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Is the heat surrounding adipose tissue mitochondria warranted?

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Abstract

Purpose of review—Mitochondrial uncoupling proteins uncouple oxidative phosphorylation. The physiological role ascribed to this process is thermoregulation. The metabolic consequence of mitochondrial respiration uncoupled from ATP production is increased substrate oxidation and metabolic rate. The recent discovery of uncoupling protein 1 (UCP1) positive mitochondria in human adipose tissue has rekindled interest in the role of UCP1 in energy balance and metabolic health.

Recent findings—Recently, there have been numerous reports of functional brown adipose tissue in humans. Further, data from cell and murine studies suggest that beige adipocytes can be induced within white adipose tissue. The presence of brown/beige adipocytes with mitochondria expressing UCP1 negatively correlates with adiposity. Further, activation of these adipocytes alters energy balance and substrate metabolism. However, in humans, brown fat content varies significantly. Further, although beige adipocytes can be induced in white adipose tissue of rodents, whether this is also true in humans remains unclear.

Summary—The presence of UCP1-positive mitochondria in human adipose tissue represents an exciting therapeutic target for treating obesity and its metabolic complications. Understanding the mechanisms governing brown fat activation will be crucial if the therapeutic potential of UCP1 is to be realized.

Keywords

adipose tissue; brown fat; mitochondria; uncoupling protein 1

INTRODUCTION

Obesity results from discordance in energy intake and energy expenditure. Thus, obesity should be treatable by reducing energy intake and/or augmenting energy expenditure. However, despite a clear understanding of the thermodynamics of weight balance, a lack of

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Conflicts of interest
There are no conflicts of interest.

adherence to diet and exercise prescription means that these strategies often fail to positively impact obesity in humans. Indeed, the prevalence of obesity has risen in recent decades to epidemic proportions, posing a significant clinical and economic burden in both the developed and developing world.

Therapeutic strategies, which alter energy balance without reducing caloric intake or increasing physical activity, represent a means of treating obesity and in particular, the metabolic abnormalities that accompany obesity. Although 2,4-dinitrophenol (DNP) proved efficacious with regards to augmenting energy expenditure in humans, potentially lethal side-effects curtailed its use [1]. Currently, no therapeutic agents, which can alter energy expenditure in humans, are licensed for use in the treatment of obesity.

The recent observation that a significant proportion of humans have depots of brown adipose tissue (BAT) [2-7] represents a genuine opportunity for researchers interested in strategies that increase resting energy expenditure. Activation of mitochondrial uncoupling protein 1 (UCP1) in BAT results in increased substrate oxidation to sustain high levels of leak respiration (mitochondrial respiration not linked to ATP production). Further, recent evidence suggests that some white adipose tissue (WAT) depots in humans contain pockets of UCP1-positive adipocytes [8], often termed beige adipose tissue (BeAT) or BRITE (brown-in-white) fat. Moreover, a significant body of work in cells and rodents suggests that BeAT is inducible in WAT depots [9,10,11■■]. This is intriguing given that humans have far larger WAT depots (kilograms) compared with BAT depots (grams).

THE DIFFERENT SHADES OF FAT

There are numerous WAT depots within the human body, which play differing metabolic and endocrine roles. However, with regards to metabolic rate, these WAT depots are thought to play a minimal role. Indeed, the principle role of WAT appears to be energy storage; only a small number of mitochondria are present to provide ATP for local cellular needs. The identification of symmetrical 2-deoxy-2-(18F)fluoro-D-glucose uptake in the subclavicular region of humans [2-5], particularly following mild cold exposure [2], prompted a paradigm shift in current scientific thinking regarding adipose tissue mitochondrial function. These studies confirmed that adult humans have functional BAT with UCP1-containing mitochondria. Subsequently, humans have at least two distinct depots of adipose tissue, BAT and WAT. With that said, there is significant debate as to whether the supraclavicular BAT seen in humans is truly bona-fide BAT like that seen in animals, or more like the inducible BeAT seen in rodents, as respiratory capacities of human WAT and BAT are not as strikingly different as those of rodents [11■■,12].

