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MINI-REVIEW

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Loading and firing the brown adipocyte

Mohammed K. Hankir

Department of Experimental Surgery, University Hospital Wuerzburg, Wuerzburg, Bavaria, Germany; German Research Foundation Collaborative Research Center in Obesity Mechanisms, University of Leipzig, Leipzig, Saxony, Germany

ABSTRACT

Brown adipose tissue (BAT) is specialized to both store and expend chemical energy making it an ideal therapeutic target for various metabolic diseases. Fatty acids derived from lipid droplets within brown adipocytes acting on mitochondrial uncoupling protein 1 (UCP1) were long thought to be essential for non-shivering thermogenesis. Here, the roles of white adipose tissue and the liver in the provision of fuel to BAT as part of a coordinated response to temperature and dietary challenges are described. UCP1-independent modes of brown adipocyte heat production are also highlighted. A model that accommodates the findings obtained so far is further presented in which according to the conditions imposed on brown adipocytes, the relative contributions of circulating lipids and glucose for their normal function varies. Gaining deeper insight into the molecular processes which poise brown adipocytes to protect against whole-body thermal and energy imbalance represents a promising future area of metabolic research.

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Introduction

To fulfill their dedicated role in heat production, brown adipocytes must be able to efficiently **(1)** generate and **(2)** dissipate the proton gradient across the inner mitochondrial membrane (IMM). The first demand is met somewhat straightforwardly by the high rate of nutrient fluxes through the cell.[1] This is what makes activated brown adipose tissue (BAT) easily identifiable in positron emission tomography (PET) images when radioactive analogues of glucose and fatty acids are administered to humans and animals.[2,3] The second demand is more specialized, and largely requires the action of uncoupling protein 1 (UCP1); a thermogenic symporter embedded in the IMM that shuttles protons from the intermembrane space into the mitochondrial matrix generating considerable inward current in the process.[4]

The rich innervation of BAT by sympathetic efferent fibers forms a physical conduit to the hypothalamic thermoregulatory network.[5] This intricate collection of neurons not only receives sensory information about external temperature from cutaneous afferent fibers,[6] but also directly sense cooling in their local microenvironment in their own right.[7] Superimposed on this core network, are populations of cells that respond to circulating nutrients[8] and feeding-related hormones such as ghrelin[9] and glucagon-like peptide 1 (GLP-1)[10] which makes BAT sensitive to nutritional status. Ultimately, a decrease in temperature and/or a surplus of energy in the organism stimulates sympathetic post-ganglionic neurons to release noradrenaline and activate BAT, and, *vice-versa*. In this way, whole-body temperature and energy balance are maintained within homeostatic limits.

Similar processes to those for BAT have been found to apply for the browning of white adipose tissue (WAT),[10-13] which engenders the formation of thermogenic brown adipocyte-like cells (beige adipocytes) that inducibly express UCP1.[14] Interestingly, while UCP1 behaves in these cells in very much the same way as it does in brown adipocytes in terms of its ability to transfer protons bound to fatty acids across the IMM, it differs in its magnitude of tonic inhibition by purine nucleotides.[15] Thus, as well as being transport substrates of UCP1 in their charged (protonated) form, (uncharged) fatty acids also activate the protein by competitively displacing bound ATP with three times higher affinity in inguinal beige adipocytes than in classical brown.[15] It is also becoming increasingly clear that UCP1-independent forms of thermogenesis exist - particularly in beige adipocytes, which will be touched upon in this text.

When BAT function declines as with aging,[16,17] so too does metabolic health. Conversely, chronic activation of BAT by cold or a selective β-3 adrenergic

CONTACT Dr. Mohammed K. Hankir hankir_m@klinik.uni-wuerzburg.de Centre of Operative Medicine, Oberduerrbacherstraße 6, Wuerzburg, Bavaria 97080, Germany.

