT deposits that wane but do not entirely disappear, as the animals mature. Humans conform to this model and the fact that many adult humans possess active BAT was shown using fluorodeoxyglucose positron emission tomography (FDG-PET) (Nedergaard et al., 2007). Subsequently many other studies confirmed this observation with more detailed examination combined biopsy with immunohistological inspection and RNA-sequencing (Au-Yong et al., 2009; Cypess et al., 2009; Sacks, 2009; Saito et al., 2009; van Marken Lichtenbelt et al., 2009; Virtanen et al., 2009; Zingaretti et al., 2009).

Whether these residual deposits of BAT in adult humans contribute significantly to whole body thermogenesis is debated and has been reviewed by (Fernandez-Verdejo, 2019; Marlatt et al., 2018). Another issue is whether these stores can be induced by dietary over-consumption of calories and thereby are an adaptive mechanism limiting excess fat deposition (Rothwell and Stock, 1979). The fact that individuals with higher body mass index (BMI) tend to have lower levels of BAT may indicate that BAT prevents fat gain (Cypess et al., 2009; Saito et al., 2009; van Marken Lichtenbelt et al., 2009; Yoneshiro et al., 2011), but this relationship may equally be because fatter individuals have greater insulation and thus less need for thermoregulatory heat production (Speakman, 2018). Recent work using a panel of 29 different diets that varied in macronutrient composition showed no evidence that excess adiposity can be counteracted by stimulated metabolism in mice (Hu et al., 2018), that have substantially more BAT than adult humans. Moreover, in humans, there is no relationship between levels of obesity and latitude (Speakman and Heidari-Bakavoli, 2016) which would be anticipated if seasonally cold stimulated BAT activity (Saito et al., 2009) defends against fat gain.

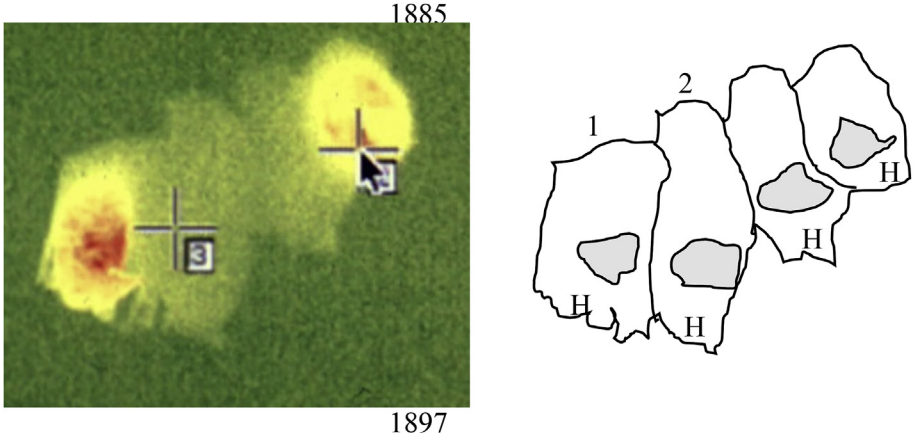

Fig. 1. Four little brown bats (*Myotis lucifugus*) in hibernation captured with a thermal imaging camera. Schematic diagram of the bats is shown to the right. With H denoting the location of the head of each bat. Approximate locations of the interscapular areas are indicated by a grey shaded area. Bats 1 and 4 are in the process of arousal. The false-colour thermograph clearly shows the greater heat production in the interscapular area above the brown adipose tissue. The targets 2 and 3 refer to the sites where surface temperatures were measured. The temperature at location 3 was 8.7 °C and at location 2 was 12.9 °C. Cave wall temperature was 6.9 °C (image with permission from TH Kunz). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

1.1. Mechanisms of heat production in NST

BAT generates NST via a mechanism involving a unique protein on the inner membrane of its mitochondria (Ricquier and Kader, 1976). Called uncoupling protein 1 (UCP1), this protein facilitates protons, pumped into the intermembrane space by the actions of the cytochrome system (complexes 1 to 4), to travel back to the mitochondrial matrix releasing their chemiosmotic potential directly as heat. Normally, such protons travel back to the matrix via cytochrome complex 5 and their chemiosmotic potential is harnessed to synthesize adenosine tri-phosphate (ATP) (Cannon and Nedergaard, 2004). Hence, BAT utilizes engineered mitochondrial inefficiency to generate heat. The mechanism by which UCP1 transports protons across the inner-membrane was unclear until 2012, when it was shown using the mitochondrial patch clamp method to measure the proton currents that UCP1 is a long-chain fatty acid (LCFA) anion/H ($^+$) symporter (Fedorenko et al., 2012).

BAT can be readily distinguished from white adipose tissue (WAT) because it is highly vascularized and consists predominantly of brown adipocytes with relatively small lipid droplets and cytoplasm packed with mitochondria, which give it a distinctive brown appearance, from which it gets its name. This distinction has been blurred more recently by the discovery of cells able to display both white and brown phenotypes, variously called brown-in-white, or 'brite' adipocytes, or alternatively 'beige' adipocytes, that in some circumstances can give WAT a brown-like appearance (Petrovic et al., 2010; Wu et al., 2012). Nevertheless, BAT, consisting mostly of classic brown adipocytes has been anatomically identified in subcutaneous, intraperitoneal and intrathoracic areas in both humans and small rodents (Heaton, 1972; Sacks and Symonds, 2013). Subcutaneous BAT has been suggested to serve as a 'warming vest' to maintain core body temperature in human and rodents and is located in interscapular, subscapular, suprascapular and axillary areas. Intraperitoneal BAT, in contrast, is mainly located in the perirenal and ventral spinal region, and intrathoracic BAT is found around large mediastinal blood vessels, heart, trachea and descending aorta areas (Frontini and Cinti, 2010). Among these brown fat depots, interscapular BAT (iBAT) is generally the largest depot in rodents and has been the most well-studied. Whether other brown fat depots are functionally equivalent to iBAT remains understudied.

Activated BAT leads to enhanced energy expenditure and is associated with improved glucose tolerance in rodents and humans (Weir et al., 2018), highlighting the importance of understanding the factors that regulate brown adipocyte thermogenesis. Compared to WAT in transcriptome analysis, BAT has been identified to have a myogenic gene expression signature (Timmons et al., 2007). Later, the lineage tracing method via CRE-dependent recombination revealed that classic interscapular brown adipocytes arose from a Myf5$^+$/Pax 7$^+$ skeletal muscle stem cell origin (Lepper and Fan, 2010; Seale et al., 2008). Although recent studies suggested that Myf5$^+$ is a body location marker rather than a marker of a specific cell lineage (Berry et al., 2016; Sanchez-Gurmaches and Guertin, 2014). It was well-recognized brown adipocytes are distinct to white adipocytes in morphology, cellular lineage, and transcriptional pattern. Adipogenesis is tightly regulated by two key transcriptional factors: peroxisome proliferator-activated receptor γ (PPARγ) (Tontonoz et al., 1994a, 1994b) and CCAAT-enhancer-binding protein α (C/EBPα) (Rosen et al., 2002). Brown fat transcriptional factor screening using RNA-seq indicated that the zinc finger protein, PR domain-containing 16 (PRDM16), specifically activated brown adipocytes adipogenesis (Seale et al., 2007). PRDM16 forms a transcriptional complex with C/EBPβ to control the cell fate switch in brown adipocytes (Kajimura et al., 2009). The sympathetic neurite density is also regulated by PRDM16 in adipocytes. Mice with an adipocyte specific deletion of PRDM16 have a significant reduction in sympathetic neurite density, suggesting that adipocytes can interact with neurons to modulate neurite density. This interaction may be mediated by factors secreted from adipocytes that signal to nerve endings (Chi et al., 2018). Chromatin immunoprecipitation analysis combined sequencing (ChIP-seq) suggested that early B cell factor-2 (*Ebf2*) regulates PPARγ binding activity to determine brown versus white adipocyte identity (Rajakumari et al., 2013).