With regards to rodents, the picture appears to be clearer. In addition to abundant visceral and subcutaneous WAT depots, distinct BAT depots can be found in the intrascapular region. Furthermore, inducible BeAT can be found in WAT depots, particularly inguinal subcutaneous fat, meaning that adipose tissue in rodents can be classified into three distinct groups according to their oxidative capacity. In what can be considered as analogous to white, intermediate and red skeletal muscle fibers, BAT, BeAT and WAT represent three adipose tissue types with high, intermediate and low oxidative capacity. Similar to that of

skeletal muscle, oxidative capacity is governed by vascularization, mitochondrial density (size and number) and intrinsic function (Table 1). However, the distinguishing feature of BAT and BeAT-influencing oxidative capacity is the abundance of UCP1.

MITOCHONDRIA DICTATE METABOLIC RATE

What we now know as mitochondria were first identified in the cytoplasm of striated muscle by the Swiss anatomist Albert von Kölliker in the mid 1800s. These organelles were studied more comprehensively by the German anatomist Richard Altmann in the late 19th century. In his seminal work *The Elementary Organism* (1890), Altmann described small subcellular granules similar in size to bacteria. Altmann postulated that these 'Bioblasts' represented basic units of cellular life that were somewhat autonomous from the cell. A few years after the publication of *The Elementary Organism*, the term mitochondria, meaning stringy granule, was coined to the German microbiologist Carl Benda.

In the first half of the 20th century, work focused on characterizing the role of mitochondria in energy metabolism. This culminated in the chemiosmostic theory of oxidative phosphorylation [13], for which Peter Mitchel was awarded the Nobel prize in chemistry in 1978. Oxidative phosphorylation couples electron transfer to oxygen consumption (respiration) with proton excursion across the inner mitochondrial membrane (phosphorylation). This pinpoints the mitochondrion as the site of molecular oxygen consumption in mammals. Indeed, it has been estimated that approximately 90% of whole body oxygen consumption in mammals occur within the mitochondrion [14], where cytochrome C oxidase reduces molecular oxygen to water. Subsequently, the mitochondrion is the cellular organelle that dictates metabolic rate in mammals.

OXIDATIVE PHOSPHORYLATION

Mitochondria harness redox potential generated from the oxidation of substrates by transferring electrons through a series of membrane-bound respiratory complexes and electron carriers (Fig. 1). Electrons from NADH and $FADH_2$ are shuttled to ubiquinone via complex I (NADH oxidase) and complex II (succinate dehydrogenase), respectively. Reduced ubiquinone subsequently transfers these electrons to complex III (cytochrome bc oxidoreductase) and then to complex IV (cytochrome C oxidase) via the electron carrier cytochrome C. At complex IV, electrons are transferred to molecular oxygen, forming water. As such, the mitochondrial electron transfer chain controls respiration (oxygen consumption), as oxygen is the terminal electron acceptor of the chain (Fig. 1).

The process of mitochondrial electron transfer drives proton excursion across the inner mitochondrial matrix (Fig. 1). Specifically, complexes I, III and IV pump matrix protons into the space enclosed by the inner and outer mitochondrial membranes. The accumulation of protons within the membrane space results in the development of proton motive force. Protons re-enter the mitochondrial matrix by chemiosmosis. Proton movement through the oligomycin-sensitive F_O unit of ATP synthase results in a conformational change in the F_1 unit of the enzyme complex, catalyzing the phosphorylation of ADP.

