Cell Metabolism
Minireview
Focus on Brown Adipose Tissue

The Changed Metabolic World with Human Brown Adipose Tissue: Therapeutic Visions

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That adult humans possess active brown adipose tissue potentially leads to a paradigm shift in the understanding of human metabolism and of obesity. Adaptive adrenergic thermogenesis in humans represents brown adipose tissue activity, the absence of which may contribute to middle-age obesity.

During the first decade of this century, a realization has successively developed that a significant number of adult humans possess active brown adipose tissue (Nedergaard et al., 2007; Saito et al., 2009; van Marken Lichtenbelt et al., 2009; Virtanen et al., 2009; Zingaretti et al., 2009). This was originally based on observations in cancer patients examined for the presence of metastases by positron emission tomography (PET) scanning (examining the uptake of ^{18}F-fluoro-2-deoxyglucose) (Nedergaard et al., 2007; Cypess et al., 2009). In its extrapolation, this realization may have widespread consequences for our understanding of human metabolism and metabolic pathophysiology—and thus on the development of therapeutic tools and the analysis of their effects.

Thus, until now, the accumulated data concerning brown adipose tissue function and metabolic significance obtained from studies of rodents (Cannon and Nedergaard, 2004) have been considered to be of scientific interest—but still somewhat esoteric, since these data were assumed to be without direct relevance for human physiology and pathophysiology. However, we are now in a new metabolic world where these data can indeed be extrapolated to the human situation, yielding new explanations for human metabolic phenomena and new avenues for therapeutic intervention. The activity of brown adipose tissue—and particularly the absence of activity in certain subjects—needs now to be forwarded in the discussion of several metabolic phenomena and problems—and of solutions for these. Our intention here is to point to some of these issues.

Implications for General Studies of Metabolism

The presence of brown adipose tissue in adult humans, and the fact that its activity is acutely stimulated by cold (Nedergaard et al., 2007; Saito et al., 2009), reinitiates discussions of our ability to exhibit and develop classical nonshivering thermogenesis (NST), i.e., an ability to increase—with time in chronic cold—brown fat-derived heat production and thus to cease shivering (which is our acute and immediate heat-producing mechanism). In a circular argument, it has been maintained that we cannot develop NST because we do not have brown adipose tissue. There is now at least one indication (Saito et al., 2009) that human subjects in winter may have more brown adipose tissue than the same subjects during summer, implying a recruitment of NST. The mechanism behind this is not evident, as in human civilization, exposure to cold in the winter is normally not much higher than in the summer, due to clothes and house heating. Whereas the feeling of being thermally comfortable in relatively cool surroundings is evidently positive, alterations in the ability to recruit NST have not normally been considered an important factor in human physiology.

Searching for Thermogenic Alternatives May Be Unnecessary

In retrospect, it becomes evident that significant scientific efforts have been based on the (implicit) hypothesis that "as brown adipose tissue is not found in adult humans, there must be alternative (human) mechanisms for (adaptive) thermogenesis (most likely located in muscle)." A scientific goal has therefore been to identify such alternative mechanisms. It is the conclusion of rodent experiments that all adaptive adrenergic thermogenesis originates in brown adipose tissue (Golozoubova et al., 2006; Feldmann et al., 2009). The consequence of the presence of brown adipose tissue in adult humans should therefore be that any observable adaptive adrenergic thermogenesis should be solely ascribed to brown adipose tissue activity. This does not mean that futile cycles, different ion leaks, etc. do not exist and are not thermogenic, but that there are no indications that these mechanisms can be recruited for enhanced (adrenergic) thermogenesis under physiological conditions. In broader terms, we also consider it unlikely that humans should have evolved specific adrenergic thermogenic mechanisms not observable in rodents.