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receptor agonist has not only been found to reduce adiposity,[18,19] but also to improve whole body glucose and lipid metabolism in animals[19,20] and humans,[21,22] positioning it well in the crosshairs for drug development. While an ever-increasing number of compounds other than selective β-3 adrenergic receptor agonists have been shown to stimulate BAT/brown WAT in animals, ranging from microbiota metabolites such as acetate[23] to ligands of olfactory receptors,[24] this has been difficult to translate to humans. Therefore, in order to create BAT-based therapies with genuine potential to treat metabolic disease, further understanding BAT physiology is essential. A poignant example of this comes from BAT function at its very essence. For decades it was widely thought that lipolysis in brown adipocytes triggered by noradrenaline binding to β-3 adrenergic receptors is an essential early step for thermogenesis; however, recent findings indicate that this is not the case, and that inhibiting lipolysis in brown adipocytes actually results in even greater heat production in response to cold.[25,26]More to the point, long-term inhibition of BAT lipolysis leads to improved glucose tolerance and reduces hepatic steatosis caused by chronic consumption of a high-fat diet in mice, despite the absence of any changes in feeding behavior and body weight.[26]

In this Mini-Review, these findings will be extensively and critically discussed in the context of others which together show that cold exposure causes a sequential, multi-tissue response to stimulate BAT. The relative roles of lipid species from within and without the brown adipocyte in regulating thermogenesis will be described, as well as that of glucose taken up from the circulation under normal and stressful conditions. Finally, a model will be put forward that integrates these findings and which highlights the remarkable plasticity of brown adipocyte fuel utilization.

The significance of lipolysis for BAT thermogenesis

A BAT-centric view

The multilocular nature of brown adipocytes means that more stored triglycerides are exposed to intracellular lipases. This provides perhaps the most intuitive line of reasoning that liberated fatty acids from within the cell are best placed to effectuate heat production through UCP1. Historically, similar logical inferences were made from studies on various BAT preperations.[27] Thus, because β-3 adrenergic receptor activation increases cyclic AMP production which stimulates lipolysis through protein kinase A (PKA), and that fatty acids directly applied to isolated mitochondria stimulate uncoupled respiration, the β-3 adrenergic receptor → cAMP → PKA → lipolysis → free fatty acid → UCP1 thermogenesis cascade in brown adipocytes seems obvious. The same can be said about atrial natriuretic peptide (ANP) acting on natriuretic peptide A receptors in brown/beige adipocytes but on the cGMP → protein kinase G (PKG) signaling pathway.[28] Indeed, ANP increases intracellular cGMP concentrations and stimulates lipolysis in a human beige adipocyte cell line while the increased oxygen consumption in these cells in response to the same treatment is blocked by a selective PKG inhibitor.[28] As with PKA, PKG is thought to promote lipolysis by phosphorylating hormone sensitive lipase (HSL) and the lipid droplet-associated protein perilipin[29]thereby generating monoacylglycerol (MAG) from diacylglycerol (DAG), which is then broken down into glycerol and the remaining fatty acid by monoacylglycerol lipase (MGL).

Direct testing of the role of lipolysis in brown and beige adipocyte thermogenesis, be it by targeting the PKA and/or PKG signaling arms, however, was only made relatively recently.[30] In a pioneering study, it was found that application of the adrenergic receptor agonist isoproterenol to isolated murine brown and inguinal beige adipocytes stimulated UCP1-mediated uncoupled respiration.[30] Moreover, this was largely cancelled out in the presence of a selective inhibitor of adipose triglyceride lipase (ATGL), which generates DAG from triacylglycerol (TAG) during the first step of lipolysis.[31] Additional application of a HSL inhibitor removed the residual response of these cells.[30] Because both lipases account for almost all lipolysis of strored triglycerides within white and brown adipocytes,[26,32] this provided strong evidence for the importance of endogenous fatty acids in activating UCP1 downstream of a physiological stimulus. A major drawback of the study of Li *et al* however was that extracellular fatty acids needed to be scavenged by albumin. While this successfully unmasked UCP1-dependent respiration by removing leak, it made it impossible to determine the relative contributions of fatty acids from intracellular and extracellular sources. Interestingly, fatty acids generated through the action of phospholipase 2 (PLA2) on membrane lipids on the cytoplasmic face of the IMM seem to also contribute to UCP1 activity in brown and beige adipocytes.[4,15] The reason why this was previously overlooked by Li *et al* using microplate respirometry[30] might be due to the higher resolution afforded by patch-clamping of individual mitochondria.[4,15] These issues notwithstanding, the findings suggest that different sources of fatty acids from within the cell can trigger UCP1 function.