More recently, it has been demonstrated that a unique lineage of cells, called 'brown in white (brite)' adipocytes or 'beige' adipocytes have the capacity to show both brown and white adipocyte phenotypes under different conditions (Vitali et al., 2012). Emerging evidence demonstrated that these bi-potent beige/brite adipocytes are highly heterogeneous. It has been previously suspected that white adipose progenitor cells arise from smooth muscle cell (SMC) since there is a positive correlation between the proliferated adipocytes and blood vessels (Cinti et al., 1984; Fukumura et al., 2003). SMCs could subdivide into three populations based on their heterogeneity: vascular SMCs, smooth muscle-like cells (e.g., myoepithelial cells) and non-SMCs (e.g., pericytes). It has been indicated that Myh11$^+$ (Long et al., 2014) and a-SMA$^+$ (Berry et al., 2016; Jiang et al., 2014) vascular SMC lineage can give rise to beige/brite adipocytes. Mammary Krt14$^+$ myoepithelial cells also have the potential to demonstrate a beige/brite adipocyte phenotype under special circumstance (Li et al., 2017b). It is also important to note that a portion of beige/brite adipocytes contains pericyte marker platelet-derived growth factor receptor alpha (PDGFR-α) (Berry and Rodeheffer, 2013; Lee et al., 2012) or PDGFR-β (Vishvanath et al., 2016). These PDGFR-a$^+$ and PDGFR-β$^+$ cells have beige/brite adipocyte potential with robust expression of UCP1 upon stimulation by cold ambient temperature or CL-316243, a selective β3-adrenoceptor (*Adrb3*) agonist, and contribute to the beige adipocytes induced by high-fat diet. Although both cold ambient temperature stimulation and β3 agonist activate thermogenesis in brown and beige/brite adipocytes and induce UCP1 expression, these methods are commonly used to stimulate adipose tissue browning, but the underpinning cellular mechanism is distinct. The latest studies showed that cold challenge requires the β1-adrenoceptor (*Adrb1*) to promote the formation of new beige adipocytes, while the β3-adrenoceptor (*Adrb3*) recruits beige adipocytes via converting mature white adipocytes (Jiang et al., 2017). The heterogeneity of beige/brite adipocytes also affected by age. In the a-SMA$^+$ lineage tracing model, the adult adipocytes show a-SMA$^+$ origin and developmental stage adipocytes do not. More interestingly, it was suggested there is an essential role for PPARγ and C/EBPα in adipogenesis *in vitro*, C/EBPα is only required for adipogenesis at the adult stage and completely unnecessary during the developmental stages in mice (Wang et al., 2015).

BAT thermogenesis has been shown to depend on a variety of regulatory factors. The main goal of this review is to summarise these factors involved in 'switching on the furnace' and to highlight other heat producing mechanisms independent of UCP1 that may contribute to its capacity to generate heat. The coverage is not 100% complete but includes the most important and wellknown factors.

2. Thermogenic effectors

2.1. Catecholamines

Norepinephrine (NE), which belongs to the catecholamine family, is released from activated sympathetic nerve terminals to trigger a signal transduction cascade and promote the expression of thermogenic genes through the adrenergic receptors on the brown adipocyte surface (Arch et al., 1984; Collins, 2011). In addition, orally administered Myrbetriq, a FDA approved β3-adrenoceptor agonist for treating overactive bladder syndrome, elevates resting metabolic rate (RMR) and increases ^{18}F-FDG uptake indicating enhanced BAT thermogenesis in humans (Cypess et al., 2015). NE and its analogs activate the canonical adenylyl cyclase (AC)–cyclic adenosine monophosphate (cAMP)–protein kinase A (PKA) pathway and then promote the release of free fatty acids (FFAs). The activated adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) catalyze the first two key steps of triglyceride (TG) hydrolysis in lipolysis. The activation of UCP1 and maximal

mitochondrial oxidation require highly mobilized fatty acids in brown and beige/brite adipocytes upon cold temperature stimulation. The standard model suggested that FFAs from BAT lipolysis are essential for UCP1 dependent thermogenesis (Li et al., 2014). However, recently two groups simultaneously reported that BAT does not require intracellular lipolysis, and external FFAs from WAT or muscle can act as the metabolic substrate (Schreiber et al., 2017; Shin et al., 2017). These studies provide a novel insight for FFA mediated cold-induced thermogenesis and activation of UCP1 (Cannon and Nedergaard, 2017). Although the intracellular lipolysis is dispensable in BAT, an extracellular energy source is absolutely essential for prolonged thermogenesis, because BAT only occupies a small portion of body weight and the stored lipid droplets cannot support thermogenesis over a protracted period (Cannon and Nedergaard, 2017). Transmembrane receptor platelet glycoprotein 4 (CD36) and fatty acid transport proteins (FATPs) deliver circulating FFAs into brown adipocytes. Inefficient transportation of FFAs in mice lacking CD36 leads to hypothermia under cold exposure (Febbraio et al., 1999; Hajri et al., 2002; Laugerette et al., 2005; Putri et al., 2015). More importantly, the activation of BAT thermogenesis could control TG clearance in humans with obesity (Bartelt et al., 2011). In rodents and adult humans, BAT also efficiently utilizes glucose (Bartelt et al., 2011; Cawthorne, 1989; Cypess et al., 2009; van Marken Lichtenbelt et al., 2009). Although emerging evidence suggests that beige/brite adipocytes also sustain thermogenesis via combusting glucose and fatty acids (Zhang et al., 2018), there is a strong preference difference between brown fat and beige/brite fat for these substrates. Energy substrates are sequestered into BAT at a high priority to maintain thermoregulatory functions under normal circumstances and in some cases such as developmental deficiency in brown fat (Schulz et al., 2013) or losing UCP1 (Ikeda et al., 2017) compensatory changes for the priority of these substrates transfers to beige fat. These characters together reinforce the potential capacity of BAT for combating the metabolic syndrome (Nedergaard et al., 2011).