MITOCHONDRIAL COUPLING CONTROL: THE PHYSIOLOGY OF UNCOUPLING PROTEIN 1-POSITIVE MITOCHONDRIA

Not all mitochondrial respiration is linked to ATP production *in vivo*. Indeed, it has been estimated that around 80% of mitochondrial oxygen consumption is coupled to ATP production in mammals [14]; the remaining 20% of mitochondrial respiration is uncoupled from phosphorylation. This discordance is explained by proton leaks, where protons within the enclosed mitochondrial membrane space can re-enter the mitochondrial matrix independently of ATP synthase. As such, leak respiration (the transfer of electrons to oxygen that is not accompanied with mitochondrial ATP production) represents a significant portion of whole body oxygen consumption. Thus, the coupling of oxidative phosphorylation *in vivo* represents a key regulator of whole body metabolic rate.

The local ATP demands of a tissue dictate the number and functionality of mitochondria that reside within that particular tissue. For example, adipocytes require ATP for cellular housekeeping functions only (protein turnover etc). Therefore, adipocytes have few mitochondria per unit of tissue. Contrastingly, myocytes require ATP for both cellular housekeeping and for muscular contraction. As such, myocytes are densely populated with mitochondria. Further mitochondrial coupling control is also governed by ATP turnover, where tissues such as cardiac muscle are particularly sensitive to ADP.

A key feature of BAT and BeAT, which sets them apart from other tissues, is the disassociation of their mitochondrial density and functionality from ATP production. This difference in bioenergetics is mediated by UCP1. UCP1, originally named thermogenin, has the ability to almost completely dissipate mitochondrial membrane potential [15], meaning the proton gradient of the mitochondrial membranes is lost as heat. Although numerous other homologues of UCP1 exist in other tissues, such as muscle and liver, it is thought that these UCPs play a much smaller role in inner mitochondrial membrane proton conductance. Indeed, it is has been postulated that these other UCPs permit a small degree of proton conductance to maintain electron transfer to oxygen and prevent free radical production.

UCP1 does not appear to be intrinsically active in BAT mitochondria [16■], where purine nucleotides (presumably ADP and ATP *in vivo*) inhibit UCP1 [12]. As such, there is little residual proton conductance. However, upon activation by fatty acids, UCP1-containing mitochondria respire at a marked rate, but do not produce any measurable membrane potential [11■■,12,16■]. Further, chemically uncoupling activated BAT mitochondria with the ionophore carbonyl cyanide-4-(trifluoromethoxy) phenylhydrazone (FCCP) only marginally increases respiration above that of leak respiration (respiration with substrates alone and no phosphate acceptor) [11■■,17,18]. This suggests that electron transfer in BAT is almost completely uninhibited when UCP1 is activated, meaning that fuel demand will be elevated above that of a well coupled mitochondria. For example, leak respiration is generally low in muscle mitochondria, and respiration is only elevated when both substrates and ADP are provided. As such, electron flow and thus substrate oxidation in muscle are dependent on ATP needs, where phosphorylation rather than electron transfer is the rate-limiting step. This is not the case in BAT mitochondria when UCP1 is activated, where mitochondrial respiration and thus fuel oxidation are not curtailed in such a manner. Indeed,

only GDP appears to reduce mitochondrial respiration and restore mitochondrial membrane potential in BAT mitochondria [11■■,12,16■], underscoring the fact that activated UCP1 is responsible for proton conductance in BAT mitochondria.

Intriguingly, it has recently been shown that mice acclimated to 4 °C develop functional UCP1 in inguinal WAT [11■■]. Isolated mitochondria from this WAT depot exhibit marked increases in leak respiration in response to fatty acids, pyruvate, or glycerol-3-phosphate. Further, this leak respiration can largely be blocked by GDP. Again, what is quiet striking is that in mice acclimated to 30 °C, uncoupling both BAT and inguinal WAT mitochondria with FCCP results in a marked increase in respiration above that of leak respiration with substrates alone, suggesting that mitochondrial leak respiration (i.e. thermogenesis) in these animals is well within the maximal capacity of the mitochondria to transfer electrons to oxygen. However, the addition of FCCP to mitochondria of 4 °C acclimated mice, where UCP1 has been inhibited by GDP, results in mitochondrial respiratory rates almost identical to those when mitochondrial were provided with substrate alone (in the absence of GDP) [11■■]. This again highlights the unusual functional characteristics of mitochondria with activated UCP1, where electron transfer and fuel oxidation precede at or near the maximal capacity of the mitochondria. This is something not seen in mitochondria in other tissues, where respiration is limited by proton accumulation within the mitochondrial membrane.