In the whole organism, deletion of ATGL leads to severe cold intolerance in the fasted state associated with marked hypertrophy of BAT.[33.] Later it was shown that

deletion specifically in adipocytes, by crossing aP2-Cre mice with floxed ATGL counterparts, results in a similar phenotype, and that AMP kinase (as opposed to PKA) in brown adipocytes is the likely ATGL effector downstream of cold.[34] Furthermore, acutely inhibiting lipolysis by systemic administration of nicotinic acid, an agonist of G-protein coupled receptor 109a (GPR109a) which opposes the β-3 adrenergic receptor by decreasing cAMP production, blunts BAT thermogenesis in rats[3] and humans.[35] Conversely, transgenic overexpression of ATGL in adipose tissue (again under the aP2 promoter) results in enhanced lipolysis in BAT and increased body temperature in mice.[36] Interestingly, this was recapitulated in mice lacking the 2-pore domain potassium channel KCNK3 in adipose tissue.[37] These animals displayed increased HSL activity in brown adipocytes which was postulated to be due to direct positive allosteric regulation of adenylate cyclase by extracellular calcium derived through voltage gated calcium channels.[37] So it would seem that the reductionist setting of *in vitro* experiments also apply *in vivo* across species when it comes to lipolysis within brown adipocytes underlying their thermogenic function.

A WAT-centric view

Two recent studies have cast significant doubt on the above assertion.[25,26] Unlike previous studies, UCP-1-Cre mice were employed to interfere with lipolytic machinery specifically in BAT, although Schreiber *et al.*[25] used a tamoxifen-inducible strain which circumvents some of the developmental issues that can be associated with germ-line deletion. Shin *et al.*[26] specifically targeted comparative gene identification-58 (GGI-58), a lipid droplet-associated protein that serves as an essential coactivator of ATGL,[38] while Schreiber et al. inactivated ATGL itself. Remarkably, lack of CGI-58 or ATGL only in BAT did not lead to cold intolerance in the fasted state and was associated with increased body temperature in mice as mentioned earlier.[25,26] It was then reasoned that if exogenous nutrients can fuel BAT, then the simple provision of food during cold exposure should suffice to protect mice from hypothermia lacking lipolytic machinery in all adipocytes. This was indeed found to be case [25,26] and likely involved the increased local action of lipoprotein lipase in BAT vascular endothelial cells which completely liberates fatty acids from triglyceride rich lipoproteins produced during feeding and which are subsequently taken up by brown adipocytes via cluster of differentiation 36 (CD36)-mediated transport,[20,39] although this remains to be proven. Perhaps the most persuasive argument from both studies that WAT lipolysis powers BAT when its lipolytic machinery is not working during fasting is the markedly increased circulating fatty acids upon acute cold exposure[25] and the decreased WAT depot size[26] found in the respective mouse models. It should be added that under these conditions, the critical role of fatty acid binding protein 3 (FABP3) in shuttling exogenous fatty acids across the brown adipocyte probably becomes even more prominent,[40] while that of acyl-coA synthetase 1 (ACSL1) in the transfer of fatty acids from lipid droplets to mitochondria becomes obsolete.[41] In this manner, exogenous fatty acids would substitute for endogenous fatty acids both to activate UCP1 and to serve as fuel.