2.2. Thyroid hormones

Thyroid hormones contribute to BAT thermogenesis and affect energy balance in rodents and humans. Abundantly expressed type2 deiodinase (*Dio2*) in brown fat converts thyroxine (T4) into the active thyroid hormone triiodothyronine (T3). T3 promotes the expression of thermogenic genes including peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), the master transcriptional coactivator of mitochondrial biogenesis in brown fat depots (Puigserver and Spiegelman, 2003). *Dio2* knockout mice are intolerant to cold stimulation, suggesting an essential role of thyroid hormones for adaptive BAT thermogenesis (de Jesus et al., 2001). Thyroid hormone also induces NST in humans (Skarulis et al., 2010). Although direct T4 treatment enhances BAT thermogenesis and increases body temperature in mice kept at 30 °C, the activity of UCP1 is not required for this action, suggesting that thyriod hormone additionally mediates UCP1-independent thermogenesis (Dittner et al., 2019). However, the significance of studies performed in mice at 30 °C for translation to humans has been questioned (Speakman and Keijer, 2013; Speakman, 2013; Keijer et al., 2019).

2.3. Parathyroid hormone

Beyond the regulation of bone development and serum calcium, an important role for the parathyroid hormone (PTH) and paracrine ligand PTH-related protein (PTHrP) in modulating lipolysis and thermogenesis has emerged. The lipolysis effect of PTH/PTHrP was first reported in 1973 (Werner and Low, 1973). More recent studies reported that cancer cachexia could cause severely lipoatrophy, increased energy expenditure and activated BAT in rodents and some types of patient (Bianchi et al., 1989; Petruzzelli et al., 2014; Shellock et al., 1986). Moreover, both cancer cachexia and chronic kidney disease involved the release of substantial PTHrP as the key regulator mediating lipoatrophy and activated thermogenesis (Kir et al., 2014). Adipocyte-specific depletion of PTHR blunted the fat wasting and thermogenic effects (Kir et al., 2016). However, UCP1-dependent thermogenesis is dispensable in cachexia derived fat wasting (Rohm et al., 2016), suggesting that PTH/PTHrP are mostly acting as pro-lipolytic factors during cachexia.

2.4. Natriuretic peptides

The cardiac natriuretic peptides are heart hormones for regulating expanded extracellular fluid and responding to blood pressure. Atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) have been implicated in regulation of BAT thermogenesis and browning of WAT (Bordicchia et al., 2012). ANP and BNP are mainly secreted from cardiomyocytes (de Bold et al., 1981; Mukoyama et al., 1991; Sudoh et al., 1988) and they bind natriuretic peptide receptors (NPRs) and stimulate intracellular guanosine 3′,5′-cyclic monophosphate (cGMP) levels. NPRs are widely expressed in multiple tissues, including adipose tissue (Jeandel et al., 1989), heart, brain, bone and others. The ANP/BNP activate guanylyl cyclase (GC)-cGMP- protein kinase G (PKG) pathway, similar to the AC-cAMP-PKA pathway, leading to lipolysis in adipocytes via the phosphorylation of HSL (Sengenes et al., 2003). Cold temperature stimulation increases circulating ANP/BNP and the expression of NPRs in BAT. ANP/BNP activate the p38-MAPK pathway (Bordicchia et al., 2012) and the mammalian target of rapamycin complex 1 (mTORC1) (Liu et al., 2018). More importantly, the ANP/BNP induced UCP1 activation demonstrates involvement of the heart in regulation of BAT thermogenesis, in an adrenergic signal independent manner (Whittle and Vidal-Puig, 2012).

2.5. Gut hormones and microbiome-derived metabolites

Following ingestion of a meal, there is a rise in heat production, called diet-induced thermogenesis (DIT), which leads to an increase in body temperature. This latter increase has been hypothesized as a primary signal of satiation switching off food intake. DIT has been recently associated with secretin (Li et al., 2018a), a hormone released from the gut that is synthesized in the duodenum and proximal jejunum by enteroendocrine S cells (Braun et al., 2018). Secretin receptor (SCTR) is the highest expressed gut hormone receptor in rodent BAT. Differentiated brown adipocytes also demonstrated much higher SCTR expression compared to undifferentiated stromal vascular cells (SVF). A single injection of secretin induced significant heat production in wild-type mice, but not UCP1 knockout mice. It was also shown that secretin-mediated satiation requires UCP1 expression, validating the suggested role of DIT in the process of satiation. This secretin phenotype was also confirmed in a human cohort, which highlights the role of secretin in Gut-BAT-Brain axis regulated diet-induced thermogenesis (Fig. 2).

Glucagon-like peptide-1 (GLP-1) is also a mediator of DIT. It is secreted postprandially from the ileum to modulate glucose-induced insulin release. In addition to its role in insulin secretion, emerging evidence suggested that GLP-1 regulates BAT thermogenesis and glycemia clearance via the CNS (Kooijman et al., 2015; Lockie et al., 2012). GLP-1 receptor (GLP-1R) is widely distributed in the brain especially in the hypothalamus which dominates food intake regulation and energy balance. Central administration of GLP-1, or liraglutide, a FDA approved GLP-1 analogue for treating type2 diabetes and obesity, increases the sympathetic output to BAT, boosts BAT thermogenesis and promotes WAT browning in mice. Several studies have indicated that the activation of GLP-1R in the hypothalamic ventromedial nucleus (VMH) (Beiroa et al., 2014; Lopez et al., 2015) or the dorsomedial hypothalamus (DMH) (Lee et al., 2018b) mediates the central GLP-1 effect on BAT thermogenesis.

Serotonin (5-HT) is a neurotransmitter found throughout the CNS and several peripheral tissues where it regulates behavior and many

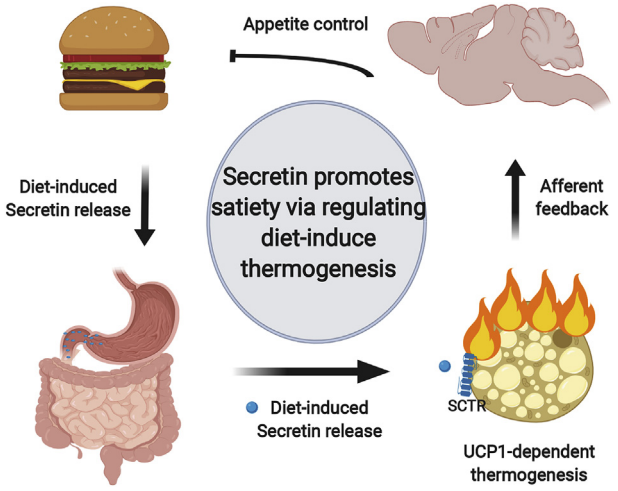

Fig. 2. Schematic diagram for secretin-mediated satiety via a Gut-BAT-Brain axis in mice. Li et al., (2019) identified that the circulating gut hormone secretin through secretin receptor (SCTR) on brown adipocytes mediates diet-induced BAT thermogenesis, elevates energy expenditure and promotes satiety sequence in both mouse and human. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