The Role of "Brite" Adipose Tissue

Within classical white adipose tissue depots, a particular type of adipocytes sometimes occur. These "brite" (brown-in-white) adipocytes manifest several classical brown adipocyte characteristics, most notably the presence of UCP1. There is, however, reason to believe that these cells do not represent brown adipocytes of the same lineage as those found in classical brown adipose tissue depots (Himms-Hagen, 2000), since the brite adipocytes do not express the novel molecular markers characteristic of classical brown adipocytes (Petrovic et al., 2010). Based mainly on the contention that adult humans do not possess brown adipose tissue, techniques to promote the growth of these brite adipocytes have been directly or indirectly advocated as a means to counteract obesity. To date, there have been no quantitative investigations, even in mice, of the relative contribution of these brite depots to total adrenergic

thermogenesis (e.g., the total amount of UCP1 in the brite adipose tissue depots has not been compared to that in the classical brown adipose tissue depots). In humans, in PET scans, classical white adipose tissue depots are not visible as areas demonstrating glucose uptake under conditions in which brown adipose tissue is activated and visible. Thus, these brite depots may not be of major thermogenic significance in humans, but alternatively, their invisibility may be due to a brite adipocyte-specific lack of thermogenic glucose uptake or limitations in the level at which they can be detected. What the brite adipocytes represent physiologically is difficult to say. Their occurrence is definitely of molecular and developmental interest, but therapeutically it would now rather seem to be of interest to promote the persistence of the genuine brown adipose tissue depots in adult humans.

The Basic Problem of Brown Fat Activation

In some discussions in the field, it appears that UCP1 is presumed to be innately active within the (brown fat) cells (i.e., it should be sufficient to increase the total amount of UCP1 in order to enhance thermogenesis). This is not so. Although in isolated mitochondria UCP1 is uninhibited and therefore spontaneously active, in intact cells UCP1 is constantly inhibited by purine nucleotides in the cytosol (mainly ATP; experimentally GDP is routinely used as an inhibitor, but this is only for practical reasons) (Figure 1) (Cannon and Nedergaard, 2004). This inhibition has thus to be overcome through a process that probably involves fatty acids interacting directly with UCP1 and which is initiated physiologically by norepinephrine. Therefore, (pharmaceutical) projects based solely on increasing the total amount of brown adipose tissue or UCP1 in the body may be basically flawed—because the extra UCP1 will not automatically be active. There are indeed no indications that the amount of UCP1 influences *basal* brown adipocyte metabolic rate or total body metabolic rate—metabolism is only influenced when UCP1 is physiologically or pharmacologically activated. Rodents adapted to the cold (probably also humans) develop large amounts of brown adipose tissue—but immediately (i.e., within seconds) after they are transferred to warmer conditions, brown adipose tissue activity is turned off. Thus, the animal decides continuously how much of its total thermogenic activity it needs to compensate for heat loss, as a specific quantity (watts) and not as a percentage of capacity available. Similarly, we must assume that centers in the brain also determine how much of the capacity of the tissue that is required during metaboloregulatory thermogenesis, i.e., the total amount of combustion (watts) needed to adequately balance food energy intake (or body energy content), and that this is independent of the total amount of UCP1 and thus the capacity for thermogenesis. Thus, any pharmaceutical goal to increase the total amount of brown adipose tissue in the body must also encompass a method to ensure that the tissue is adequately stimulated, in reality by providing an adrenergic stimulation of the tissue. In reality the necessity for acute stimulation of activation is advantageous as we—if UCP1 were innately active within the brown adipocytes—would pharmaceutically create a tissue that in an uncontrolled way would drain our energy (cf. dinitrophenol).

A Bimodal Distribution of Brown Adipose Tissue

From observations on the occurrence of UCP1-positive cells in the neck region, a bimodal distribution of such cells was noted:

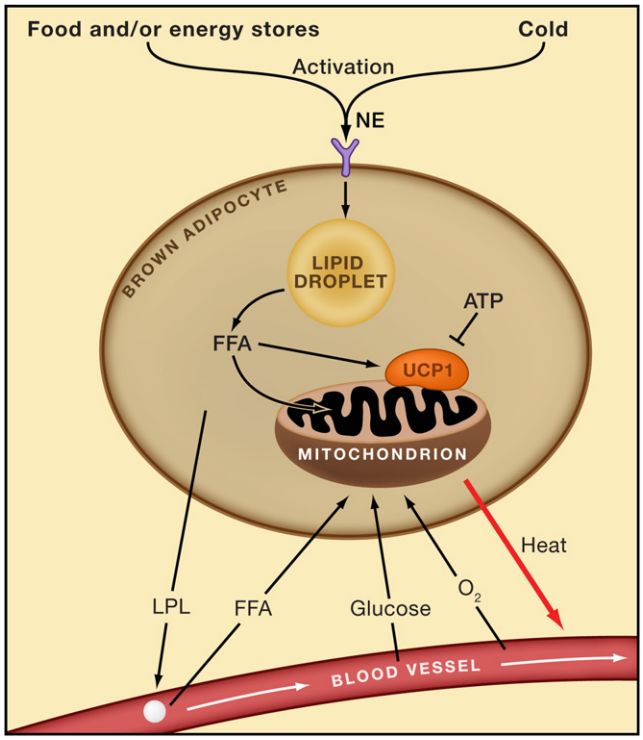

Figure 1. Regulation of the Activity and Recruitment of Brown Adipose Tissue

In the resting state, the protonophoric activity of UCP1 in the mitochondrial inner membrane is inhibited by cytosolic purine nucleotides, notably ATP. When brown adipose tissue is activated from centers in the brain affected by environmental temperature or acute food intake (or body energy stores), norepinephrine (NE) is released from the sympathetic nerves innervating the tissue. In the mature brown adipocytes, this leads to hydrolysis of the triglycerides stored in the lipid droplets, and the released fatty acids (FFA) in some way activate UCP1, overcoming the inhibition. Due to the uncoupling activity of UCP1, the combustion of different substrates may now proceed: fatty acids released from triglycerides (fat droplets) in the tissue are initially the main source, but successively the main substrates for heat production are delivered from the circulation. NE induces release of lipoprotein lipase (LPL) that degrades chylomicrons and VLDL in the circulation, and the released fatty acids are combusted, and there is also stimulated glucose uptake into the cells (making active brown adipose tissue visible in fluorodeoxyglucose PET scanning). The combustion of all these substrates demands high oxygen uptake, and the blood leaving the tissue is heated but extremely oxygen depleted. During chronic stimulation, NE also stimulates the progenitor cells in the tissue to proliferate and the brown preadipocytes to differentiate (a process that can also be stimulated by PPARγ ligands). NE has also an antiapoptotic effect on the cells. Thus, chronic stimulation will increase the total capacity of the tissue, a process referred to as recruitment.

a given subject would seem to either have or not have such cells (Zingaretti et al., 2009). Similarly, evaluations of total glucose uptake by PET techniques indicate a bimodal distribution between different individuals, provided that a broad span of age groups are investigated (Saito et al., 2009); among younger individuals, nearly everyone seems to possess brown adipose tissue (van Marken Lichtenbelt et al., 2009). Even among individuals possessing brown adipose tissue, the range of total glucose uptake (activity) is very large (nearly two orders of magnitude); taken together, this means that a significant contribution of brown adipose tissue to metabolism is expected in certain individuals and not in others. This may be an explanation for

previously observed differences in human responsiveness to pharmaceutical treatments and experimental tests. It is foreseeable that future metabolic studies should include a prior estimate of an individual's total brown adipose tissue. Unfortunately, there are presently no simple and sufficiently sensitive methods available to determine this, other than the rather expensive PET method, which also involves administration of relatively high doses of radioactivity into healthy subjects.

Implications for Understanding the Etiology of Obesity

Cause or Effect

All studies to date agree that the absence of brown adipose tissue is correlated with obesity also in humans. Although this is only a correlation, it is reasonable today to extrapolate from mouse data to humans. Broadly speaking, since the absence of UCP1 activity is sufficient to cause or aggrevate obesity in mice (Feldmann et al., 2009), the absence of brown adipose tissue activity can be an explanation for at least a subset of human obesities. Particularly what can be termed "age-induced obesity"—the general tendency of humans in middle age to show an increasing propensity to develop obesity—is reasonable to discuss in the context of being caused or advanced by diminished brown adipose tissue activity.

Enough for Making an Obese Difference

It can be estimated from PET scans that not much brown adipose tissue is found in adult humans (some tens of grams). It may therefore be questioned as to whether it could have any metabolic significance. However, the very marked effects of UCP1 ablation on body composition of mice living at thermoneutrality (Feldmann et al., 2009) indicate that even minor amounts of brown adipose tissue can substantially affect metabolism. Evidently, even small but consistent imbalances in the energy input/output equation ultimately lead to obesity/leanness. It is clear from the mouse experiments that the organism does not always compensate for an absence of brown adipose tissue activity by undereating, particularly when challenged with a palatable diet.