While the findings from the studies of Schreiber *et al.* and Shin *et al.* were largely consistent with each other, there were some notable differences. For instance, Shin *et al.* found that lack of CGI-58 in BAT led to higher mRNA expression levels of glucose and fatty acid transporters such as glucose transporter 1 (*Glut1*) and *Cd36* in brown adipocytes, respectively.[26] The former change is likely what made mice more efficient in clearing a glucose load due to increased uptake by BAT.[26] This contrasts with previous findings in which inhibiting BAT lipolysis with nicotinic acid decreased BAT glucose uptake.[3,35] However, this type of pharmacological approach is non-specific and may have interfered with glucose uptake mechanisms in brown adipocytes independently of lipolysis.[42] Shin *et al.* also found that isolated CGI-58 deficient brown adipocytes functioned normally in microplate respirometry experiments, but when extracellular fatty acids were scavenged, they consumed significantly less oxygen compared to wild-type brown adipocytes treated with isoproterenol. These results not only recapitulate the *in vivo* findings that exogenous fatty acids are essential for brown adipocyte thermogenesis in the absence of lipolysis, but also confirm the earlier findings of Li *et al.* [30] Additionally, Shin *et al.* found a general tendency of increased UCP1 protein *per* BAT depot alongside browning of inguinal WAT whereas Schreiber *et al.* did not report such changes. The reason for this is unclear, but may be due to more defective BAT development/function in mice lacking CGI-58 which would provoke a compensatory browning of WAT.

BAT lipolysis cell-autonomously generates a novel thermogenic lipokine

A link between brown adipocyte lipolysis and the novel lipokine 12, 13-dihydroxy-9Z-octadecenoic acid (12, 13-diHOME) has recently been made in a rare translational study performed on mice and humans and should be mentioned here.[43] Using liquid chromatography coupled to mass spectrometry on plasma samples, 12, 13-diHOME levels were found to increase in the circulation

upon acute cold exposure in both species. This strongly correlated with BAT activity determined by ^{18}F-Fluro-deoxglucose PET imaging in humans which suggested that 12, 13-diHOME is a cause and/or a consequence of thermogenesis. The source of 12, 13-diHOME was next localized to BAT in mice since cold exposure led to higher epoxide hydrolase 1 and epoxide hydrolase 2 (*Ephx1 and Ephx2*) expression, the enzymes involved in 12, 13-diHOME synthesis from linoleic acid, specifically in this tissue. Interestingly, 12, 13-diHOME synthesis did not occur in WAT upon acute cold exposure but was found in inguinal beige adipocytes of mice genetically engineered to lack BAT. Then, in a series of interventional experiments, administration of 12, 13-diHOME not only partially prevented the drop in body temperature in response to cold, but also lowered serum triglycerides associated with enhanced BAT uptake. Because 12, 13-diHOME increased the trafficking of CD36 and fatty acid transport protein 1 (FATP1) from the cytosol to the cell membrane in brown adipocytes, a model was proposed in which cold causes the synthesis of 12, 13-diHOME from fatty acids released by lipolysis, which then acts as an autocrine to promote further fatty acid uptake and thermogenesis. It would be important to determine in future studies whether mice with inactivation of EPHX1/EPHX2 are indeed cold intolerant. Additionally, it would be interesting to determine if mice lacking lipolytic machinery in BAT no longer present with the increase in circulating 12, 13-diHOME in response to cold exposure. This would confirm that endogenous fatty acids generated by brown adipocyte lipolysis are converted to a lipid signaling molecule that, upon release, further promotes thermogenesis through enhancing exogenous fatty acid uptake.