physiological processes including energy and glucose homeostasis. 5-HT is synthesized from dietary l-trytophan in a two-step enzymatic reaction including tryptophan hydroxylases (TPHs) (Walther and Bader, 2003). Since 5-HT has minimal capacity to cross the blood-brain barrier, two 5-HT pools separately exert 5-HT functions in mammals (Berger et al., 2009). Central 5-HT is produced by raphe neurons in hindbrain. Peripheral 5-HT is mainly produced in intestinal enterochromaffin cells and stored in the circulating platelets (Gershon, 2013). 5-HT can also be secreted locally in enteric neurons, pancreatic cells, and adipose tissue. Delineation of 5-HT signaling is extremely difficult because it involves a large number of receptors (17 in humans and 14 in mice) (Wyler et al., 2017). However, several 5-HT pathways have been reported to regulate BAT thermogenesis, and centrally control body temperature. Pharmacological stimulation of central 5-HT release increases the sympathetic output to BAT and promotes BAT thermogenesis (Madden and Morrison, 2006; Morrison, 2016). The transcriptional factor *Pet-1* is specifically required across different stages of life to regulate serotonergic function (Liu et al., 2010). Selective deletion of *Pet-1* neurons in $DTR^{f/f}ePet1^{Cre}$ mice with treatment of diphtheria toxin (DT) impairs BAT thermogenesis and causes BAT steatosis (Cerpa et al., 2014; McGlashon et al., 2015). Unlike central 5-HT, peripheral 5-HT appears to inhibit thermogenesis. Pharmacological or genetical inhibition of peripheral 5-HT synthesis decreased adipose tissue lipogenesis, and increased BAT thermogenesis (Crane et al., 2015; Oh et al., 2015). Adipose specific knockout *Tph1* in mice presents a similar phenotype as global deletion of *Tph1* in protecting against high-fat diet (HFD)-induced obesity and leading to increased UCP1 expression (Oh et al., 2015). These studies highlight the distinct roles of central and peripheral 5-HT in regulating BAT thermogenesis (Sun et al., 2018; Wyler et al., 2017).

The gastrointestinal peptide hormone ghrelin is known as an orexigenic hormone. Mounting evidence however suggests wider central and peripheral roles of ghrelin in energy balance including food intake, glucose metabolism and energy expenditure (Mani et al., 2019; Mani and Zigman, 2015; Muller et al., 2015). Circulating ghrelin is significantly elevated during fasting and attenuated upon meal initiation. Circulating ghrelin stimulates food intake and promotes obesity and insulin resistance (Davies et al., 2009; Tschop et al., 2000). Ghrelin hormone secretagogue receptor (GHSR) is widely expressed in the brain and several peripheral tissues. Central administration of ghrelin suppresses NE release and sympathetic output to BAT and this action reduces energy expenditure (Mano-Otagiri et al., 2009; Yasuda et al., 2003). Reduced adiposity observed in aged GHSR-null mice is due to increased energy expenditure, but not due to reduced food intake or increased physical activity (Lin et al., 2011). In mice neuron-specific deletion of GHSR completely prevents HFD induced obesity, significantly improves insulin sensitivity and activates BAT thermogenesis and browning of inguinal WAT (Lee et al., 2016; Wu et al., 2017). Calorimetry analysis revealed that deletion of GHSR using aP2 promoter driven Cre had normal food intake and physical activity at both young and old age. Intriguingly, while energy expenditure was normal at young age, it was significantly increased in aged $GHSR^{aP2-KO}$ mice. Both young and aged $GHSR^{aP2-KO}$ mice exhibited improved insulin sensitivity and glucose tolerance. Consistent with the impact on energy expenditure, aged $GHSR^{aP2-KO}$ mice have higher core body temperature during cold challenge and higher *Ucp1* mRNA expression (Lin et al., 2018).

Not only gut hormones, but gut microbiota-derived metabolites such as butyrate can also activate BAT thermogenesis. Butyrate is a short-chain fatty acid (SCFA) generated during microbial fermentation in the gut. Most of the butyrate in the cecum is used by mitochondria as the energy substrate in the colon and circulating butyrate also acts as a typical histone deacetylase (HDAC) inhibitor (Candido et al., 1978). The relationship between energy expenditure and HDAC is also very complicated. HDAC1 (Li et al., 2016) and HDAC11 (Bagchi et al., 2018) are negative regulators of the brown adipocyte thermogenic program, but HDAC3 is required to activate BAT enhancers to ensure thermogenic aptitude (Emmett et al., 2017). However, other studies reported that specific ablation of HDAC3 in adipose tissue increases acetylation of enhancers in *Ppar-γ* and *Ucp1,* which supports WAT browning (Ferrari et al., 2017). The opposite HDAC3 regulation in browning might associate with a different regulation of H3K27ac during the initial and chronic stage of cold exposure and the β-adrenergic receptors are also involved in this process (Yuliana et al., 2018). Furthermore, class I and II histone deacetylase inhibitors have different function on thermogenic gene expression in brown adipocytes (Rajan et al., 2018). A previous study showed that the abundance of butyrate-producing bacteria was increased by cold stimulation (Chevalier et al., 2015; Li et al., 2019). Butyrate also increases lipolysis and improves insulin sensitivity in obese mice (Chriett et al., 2017; Jia et al., 2017; Rumberger et al., 2014). Treatment with antibiotics to deplete the gut microbiome leads to impaired thermogenesis in C57BL/6 mice (Li et al., 2019). Dietary butyrate increases energy expenditure (Gao et al., 2009) and activates BAT thermogenesis through an activated Gut-Brain-BAT axis (Li et al., 2018b). Whether dietary butyrate is also one cause of DIT is still unclear, but butyrate could rescue the impaired thermogenesis induced by the depletion of microbiota (Fig. 3). Gut microbiota-derived acetate and lactate which are shaped by an every-other-day fasting (EODF) promote WAT browning, and the depletion of gut microbiota blunts this effect (Li et al., 2017a). The detailed relationship between gut microbiota and gut hormones was already reviewed elsewhere (Fukui et al., 2018; Martin et al., 2019). Further study is needed to identify the influence of the microbiota on DIT.

2.6. Bone morphogenetic proteins

Several bone morphogenetic proteins (BMPs) have been indicating to regulate BAT thermogenesis. BMPs belong to the transforming growth factor beta (TGF β) superfamily. BMPs are growth factors and have several functions such as cell differentiation, migration, apoptosis and survival (Bragdon et al., 2011). BMPs bind to type I and type II serine-threonine kinase receptors and then phosphorylate the 'small mother against decapentaplegic' (SMADs) protein family. BMPs can also directly activate the mitogen-activated protein kinase (MAPK) pathway without the SMADs signal.