An Only Apparent Conundrum

It may initially seem contradictory that increasing fat accumulation is associated with more UCP1/brown adipose tissue—while claiming that an absence of UCP1 leads to obesity. However, it is a necessary consequence of the concept of diet-induced thermogenesis that the more a (healthy) organism inclines toward obesity, the more brown adipose tissue it will develop in an attempt to counteract the developing obesity. This will act to reduce (but will be unable to fully prevent) the development of obesity. In a situation where brown adipose tissue for some reason has been lost, this counteraction can no longer function, and thus an absence of UCP1/brown adipose tissue will promote a more severe obesity.

A Hypothesis Linking Aging, Obesity, and Brown Adipose Tissue

The involution ("atrophy") of brown adipose tissue with age, earlier thought to occur and be completed already during early childhood in man, was at that time suggested to result from the increase in body size occurring with age. The subsequent decrease in surface/volume ratio would lead to a decreased requirement for brown adipose tissue heat production for maintenance of body temperature. While the high heat loss may adequately explain the presence of brown adipose tissue in children, its presence in young adults cannot be explained in this way, nor can its involution with increasing age. Rather, the involution would seem to be an endogenously controlled process, which may result in an increased propensity for obesity with age. Principally, this involution is also seen in experimental animals with increasing age. This implies that an (endocrine) switch takes place during late adult age, diminishing the amount and activity of brown adipose tissue. One possible scenario for this is discussed here.

There are studies implying a negative effect of glucocorticoids on brown adipose tissue (Soumano et al., 2000), but little is known about the underlying molecular mechanisms. Inactive brown adipocytes become lipid filled and enlarged. It is in this context of interest that the adipose depots—particularly the supraclavicular depot—that contain islands of brown adipose tissue in younger and slimmer human subjects are those that enlarge, with lipid-filled white adipocyte(-like) cells, in Cushing's syndrome (Nieman and Ilias, 2005), supporting the existence of an inactivating effect of the glucocorticoid system on brown adipose tissue, even in adult humans.

In contrast, there is some evidence that sex hormones, both androgens (Yanase et al., 2008) and estrogens (Rodriguez-Cuenca et al., 2007), may be beneficial for brown adipocyte differentiation. Thus, a scenario can be envisaged where in younger years a general negative effect of glucocorticoids on brown adipose tissue may be opposed by positive effects of sex hormones (Figure 2). However, as sex hormone levels diminish with increasing age, the negative effect of the glucocorticoids will dominate, and a state will develop where brown adipose tissue will atrophy, despite glucocorticoid levels being normal. This will inhibit brown adipose tissue activity and ultimately lead to its total involution. As a result, these subjects will be in a metabolic state with an increased propensity to develop obesity. Accordingly, the metabolic syndrome is typically a syndrome appearing in late middle age. It may be wondered why aging "should" necessitate these consequences—but we have no satisfactory explanations for the necessity of any aging process.

Implications for the Experimental Study of Obesity

Why Are Obesity Experiments Performed with Young Cold-Exposed Mice?

Obesity is classically a problem of middle age. It is therefore remarkable that nearly all experimental investigations into obesity use young male mice. Further, these mice are housed at a temperature where their metabolism is not endogenously determined but is governed to a large extent by the need to compensate for heat loss in order to defend body temperature. At normal housing temperatures, mice have to constantly increase their metabolism 50%–100% above basal metabolic rate, a very remarkable metabolic task if transposed to humans. Furthermore, this means that the mice at such normal animal house temperatures are constantly subject to an increased sympathetic drive. Most importantly, however, it is only at thermoneutral temperatures that it is possible to identify thermogenesis that is truly metaboloregulatory; at all lower temperatures, thermoregulatory thermogenesis is activated, masking and thus making it impossible to observe the metaboloregulatory thermogenesis. Only at thermoneutrality can the essentiality of