The liver emerges as an important player in BAT thermogenesis

Adding a further component to the WAT control of BAT thermogenesis, it was found that the liver is an essential intermediary in a recent rigorous study performed on mice.[44] Non-targeted lipodomic analysis of plasma samples revealed that acute cold exposure as well as single β-3 adrenergic receptor agonist treatment were sufficient to elevate various circulating acylcarnitine species. A hepatic source was then confirmed by three lines of evidence: **(1)** that ablation of BAT had no effect, **(2)** that appropriate changes in gene expression were found specifically in hepatocytes and **(3)** that hepatocyte-specific deletion of carnitine palmitoyl transferases 1a and/or 1b (CPT1a and/or CPT1b), which catalyze the production of acylcarnitines from long-chain fatty acids, was sufficient to reduce circulating levels and cause cold intolerance. Lipolysis of WAT was also shown to precede hepatic acylcarnitine release by detailed time course experiments coupled with the fact that β-3 adrenergic receptors are not found in hepatocytes. Importantly, as with Schreiber *et al.* and Shin *et al.*, Simcox *et al.* further used adipose tissue-specific deficient ATGL mice (driven by the adiponectin promoter) to demonstrate that WAT lipolysis is necessary for the increase in hepatic *Cpt1a* and *Cpt1b* expression and circulating acylcarnitines in response to a β-3 adrenergic receptor agonist. Similar results were obtained in acutely cold-exposed mice treated with a selective ATGL inhibitor. It was then found that specifically during acute cold exposure, radiolabeled acylcarnitine is channeled to BAT where it is ultimately metabolized in the TCA cycle. This makes sense considering that acylcarnitines would be needed by BAT most under these conditions. In a final set of experiments, aged mice exhibited reduced circulating acylcarnitines. Remarkably, their cold-intolerance was improved upon acylcarnitine supplementation which was shown to be BAT mediated. While hepatocyte nuclear factor 4α (HN4α) was proposed to be the fatty acid sensor in hepatocytes responsible for acylcarnitine production, this wasn't actually demonstrated *in vivo* or *in vitro*. Also, the dynamics of circulating acylcarnitines in response to cold (3 hours before a significant rise) means that they cannot account for the rapid thermoregulation observed in a physiological setting as acknowledged by the authors. Nevertheless, it would be interesting to determine if circulating acylcarnitines are also channeled to beige adipocytes after WAT browning to support thermogenesis, thereby possibly complementing local 12, 13-diHOME action.

The role of circulating glucose in BAT thermogenesis

Most highly metabolically active cells directly rely on glucose as a major fuel source. In myocytes for example, the proton gradient across the IMM after glycolysis and the TCA cycle is used to rapidly generate ATP through the action of ATP synthetase to power actin and myosin dynamics required for muscle contraction. The situation in brown adipocytes is quite different where glucose serves mainly to create a proton gradient across the IMM to then be dissipated by UCP1 and not to produce ATP. As such, blocking glucose uptake in murine[42] and human[45] brown adipocytes is sufficient to significantly impair thermogenesis. Interestingly, because glucose uptake downstream of β-3 adrenergic receptor activation is through the exchange protein activated by cAMP 2 (EPAC2) rather than the PKA branch of cAMP signaling in brown adipocytes,[42] it

can occur in the absence of thermogenesis. This has recently been demonstrated *in vivo* in UCP1-deficient mice through ^{18}F-Flurodeoxglucose PET imaging[46,47] and has further called into question the reliability of this technique to measure BAT function.

So what normally happens to glucose in brown adipocytes during thermogenesis? A recent mechanistic study by Irshad *et al* on a murine brown adipocyte cell line and primary cells systematically addressed this long-standing question by tracking the fate of ^{14}C-labelled glucose upon β-3 adrenergic receptor activation with concomitant inactivation of key components of lipid metabolism.[48] It was found that glucose is rapidly incorporated into triglycerides through the action of diacylglycerol acyl transferase 2 (DGAT2).[48] These de novo-generated triglycerides are simultaneously hydrolyzed into fatty acids for subsequent β-oxidation as part of a highly concerted process.[48] The absolute requirement for glucose incorporation into triglycerides prior to their oxidation by brown adipocytes was backed-up by the findings that inhibition of DGAT2, both pharmacogically and by siRNA-mediated knockdown, entirely prevented $^{14}CO_2$ production in response to a β-3 adrenergic receptor agonist, as did prevention of lipolysis and mitochondrial entry of long-chain fatty acids by pharmacologically inhibiting ATGL and CPT1, respectively. Notably, it was found that palmitate and oleate do not directly feed into β-oxidation in brown adipocytes upon activation of β-3 adrenergic receptors, which contrasts with the findings of Vergnes *et al* on FABP3 deficient mice.[40] Nevertheless, the findings of Irshad *et al* are significant and echo those made from a human beige adipocyte cell line which, by expressing pyruvate dehydrogenase kinase 4 (PDK4), redirect glucose away from the TCA cycle and towards lipogenesis.[49] Interestingly, even mild cold exposure in mice is sufficient to dramatically reprogram brown adipocyte gene expression in favor of enhanced glucose uptake (e.g. increased glucose transporter 4) and breakdown (e.g. increased glucokinase) as well as *de novo* lipogenesis (e.g. increased fatty acid synthase).[50] Also, the expression of carbohydrate responsive element binding protein β (*ChREBPβ*), a regulator of lipid metabolism genes, in human supraclavicular BAT positively correlates with *UCP1* expression.[50] These findings not only substantiate those of Irshad *et al.* and Barquissau *et al*, [49] but also underline the fact that in a normal genetic landscape, brown adipocytes gear towards local fatty acid metabolism when called upon to participate in thermogenesis. This may also involve the provision of medium chain fatty acids of peroxisomal origin, which too can activate UCP1,[4] to the mitochondria for subsequent β-oxidation.[50]