Several studies confirmed that BMP4 induces fat redistribution. The

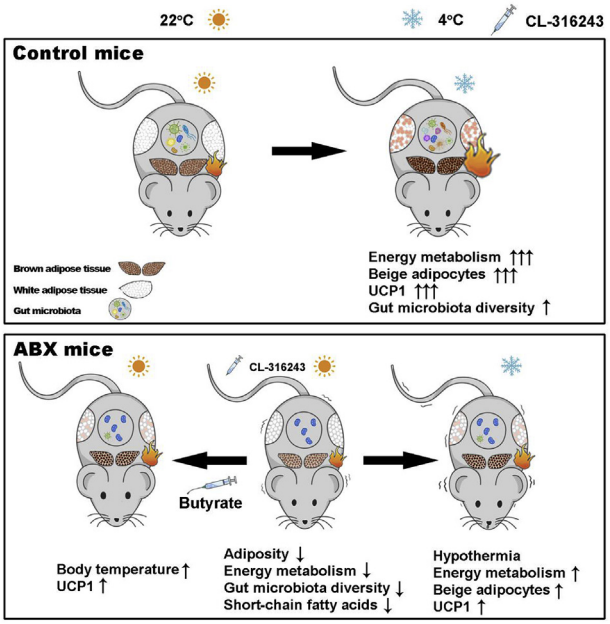

Fig. 3. Schematic diagram for the impact of gut microbiota depletion on UCP1-dependent thermogenesis. The responses of BAT and WAT to temperature challenges in mice lacking gut microbiota were evaluated with different cocktails of antibiotics (ABX). ABX treatment impaired the thermoregulatory capacity of BAT by blunting the increase in the expression of UCP1 and reducing the browning process of WAT under cold challenge and CL-316243 treatment. Gavage of the bacterial metabolite butyrate increased the thermogenic capacity of ABX-treated mice, reversing the deficit.

BMP4 signal to BAT suppresses thermogenesis, while the BMP4 signal to WAT promotes adipogenesis of the beige/brite adipocytes (Hoffmann et al., 2017; Modica et al., 2016; Modica and Wolfrum, 2017; Qian et al., 2013). Overexpression of BMP4 in BAT converts brown adipocytes into a white-like adipocyte phenotype, possibly due to inhibition of HSL activity through its downstream SMAD pathway (Modica et al., 2016). Overexpression of BMP4 in WAT, or an increase circulating BMP4, promotes preadipocyte commitment and trans-differentiation of mature white adipocytes into beige/brite adipocytes (Hoffmann et al., 2017; Qian et al., 2013).

Contrasting BMP4, BMP7 is required for brown, not white, preadipocyte terminal differentiation. BMP7 also induces thermogenic gene expression and mitochondrial biogenesis and this effect is through a p38-MAPK and PGC-1a dependent pathway (Tseng et al., 2008). Moreover, selective deletion of the type 1A BMP-receptor (*Bmpr1A*) in brown progenitor cells causes deficiency in BAT development, blunted response to the BMP7 signal and browning of WAT in a compensatory manner (Schulz et al., 2013). BMP8 also has been reported to regulate BAT thermogenesis in a direct or indirect manner. BMP8 signals to BAT, increases NE-induced NST and promotes lipolysis. Central administration of BMP8 also activates the sympathetic nervous system (SNS) signal to BAT (Whittle et al., 2012).

2.7. Fibroblast growth factor 21

Fibroblast growth factor 21 (FGF21) and its analogs have been shown to cause weight loss, increased energy expenditure and BAT thermogenesis, and both improved glucose and lipid metabolism in obese primates and humans (Gaich et al., 2013; Talukdar et al., 2016). FGF21 is secreted by several organs including liver, fat tissue and pancreas, but only FGF21 from the liver has been indicated to act as an endocrine factor in the circulation under normal physiological conditions (Markan et al., 2014). FGF21 targets multiple organs though binding to FGF receptors (FGFRs) and its co-receptor β-Klotho (KLB) (Kharitonenkov et al., 2008; Lee et al., 2018a).

The beneficial effects of FGF21 can be dissociated through central and peripheral mechanisms (Kliewer and Mangelsdorf, 2019). FGF21 increases energy expenditure and activates BAT thermogenesis in a HFD-induced obese mouse model (Xu et al., 2009) and FGF21 regulates BAT through two actions. On one hand, central administration of FGF21 increases the activity of SNS in BAT and WAT, enhancing energy expenditure. The effect requires intact β adrenoceptors (Douris et al., 2015). The FGF21 signal to the brain also regulates body weight and glycemia in a chronic manner (Lan et al., 2017). On the other hand, FGF21 can also directly target BAT, and the FGF21 signal to BAT is necessary for acute insulin sensitivity action, shown via specific deletion of KLB in UCP1 positive adipocytes (BonDurant et al., 2017). Although FGF21 boosts UCP1 expression in BAT, several studies suggested UCP1 is dispensable for the metabolic effects of FGF21 (Keipert et al., 2017; Samms et al., 2015; Veniant et al., 2015) and FGF21 is not required in long term cold stimulation (Keipert et al., 2017). These studies together indicated that FGF21 modulates BAT activity probably through both UCP1-dependent and UCP1-independent actions.

2.8. Vascular endothelial growth factors

Vascular endothelial growth factors (VEGFs) are signal proteins produced by multiple tissues, including BAT and WAT, that stimulate angiogenesis. VEGFs bind to tyrosine kinase receptors, VEGFR1 and VEGFR2, in adipose tissue. VEGF-A is highly expressed in BAT under normal conditions and acute cold stimulation. Selective overexpression VEGF-A in BAT or WAT in mice protects from HFD-induced obesity and these mice are also resistant to cold challenge, through increasing vascularization, elevated BAT thermogenesis and browning of WAT (Park et al., 2017; Sun et al., 2014). VEGF signaling in VEGFR2 promotes angiogenesis and VEGFR1 neutralizes this signal. Pharmacological blockade of VEGFR2 or overexpression of VEGFR1 causes brown adipocyte apoptosis (Bagchi et al., 2013). Selective depletion of VEGFR1 in endothelial cells augmented adipose angiogenesis, enhanced BAT thermogenesis and browning of WAT without altering fat mass. In contrast, these effects were absent in adipose or non-endothelial VEGFR1 depletion models, which suggests that VEGF signal potentiates BAT activity through targeting angiogenesis of endothelial cells (Seki et al., 2018).

2.9. Transient receptor potential vanilloid receptors

Cold ambient temperature stimulation boosts browning and upregulates UCP1 expression and the physiological signal mediating this effect is mainly due to the modulation of SNS (Morrison et al., 2014). Thermal afferent neurons transmit skin temperature into afferent neuronal activity via transient receptor potential (TRP) cation channels. At least four of the vanilloid TRP subfamily (TRPV1-TRPV4) have been related to thermal sensation. These neuronal signals are delivered from the spinal horn (Craig, 2002) to the median preoptic subnucleus (MnPO) of the preoptic area (POA) (Bratincsak and Palkovits, 2004; Nakamura and Morrison, 2008).