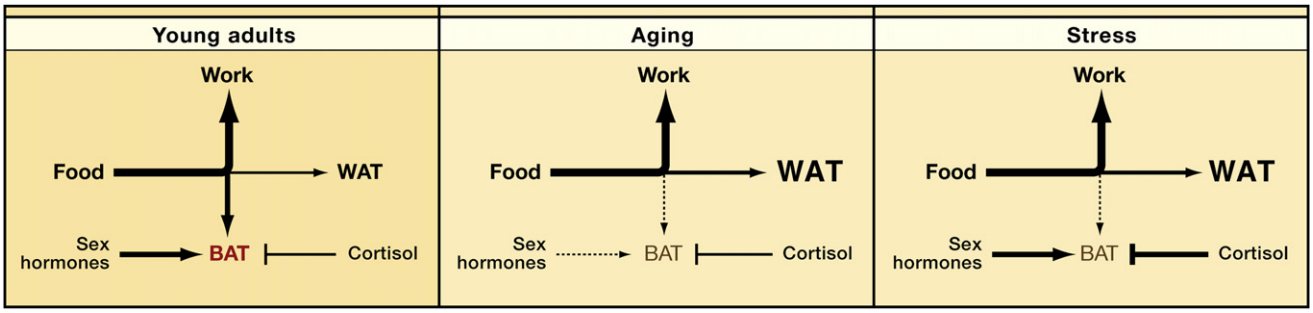

Figure 2. A Hypothesis for Age-Related Brown Adipose Tissue Involution
In the young adult, the function of brown adipose tissue (BAT) is influenced, directly or indirectly, both by sex hormones (that have been reported to promote brown adipose tissue function) and by cortisol (that inhibits brown adipose tissue function). Of the total energy intake, a certain fraction is combusted in brown adipose tissue while the major fraction is used for organismal "work": basal metabolism and physical work on the surroundings, and very little is stored in white adipose tissue (WAT). With age, the effects of the sex hormones weaken, and the inhibitory effect of cortisol is therefore *relatively* increased, diminishing brown adipose tissue function. Provided that energy intake and "work" are unchanged, this would successively lead to obesity (increased white adipose tissue). In conditions in which the amount of cortisol increases (e.g., stress or Cushing's syndrome), the *relative* influence of cortisol of course also increases, with the same final result: involution of brown adipose tissue and the development of obesity.

brown adipose tissue for diet-induced thermogenesis be established, and only at this temperature can the obesity-inducing effect of the absence of brown adipose tissue be observed.

It is to be expected that new genes influencing metabolism and thus obesity can be identified if mice are examined under thermoneutral conditions, since the effects of gene ablations may have previously been overshadowed by the requirements for thermoregulatory thermogenesis necessary at "normal" environmental temperatures. Furthermore, at environmental temperatures below thermoneutrality, gene knockouts that increase heat loss will result in a false impression of giving metabolic protection against obesity. This is particularly relevant for mutations that influence skin and fur quality.

Implications for the Treatment of Obesity

Thermogenesis Is Not Compensated

Based on the general adipostat/lipostat hypothesis for body weight control, any increase in energy output should be compensated by increased food intake, a process proposed to be mainly mediated via leptin. However, as discussed in more detail elsewhere (Cannon and Nedergaard, 2009), thermogenesis challenges the adipostat hypothesis of body weight control: increased thermogenesis often does not lead to a fully compensatory increase in food intake. Thus, activation of brown fat-derived thermogenesis would lead to weight reduction even without (conscious) attempts not to compensate increased energy expenditure with increased food intake.

Two Ways to Recruit Brown Adipose Tissue

The classical physiological method to recruit brown adipose tissue is through persistent adrenergic stimulation. This will simultaneously also activate the thermogenic effect. Administration of synthetic PPARγ ligands (thiazolidinediones) has also a recruiting effect. However, the increased amounts of brown adipose tissue/UCP1 are not sufficient per se to obtain a thermogenic effect; a means to constantly activate the UCP1 is also needed (Sell et al., 2004). The physiological relevance of this nonthermogenic recruitment process is not presently known—but it may correspond to intrauterine prebirth recruitment or prehibernation recruitment.