Despite the fact that glucose metabolism in the TCA seems to be insufficient to maintain body temperature in response to cold in animals lacking acyl-coA dehydrogenases[51] and are thus defective in β-oxidation, there are certain circumstances that it can acutely maintain body temperature. For instance, in mice deficient in UCP1 but overexpressing the transcription factor PR domain containing 16 (PRDM16) in adipose tissue, an ATP-

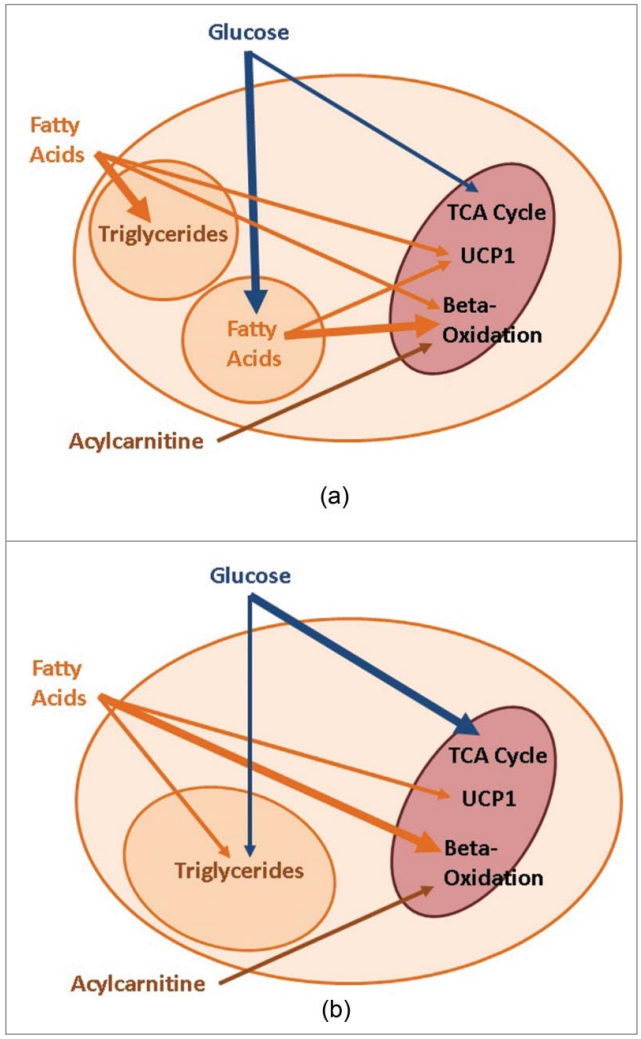

Figure 1. Plasticity of brown adipocyte substrate utilization for cold-induced thermogenesis. A). In normal cells, circulating glucose derived from food feeds mainly into a rapidly metabolisable lipid droplet pool that, after lipolysis, provides fatty acids mainly for mitochondrial β-oxidation. Circulating fatty acids derived from WAT and food are also taken up where they are mainly stored in a separate lipid droplet pool that is not so rapidly metabolized. As thermogenesis proceeds, hepatic acylcarnitines derived from fatty acids generated by WAT lipolysis start to make a significant contribution. Endogenous fatty acids would mainly activate UCP1.[58] B). In cells lacking lipolytic machinery, glucose feeds directly into the TCA cycle. Circulating fatty acids derived from WAT lipolysis and food are channeled mainly to the mitochondria for β-oxidation. Exogenous fatty acids would be required to activate UCP1.[58]