THE ROLE OF BROWN ADIPOSE TISSUE/BEIGE ADIPOSE TISSUE IN HUMAN ENERGY EXPENDITURE AND SUBSTRATE METABOLISM

Since the discovery of BAT in humans, there has been a significant research effort to ascertain whether recruitment of UCP1-positive mitochondria has metabolic consequences for humans. Early studies, showing that glucose uptake in supraclavicular regions was increased following cold exposure, suggested that pockets of BAT in humans were indeed thermogenic [3]. Further, the presence of BAT in humans is inversely correlated with BMI, suggestive of BAT being protective against obesity [4]. Indeed, BAT activity following mild cold exposure is lower in obese individuals compared with lean individuals, where BMI and adiposity are negatively correlated with BAT activity, and resting metabolic rate is positively correlated with BAT activity [2]. Collectively, these observations suggest that in humans, BAT activation plays a role in energy expenditure.

The chronic activation of BAT by cold exposure has been shown to augment energy expenditure in humans [19]. This was achieved by exposing individuals to mild (17 °C) cold exposure for 2 h/day for a total of 6 weeks. Further, increased BAT activity was accompanied by reduced adiposity [19]. Moreover, others have shown that 10 days of mild cold exposure (6 h/day) resulted in an increase in the activity of BAT, which was accompanied by increased nonshivering thermogenesis [20■]. Interestingly, these researchers showed that this cold exposure protocol did not alter subcutaneous WAT function.

Little data are available concerning the role of BAT in fuel metabolism in humans. Orava *et al.* [21] showed that acute cold exposure resulted in a 12-fold increase in glucose uptake by BAT, suggesting that BAT plays a role in plasma glucose clearance. However, these

investigators did not show differences in whole-body insulin-stimulated glucose disposal between individuals with detectable BAT (BAT+) and nondetectable BAT (BAT−), questioning the ability of BAT to modulate whole-body glucose metabolism. More recently, Quellet *et al.* [22] showed that acute cold exposure resulted in a 1.8-fold increase in energy expenditure. However, even though BAT activation resulted in increased oxidation of intracellular fatty acids, plasma substrate oxidation by BAT was minimal, casting doubt over the role of BAT in whole-body metabolism in humans.

We have recently studied the role of BAT activation in whole-body insulin sensitivity in humans. Using glucose clamps and stable isotope methodologies, we found that prolonged (5–8 h) cold exposure increases whole body glucose disposal and insulin sensitivity in humans [23■]. These data suggest that the activation of BAT can acutely alter whole-body energy expenditure, glucose homeostasis and insulin sensitivity in humans, supporting the notion that BAT may function as an antidiabetic tissue.

RECRUITING BROWN ADIPOSE TISSUE/BEIGE ADIPOSE TISSUE IN HUMANS

Several studies have shown that acute mild cold exposure activates existing BAT depots in humans. Further, chronic (6 weeks) exposure to mild cold stimulus (2 h/day) results in a significant increase in BAT activity in humans [19]. This increase in BAT activity was associated with reduced adiposity, suggesting that recruitment of BAT is possible in humans and that this has favorable metabolic consequences. However, BAT depots in humans are small, amounting to no more than a few hundred grams. In contrast, humans have vast depots of WAT, which suggest that if WAT could acquire a BAT-like phenotype in humans, huge alterations in energy expenditure and fuel metabolism could be achieved.