Activation of TRPV1 channels potentiates BAT thermogenesis. In addition to cold exposure, several dietary components are also known to regulate TRPV1 activity. Capsaicin, a TRPV1 agonist, and its analogs are active components in chili peppers and have been suggested to protect mice from HFD-induced obesity and promote BAT thermogenesis (Iwasaki et al., 2011). Dietary fish oil reduces fat accumulation and induces UCP1 expression in BAT, an effect that was also mediated via a TRPV1 dependent SNS mechanism (Kim et al., 2015). Unlike TRPV1, a chemical compound library screening suggested that TRPV4 negatively regulates oxidative metabolism and the expression of PGC-1α. Pharmacological inhibition of TRPV4 in mice elevates browning of WAT and protects mice from HFD-induced obesity (Ye et al., 2012) suggesting some coordination among different TRPVs in regulating SNS activity in

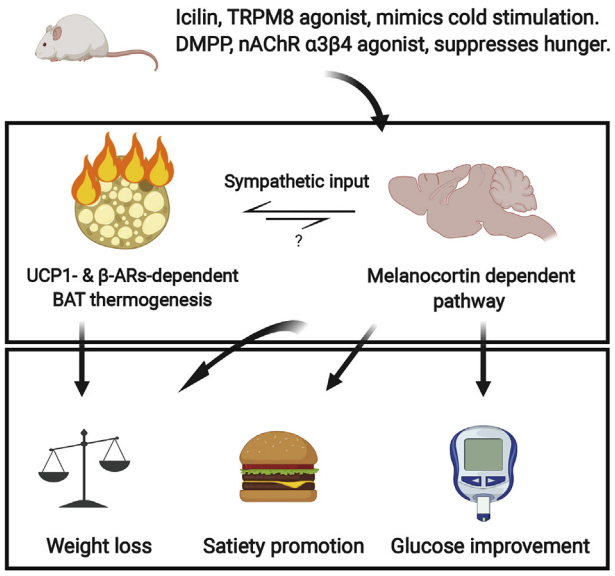

Fig. 4. Schematic diagram for the effects of icilin and DMPP co-treatment on energy balance. Clemmensen and his colleagues reported that co-treatment of icilin, the cold receptor transient receptor potential cation channel subfamily M member 8 (TRPM8) agonist, and dimethylphenylpiperazinium (DMPP), the nicotinic acetylcholine receptor (nAChR) subtype α3β4 agonist, decrease body weight, promote satiety and improve glucose metabolism in obese mice via a synergistic activation of thermogenic and anorexic pathways.

BAT and WAT.

Recent studies indicated that treatment with icilin, an agonist for cold receptor TRP cation channel subfamily M member 8 (TRPM8), boosts energy expenditure and lowers body weight without affecting food intake in HFD fed mice. The pharmacological activation of TRPM8 mimics physiological cold exposure. More importantly, targeting thermogenesis and satiety through co-treatment of icilin and dimethylphenylpiperazinium (DMPP), the nicotinic acetylcholine receptor (nAChR) subtype α3β4 agonist, promote better action in body weight and appetite control, sympathetic input to BAT and glucose metabolism. Co-treatment of icilin and DMPP increased oxygen saturation of the delivered blood to the BAT and the combined treatment induced weight loss was largely blunted in mice lacking β-adrenergic receptors (beta-less mice) and UCP1 KO mice demonstrating the essential roles of UCP1 and β-adrenergic receptors in DMPP and icilin mediated body weight control. Moreover, the melanocortin-4 receptor (MC4R) was required for the improvement of glucose metabolism, indicating that the central melanocortin pathway is indispensable for dual TRPM8 and nAChR α3β4 agonism mediated glucose benefit (Fig. 4). Together, this work opens up a new avenue for combating obesity and diabetes with co-activation of TRPM8 and α3β4-nAChRs (Clemmensen et al., 2018).

2.10. Immune regulation

Numerous resident immune cells coordinate the metabolic state, not only in host defense, but also under different circumstances such as malnutrition, over-nutrition and ambient temperature challenges. Type 2 immune signaling pathways, including activation of group 2 innate lymphoid cells (ILC2s) or stimulation of alternatively activated macrophages (AAMs - also called M2-type macrophages), were indicated to be involved in BAT thermogenesis and browning of WAT. The number of ILC2s was decreased in WAT, in both obese humans and mice. Activation of ILC2s via interleukin-33 (IL-33) drives the formation of beige/brite adipocytes in WAT, in an eosinophil or IL-4 receptor signaling independent manner (Brestoff et al., 2015). Absence of endogenous IL-33 leads to impaired adaptive thermogenesis and altered *Ucp1* mRNA splicing in mice (Odegaard et al., 2016). ILC2 derived IL-5 and muscle derived meteorin-like (Metrnl) could promote the accumulation of eosinophils in WAT (Rao et al., 2014). Depletion of eosinophils in mice under HFD condition results in accumulation of body fat and impaired glucose tolerance indicating that eosinophils play an important role in energy balance (Wu et al., 2011). Eosinophils are also the major source of IL-4 in the WAT of mice, and IL-4 is required to maintain AAMs. Previous studies challenged the idea that the sympathetic postganglionic neurons and the adrenal medulla are the only sources for catecholamines. These studies suggested that AAMs directly regulate BAT thermogenesis or browning WAT process via releasing NE from AAMs to adipocytes (Nguyen et al., 2011; Qiu et al., 2014).

However, more recent studies have suggested that adipose-tissue-resident macrophages do not express tyrosine hydroxylase (TH), the key enzyme in catecholamine synthesis, and hence AAMs are unlikely to synthesize catecholamines (Fischer et al., 2017; Wolf et al., 2017). Further study identified a special population of macrophages termed 'sympathetic neuron-associated macrophages (SAMs)'. SAMs could respectively import and degrade NE through NE transporter (SLC6A2) and degradation enzyme (MAOA), but they do not synthesize NE. This pathway is conserved both in human and mouse models. Genetic ablation of *Sla6a2* in SAMs could increase BAT content, induce browning, increase thermogenesis and lead to weight loss in obese mice (Pirzgalska et al., 2017). This function was also identified in aging-induced impaired lipolysis. Aging upregulates genes that control catecholamine degradation in AAMs and thus decreases the bioavailability of NE (Camell et al., 2017). IL-1β was also reported to attenuate the browning of WAT (Okla et al., 2018). IL-18 and IL-18 receptor 1 were also involved in the thermogenic capacity of BAT and subcutaneous adipose tissue (Pazos et al., 2015). Age-associated insulin sensitivity will be protected by selective depletion of fat-resident regulatory T cells (fTreg) (Bapat et al., 2015). Mast cells were also linked to cold induced browning WAT through releasing IL-4 cytokine and histamine in human (Finlin et al., 2017, 2019).