dependent form of thermogenesis specifically in inguinal beige adipocytes has recently been described.[51] This was shown to be due to a futile cycle of repeated calcium entrance into and exit out of the endoplasmic reticulum through the sarco/endoplasmic reticulum Ca^{2+}- ATPase 2b (SERCA2b) and the ryanodine receptor 2 (RYR2), respectively. Furthermore, these mice exhibited improved glucose tolerance associated with increased glucose uptake specifically in inguinal beige adipose tissue.[52] Global gene expression and metabolomics analyses also revealed increased glycolysis in these beige adipocytes, which knockdown experiments confirmed was due to SERCA2b function.[52] The decreased heat production, oxygen consumption and glycolysis caused by noradrenaline in beige adipocytes only lacking SERCA2b confirmed its physiological relevance. Thus, in direct contrast to brown adipocytes, glucose catabolism can provide ATP for beige adipocyte thermogenesis, likely due to the differential expression of ATP synthase between the two cell types.[15] This actually forms the basis of another form of UCP1-independent thermogenesis, first characterised in inguinal[53] and then in epigonadal[15] beige adipocytes, involving the ATP-dependent futile cycling between creatine and phosphocreatine in the mitochondrial intermembrane space. It should be added however that genetic inactivation of glycine amidinotransferase, the rate-limiting enzyme in creatine synthesis, in all adipocytes suggests that this pathway functions mainly in BAT to protect against hypothermia and obesity,[54] as determined by thermal imaging and metabolic phenotyping of mice exposed to cold and a high-fat diet at thermoneutrality, respectively.

Finally, although not so widely recognized, the liver too has long been known to generate heat in response to chronic cold, possibly contributing to adaptive thermogenesis.[55] The mechanisms however would be distinct from brown adipocytes in the absence of UCP1 expression and may involve induction of UCP.[56] Furthermore, because hepatic gluconeogenesis markedly increases upon noradrenaline treatment after cold acclimation, it has been reasoned that it could fuel BAT thermogenesis.[55] This may be one of the reasons why mice lacking ATGL in adipose tissue can tolerate chronic cold exposure as shown by the study of Schreiber *et al.*

Putting it all together

The recent studies discussed in this Mini-Review have transformed our understanding of how brown adipocytes are fueled. They reveal a degree of redundancy in BAT thermogenesis, in which fatty acids derived from WAT during fasting and food during feeding can fully compensate for defective lipolytic machinery. The findings of Shin *et al.* and Lynes *et al.* further substantiate the notion that by acting as a glucose and lipid sink, BAT can be exploited to treat hyperglycemia and hyperlipidemia respectively, independently of its effects on body weight. UCP1-independent forms of futile cycling are also starting to be characterized; such as the finding that various different extracellularly-generated acylated amino acids can powerfully stimulate uncoupled respiration in primary brown and inguinal beige adipocytes as well as myocytes, possibly by increasing the activity of other proton carriers in the IMM such as adenine nucleotide translocases 1 and 2.[57] That chronic systemic acylated amino acid treatment causes pronounced weight loss in mice mainly through enhancing energy expenditure attests to the promise of identifying novel thermogenic pathways for the treatment of human obesity. It would be important to establish in future studies if beige/brown adipose tissue is the main source and site of acylated amino acid synthesis and action, respectively, upon cold exposure which could also be the liver and/or skeletal muscle.[57] A model is presented (Fig. 1) in which in the normal setting, fatty acids derived from BAT, as well as glucose and fatty acids from the diet, all meaningfully contribute to brown adipocyte heat production in response to acute cold exposure. Later on, acylcarnitines derived from the liver assume a prominent role. When BAT lipolysis fails, WAT lipolysis in addition to glucose and fatty acids from the diet can readily step-in and compensate. This model of course needs to be tested, but for the time being manages to unify the findings obtained so far.

In summary, brown adipocyte thermogenesis can be viewed as gun which can be loaded with different bullets and then triggered by different fingers.

Disclosure of potential conflicts of interest

The author has no biomedical financial interests or potential conflicts of interest.

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