Although the adrenergic response to mild cold exposure is sufficient to acutely activate pre-existing BAT in humans, prolonged mild cold exposure for 10 days does not recruit BeAT in the subcutaneous WAT of humans (i.e. browning of WAT) [20■]. One potential issue is that mild cold exposure, regardless of its duration, may be an insufficient stress to cause browning of WAT. For example, browning in animals is achieved by acclimation to 4 °C [11■■], whereas mild cold exposure in humans usually comprises a few hours at ~16-20°C. van der Lans *et al.* [20■] demonstrated that mild cold exposure resulted in a ~1.5-fold increase in circulating norepinephrine levels. Whether these transient increases in catecholamines, which activate BAT, can cause browning of WAT is doubtful. Interestingly, Frontini *et al.* [8] reported that in a cohort of patients affected by pheochromocytoma, adrenal tumors that result in chronic catecholamine release, around 50% of patients had UCP1-positive adipocytes in omental fat depots. Unfortunately, mitochondrial function assays were not performed, so it cannot be concluded whether the oxidative capacity or more specifically the thermogenic capacity of this adipose tissue was different to that of normal WAT.

Despite a wealth of data from cells and rodents, and the study by Frontini *et al.* in omental adipocytes, evidence of browning of human subcutaneous WAT is currently lacking. We have recently shown in children with massive burns that subcutaneous WAT develops a

BAT-like phenotype. In particular, the presence of UCP1 mRNA and protein is accompanied by increased uncoupled mitochondrial respiration [24]. Furthermore, this was accompanied by hypermetabolism (elevated resting metabolic rate) in these burn victims. These data are the first to demonstrate browning of human subcutaneous WAT. Burn patients are unique in that chronic 10-fold increases in circulating norepinephrine levels are observed for months post injury, which is accompanied by persistent increases in metabolic rate [25]. We saw the appearance of subcutaneous BeAT at approximately 2 weeks post injury, suggesting that the persistent adrenergic response to burns is sufficient to cause browning of WAT. Subsequently, our data suggest that if the stimulus (adrenergic stress) is intense and persistent for over 2 weeks, classical WAT depots of humans can adopt a BAT phenotype.

The metabolic consequences of browning of subcutaneous WAT in unburned individuals remain to be seen. However, if a similar degree of browning could be induced in healthy or indeed obese individuals, it is likely that this would have a significant impact on energy expenditure and substrate metabolism. For example, BeAT mitochondria of mice acclimated to 4°C have a leak respiratory capacity (thermogenic capacity) around 20% of that of BAT [11■■]. However, when considering that humans have at best a few hundred grams of BAT but tens of kilograms of WAT, suggests the conversion of WAT to a BeAT phenotype will likely have a more profound impact on energy balance. Even a more conservative change in WAT thermogenic capacity could be of significance to energy expenditure and metabolic health in humans. By way of example, our data suggest that in response to burn injury, WAT tissue mitochondrial thermogenesis increases 2-fold to 3-fold. As WAT represents ~6.2% of resting energy expenditure in humans, or ~125 kcal/day in a 70-kg male with 20% body fat [17], a 2-fold to 3-fold increase in WAT thermogenesis computes to a 125-250 kcal/day increase in energy expenditure. If this could be achieved in humans, then this would likely impact adiposity and metabolism.

CONCLUSION

Adipose tissue mitochondria were long considered to be quiescent cellular organelles that played a minor role in whole-body metabolism. Since the discovery of functional BAT in humans, the spotlight has been put on adipose tissue mitochondria and the potential therapeutic impact of UCP1 expression. Activation of BAT and its UCP1-positive mitochondria augments energy expenditure and improves circulating substrate metabolism in humans. However, the quantity of BAT varies significantly in humans, and is never more than a few hundred grams. The possibility of BeAT induction in the far larger WAT depots of humans holds much promise. However, for the therapeutic potential of BeAT to be realized, the events leading to the induction of UCP1 mitochondria need to be better understood.