Perhaps Only β_1-Adrenoceptor-Induced Thermogenesis in Humans

In rodents, adrenergic stimulation of thermogenesis can be elicited (and probably physiologically is elicited) via the rather adipose-selective β_3-adrenergic receptor. If the same were true in humans, this would be therapeutically advantageous, as targeted β_3-agonists could be used. However, brown fat activation in humans can be inhibited by the β-adrenergic antagonist propranolol, given at doses normally used to inhibit β_1-adrenoceptors (Nedergaard et al., 2007). Since propranolol is a much weaker antagonist on β_3- than on β_1-adrenoceptors, the implication is that brown adipose tissue thermogenesis in humans is primarily regulated through β_1-adrenoceptors, even though β_3-adrenoceptors are present in the tissue. There is thus reason to think that a significant difference in β-adrenergic response between mice and humans may be encountered, making the maintenance of a chronic activated state far from trivial.

It may be added that even if β_3 treatment were able to activate thermogenesis in adult humans, this would probably only be in pre-existing mature brown adipocytes. Brown preadipocytes only possess β_1-adrenergic receptors (for stimulation of proliferation), and chronic treatment with β_3-agonists would therefore not lead to a recruitment of the precursor cells found in the brown adipose tissue depots.

Leptin

Only in very rare cases has leptin treatment provided direct beneficial effects on obesity. A more promising avenue has been to treat subjects undergoing weight reduction with leptin. This is because food restriction leads to an energetic compensation through reduction of metabolism, enhancing the difficulties of achieving weight reduction. Leptin prevents this decrease in metabolism by stimulating thermogenesis. The site of the thermogenic effect of leptin under these conditions is generally unspecified, and an effect on muscle has often been implied. At least in mice, the thermogenic effect of leptin treatment is entirely mediated by brown fat (Commins et al., 2001), implying that only subjects already possessing brown adipose tissue would be suitable targets for this treatment (although in the

best case, chronic leptin treatment should also lead to brown adipose tissue recruitment).

Implications for Diabetes

As brown adipose tissue is an adipose tissue in the sense that its cells accumulate lipid, the general concept has been that brown adipose tissue produces heat by combusting this stored lipid. However, the stores are limited, and it has thus been recognized that lipids required for combustion are also obtained from the rest of the organism, particularly from chylomicrons in the circulation, through the activity of lipoprotein lipase. Additionally, brown fat mitochondria are equally well suited to carbohydrate combustion as to lipid combustion (Figure 1). The realization that brown adipose tissue and muscle share a common origin (Kajimura et al., 2010) may make it easier to accept the concept that brown adipose tissue is not a selective lipid consumer but will also readily combust carbohydrate (indeed it is glucose uptake that is seen in the PET scans).

In an extension of this, because of its inordinately high metabolic capacity, involution or inactivity of brown adipose tissue could be a significant component in an increasing inability of the body to dispose of glucose. Insulin stimulates glucose uptake in brown adipocytes through mechanisms similar to those in other insulin-sensitive tissues. However, additionally, in brown adipocytes (as in myocytes) glucose uptake is stimulated by norepinephrine. Thus, the glucose-utilizing activity of brown adipose tissue could delay the development of a situation in which steadily increased glucose levels would successively lead to insulin resistance.

Since we are at rest (i.e., have no muscle glucose utilization due to activity) during at least one-third of our lives, glucose disposal mediated by brown adipose tissue may be a significant factor in maintaining euglycemia. Additionally, one study, so far not further explored, indicates that a specific inability of brown adipocytes to respond to *insulin* stimulation can apparently lead to a systemic glucose intolerance syndrome (Guerra et al., 2001).

A New View on the Major Goal for Therapeutic Efforts

Until now, the implicit goal for brown fat-based obesity therapies has been to increase the amount of brown adipose tissue (or at least UCP1) in already obese subjects—so that their excess energy reserves could be endogenously combusted. However, our new insights into the physiology of human brown adipose tissue could lead to an alteration in our goals. With the understanding that practically all humans at a young adult age possess active brown adipose tissue and that most humans lose the tissue with age, a major therapeutic interest could perhaps lie in obtaining a means to keep the tissue recruited and to avoid its involution, and to ascertain that the tissue that is present is being adequately activated, thus reducing obesity development. Individuals identified as having declining brown adipose tissue activity would be the target group. An understanding of the processes that keep the brown adipocyte precursors in proliferatively competent states capable of differentiation and that inhibit the apoptosis/cell death responsible for involution of the tissue would become the basis for new targets for therapeutic intervention.

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