Although adipose tissue resident AAMs do not directly mediate the activation of UCP1. It is important to note that AAMs are necessary for energy balance and glucose metabolism. The expression of PPARγ is increased in macrophages during IL-4 induced AAM activation. Disruption of the expression of PPARγ specifically in macrophages causes spontaneous obesity and impaired glucose homeostasis (Odegaard et al., 2007). IL-6 could further limit the expression of genes encoding inflammatory cytokines and augment the responsiveness of macrophages to IL-4, and thus limit obesity-associated resistance to insulin (Mauer et al., 2014). Moreover, mice with depletion of the transcriptional regulator methyl-CpG binding protein 2 (*Mecp2*) in $CX3CR1^{+}$ macrophages are prone to develop a pro-obese phenotype and this is correlated with decreased sympathetic innervation and NE content, which leads to impaired BAT function (Wolf et al., 2017). BAT also regulates the activation of AAMs in a paracrine manner. Activated BAT secretes chemokine C-X-C motif chemokine ligand-14 (CXCL14) and CXCL14 promotes the recruitment of AAMs in both BAT and WAT. CXCL14 boosts BAT activity and WAT browning and this action requires the type 2 immune signaling pathway (Cereijo et al., 2018). Inflammatory activation of macrophages could also inhibit beige adipogenesis through direct adhesive interactions between macrophages and adipocytes mediated by the integrin α4 and its counter-receptor VCAM-1. This interaction also operates in the human system. An inverse correlation between the expression of UCP1 and that of VCAM-1 also occurs in subcutaneous WAT samples from patients undergoing abdominal surgery (Chung et al., 2017). The cellular mechanism linking macrophages to thermogenesis has been a topic of considerable debate. More studies will help to elucidate this complex interaction termed neuro-immunometabolism.

Invariant natural killer T (iNKT) cells in adipose tissue were reported to protect against diet-induced obesity and metabolic disorders through regulatory cytokine production including IL-2, IL-4 and IL-10 (Lynch et al., 2012, 2015). Stimulated iNKT cells induced weight loss is

assciocated with browning of WAT through partially activation of FGF21 expression. Interestingly, GLP-1 analogue liraglutide treatment activated iNKT cells in mice and human (Lynch et al., 2016). Activation of adipose iNKT cells require CD1d and adipose specific deletion of CD1d leads to early onset obesity, reduction of IL-4 expression and abolished M2 macrophages accumulation (Huh et al., 2017). The release of IL-10 is the hallmark in adipose iNKT cell activation. However, recent study suggested global deletion of IL-10 ameliorates insulin sensitivity, protects against HFD induced obesity and promotes WAT browning in mice (Rajbhandari et al., 2018). Adipose selective deletion of IL10 receptor α (IL10R α) protects HFD induced obesity and increases energy expenditure (Rajbhandari et al., 2019). The crosstalk in thermoregulatory between iNKT cells and adipocytes has proven complicated and further study is needed to clarify.

2.11. Heat production in BAT independent of UCP1

To investigate the function of UCP1, Kozak's group developed a UCP1-deficient mouse model (Enerback et al., 1997), and found these UCP1 null mice are sensitive to acute cold exposure. However, they also observed that about 15% of these UCP1 null mice were resistant to cold, suggesting a non-shivering thermogenesis mechanism in addition to UCP1-mediated thermogenesis. They established UCP1 null mice on a hybrid background of C57BL/6J and 129/SvImJ and found that these UCP1 null mice were resistant to cold (Hofmann et al., 2001). Furthermore, UCP1 null mice on an inbred background can survive in cold condition by decreasing temperature gradually (Golozoubova et al., 2001; Hofmann et al., 2001; Ukropec et al., 2006), predominantly by upregulating shivering. These variable responses to cold in UCP1 null mice suggested that there must be alternative pathways for thermogenesis and raised interests in UCP1-independent heat production (Fig. 5).

As early as 1976, it was suggested that energy metabolism of adipose tissue closely depends on the creatine pathway (Berlet et al., 1976). There are large amounts of creatine, phosphocreatine (PCr) and creatine phosphokinase in adipose tissue. Disruption of creatine pathway by feeding rats with β-guanidinopropionic acid (β-GPA), a creatine analogue, have been shown to impair thermogenic activity in

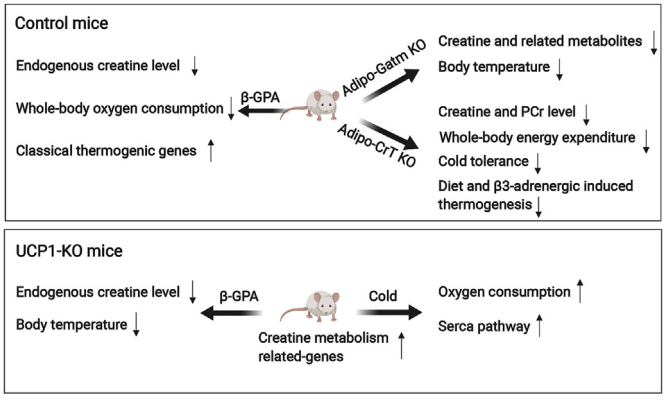

Fig. 5. Schematic diagram for UCP1-independent thermogenesis. One mechanism is through the creatine-driven thermogenesis pathway. With the declining endogenous creatine level by β-GPA administration, the whole-body oxygen consumption was reduced, while classical thermogenic genes were upregulated. This result was later confirmed with the genetically manipulated mouse model. Specifically, creatine level was blunted in mice with adipose specific inactivating of GATM or CrT. These mice showed lower body temperature, reduced energy expenditure and thermogenesis. To test the relationship between creatine and UCP1 directly, UCP1–KO mice were used. Creatine metabolism related-genes were upregulated, and body temperature was lower by β-GPA treatment. The alternative mechanism is through the SERCA-mediated calcium cycling pathway. In UCP1–KO mice, SERCA pathway was activated under cold exposure, which enhanced oxygen consumption.

BAT (Yamashita et al., 1995). A recent study reported that the CL-316243-induced increase in whole body oxygen consumption was blunted by 40% with β-GPA administration and this was associated with BAT function (Kazak et al., 2015). Genes involved in creatine metabolism were upregulated when UCP1 was absent, and instead – the expression of classical thermogenic genes were increased with the disruption of creatine metabolism, suggesting a compensatory relationship between creatine- and UCP1-dependent thermogenesis in mice (Kazak et al., 2015). The significant lower body temperature in UCP1 null animals with reduced endogenous creatine levels by β-GPA, suggested that creatine makes a greater contribution to cold-induced thermogenesis when UCP1 is absent than when it is present (Kazak et al., 2015).