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KEY POINTS

- UCP1-positive mitochondria can increase energy in humans when activated.
- Browning of classical white adipose tissue in humans is possible after prolonged adrenergic stress.
- The recruitment/activation of UCP1-positive mitochondria represents a means of treating obesity and its metabolic complications.
- Effective strategies that recruit/activate UCP1-positive mitochondria are needed before the therapeutic potential of uncoupled mitochondria can be realized.

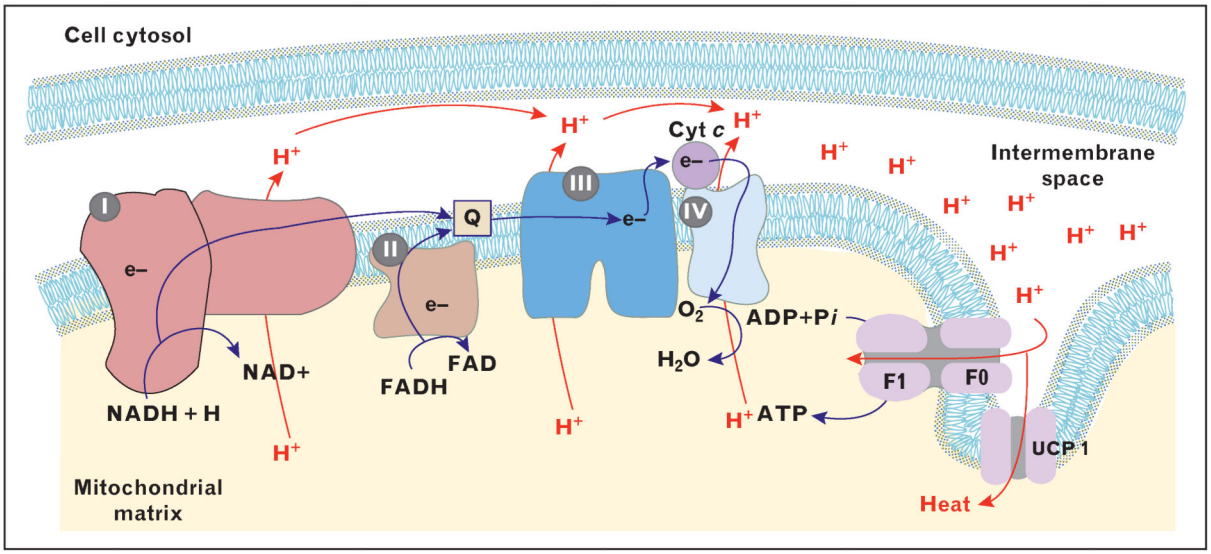

FIGURE 1.

Schematic representation of the components of the electron transport chain. ADP, adenosine diphosphate; ATP, adenosine triphosphate; Cyt c, cytochrome C; e, electrons; F_1F_0, ATP synthase; FAD, oxidized flavin adenine dinucleotide; $FADH_2$, reduced flavin adenine dinucleotide; H, protons; H_2O, water; I, NADH oxidase; II, succinate dehydrogenase; III, cytochrome bc oxidoreductase; IV, cytochrome C oxidase; NAD, oxidized nicotinamide adenine dinucleotide; NADH, reduced nicotinamide adenine dinucleotide; O_2, molecular oxygen; Pi, inorganic phosphate; Q, Ubiquinone; UCP1, uncoupling protein 1.

Table 1

Adipocyte characteristics

	WAT	BeAT	BAT
Cell size	XXX	XX	X
Lipid droplet size	XXX	XX	X
Lipid droplet number	X	XX	XXX
Mitochondrial density	X	XX	XXX
UCP1 expression	X	XX	XXX
IMM proton conductance	X	XX	XXX
Proportion of body mass	10–50%	?	0–0.2%

BeAT, beige adipose tissue; IMM, inner mitochondrial membrane; UCP1, uncoupling protein 1.