Mechanistically, mitochondrial creatine kinase (Mi-CK) is coupled with oxidative phosphorylation through the ATP/ADP carrier (AAC) (Jacobus and Lehninger, 1973). Creatine and Mi-CK mediate ATP hydrolysis, which could stimulate the cycling of ATP production and consumption, suggesting that creatine could dissipate the mitochondrial ATP pool to drive high-energy phosphate-dependent substrate cycling, which requires ADP-dependent respiration (Kazak et al., 2015). Creatine-driven futile substrate cycling requires futile hydrolysis of PCr. This could involve direct hydrolysis of PCr or involve multiple transphosphorylation catalyzed by multiple enzymes. PHOSPHO1 was a candidate protein involved in creatine-driven substrate cycle based on the reciprocal relationship between *Phospho 1* and *Ucp1* in mouse and human cultured cells (Kazak et al., 2015). Glycine amidinotransferase (GATM) is the first and rate-limiting enzyme of creatine synthesis, and adipose specific deletion of GATM (Adipo-Gatm KO) in mice reduces creatine and related metabolites in adipose tissue and results in a lower body temperature, providing strong evidence for a contribution of the GATM and creatine pathway in BAT thermogenesis (Kazak et al., 2017). Creatine can also be transported into adipocytes by a creatine transporter (CrT) (Fitch et al., 1968). Moreover, BAT sequestrates substantial creatine from circulation (Berlet et al., 1976). Also CrT expression levels are highest in BAT of the adipose tissue depots (Kazak et al., 2019). Adipose specific deletion of the cell-surface CrT (Adipo-CrT KO) substantially decreases creatine and phosphocreatine levels in adipocytes and decreases whole-body energy expenditure in mice. Additionally, deletion of CrT cause cold intolerance and impaired diet and β3-adrenergic-induced thermogenesis (Kazak et al., 2019). The mice with double-knockout of cytosolic brain creatine kinase (CK–B) and the mitochondrial ubiquitous creatine kinase (UbCKmit), are sensitive to cold and showed an impaired capacity for adaptive thermoregulation (Streijger et al., 2009). Thus, additional evidence supports the function of the creatine pathway in thermoregulation in mice. In humans, creatine metabolism is selective in BAT compared to WAT using microarray and proteomic analysis (Muller et al., 2016; Svensson et al., 2011). Moreover, the CRT expression level is inversely related with BMI and insulin resistance, and two mitochondrial creatine kinases (CKMT1A and CKMT2) are prominently correlated with UCP1 expression, suggesting that the creatine metabolism might also be involved in human adipose tissue metabolism (Din et al., 2018; Kazak et al., 2019).

Billfish have modified ocular muscle cells that function to warm the brain and eyes during dives into deep cold water. This so-called 'heater organ' generates heat via a futile cycle of ATP-dependent cycling of calcium at the sarcoplasmic reticulum (SR) via SERCA and ryanodine receptors (RyRs) (Morrissette et al., 2003; Block and Franzini-Armstrong, 1988). Mutations in the RyR1 gene cause malignant hyperthermia in humans and pigs (Fujii et al., 1991; Quane et al., 1993). Cold adapted UCP1 null mice have increased oxygen consumption and showed a robust induction of sarco/endoplasmic reticulum $Ca2^{+}$-ATPase (SERCA) in inguinal fat. Together with the induction of total phospholamban and its phosphorylated form, the results indicated that UCP1-independent alternative thermogenesis exists, based in part on substrate cycling associated with WAT under cold condition (Ukropec et al., 2006). Some *in vitro* studies have indicated that sarcolipin (*Sln*)

can increase heat production by uncoupling SERCA-mediated ATP hydrolysis from $Ca2^+$ transport (Mall et al., 2006; Smith et al., 2002). A *Sln* knockout mouse study showed that *Sln* is necessary for muscle-based thermogenesis and impacts whole-body energy metabolism (Bal et al., 2012). Moreover, enhanced ATP-dependent $Ca2^+$ cycling via Serca2b and RyR2 contributes to beige fat thermogenesis and glucose metabolism in a UCP1-independent manner (Ikeda et al., 2017).

N-acyl amino acids (NAAs) are endogenous metabolites that function as uncouplers of mitochondrial respiration, even in cells lacking UCP1. Peptidase M20 domain containing 1 (PM20D1) is a biosynthetic enzyme for a class of N-lipidated amino acids *in vivo*. Both PM20D1 and its N-acyl amino acid products are physiologically co-regulated by cold exposure. Overexpression PM20D1 or administration N-Acyl amino acids to mice increases energy expenditure and improves glucose homeostasis in a UCP1-independent manner (Long et al., 2016). However, these studies need to be expanded to include UCP1 null mice. Further, global PM20D1-KO mice dramatically reduces NAA hydrolase/synthase activities in tissues and blood with concomitant bidirectional dysregulation of endogenous NAAs. Surprisingly this did not lead to significant changes in body weight and energy expenditure under normal chow diet or HFD conditions. But after a long term HFD feeding, PM20D1-KO mice exhibited worsened glucose metabolism than wild-type control mice. Moreover, PM20D1-KO mice maintained slightly higher rectal temperatures than wildtype mice throughout this time course. These temperature differences occurred in the absence of any changes in a panel of mitochondrial proteins or UCP1 protein levels in the BAT or WAT. Similarly, PM20D1-KO mice did not have any increases in the expression of genes corresponding to alternative adipose futile cycling pathways, including creatine cycling and sarco/endoplasmic reticulum $Ca2^+$-ATPase (SERCA) cycling. Taken together, these data implicate PM20D1-regulated NAAs in the defense of body temperature, independent of any changes in known thermogenic programs (Long et al., 2018).

3. Conclusions

BAT probably evolved in mammals primarily as a source of endogenous heat to support an endothermic existence. BAT is abundant in small mammals and the neonates of large animals. It is activated seasonally by lowered ambient temperatures and photoperiod. Probably the best known activator is norepinephrine (NE) released from sympathetic nerves and binds to adrenergic receptors expressed on brown adipocytes. NE stimulates free-fatty acid release which was previously thought essential for activation of UCP1. Recent work however has questioned the necessity of intracellular lipolysis and indicated activating FFAs can be derived from extracellular sources. Thyroid hormones also impact metabolic rate via effects of type 2 deiodinase which is expressed in brown adipocytes. Knocking out DIO2 makes mice cold intolerant (de Jesus et al., 2001). Another a potent regulator of BAT activity is parathyroid hormone which may be an important mediator of elevated energy expenditure during cancer cachexia, although this is disputed by observations that cachexia wasting is not blunted in UCP1 KO mice (Rohm et al., 2016). Cardiac natriuretic peptides have also been implicated in the regulation of BAT thermogenesis and the interconversion of beige adipocytes from their white to brown form (Bordicchia et al., 2012). Activation of BAT thermogenesis may be an important component of the rise in heat production following food intake. Recent work suggests the gut derived hormone secretin may play a key role in this effect, directly linking BAT activation to the alimentary tract (Li et al., 2018a). In addition to the effect of secretin, metabolites derived from gut microbiota such as butyrate may be important activators of BAT, particularly during cold exposure (Li et al., 2018b, 2019). Additional regulatory factors include bone morphogenic proteins, fibroblast growth factor 21 (Gaich et al., 2013), Vascular endothelial growth factors (Sun et al., 2014) and transient receptor potential vanilloid receptors, which are important components of thermal sensing and hence how? brown adipose tissue responds to the cold (Clemmensen et al., 2018). The main challenge for the future is to understand how these diverse regulatory factors combine to control heat production, and what their relative importance is in differing circumstances. Non-shivering heat production in BAT is mostly a result of the activity of UCP1. However, in the absence of UCP1 other heat producing mechanisms are exposed including creatine dependent cycles (Kazak et al., 2015, 2019) and a futile cycle of $Ca2^+$ shuttling into and out of the endoplasmic reticulum via the SERCA and ryanodine receptor linked to sarcolipin ().

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