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HOW BROWN FAT INTERACTS WITH WHITE FAT

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Abstract

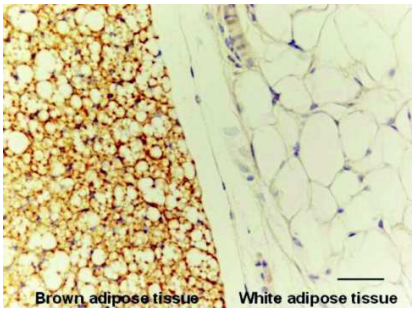
Brown adipose tissue, an essential organ for thermoregulation in small and hibernating mammals due to its mitochondrial uncoupling capacity, was until recently considered to be present in humans only in newborns. This fat is composed of several small lipid (fat) droplets and a large number of iron-containing mitochondria (the cell's heat-burning engine). Brown adipose tissue is uniquely able to rapidly produce large amounts of heat through activation of uncoupling protein (UCP) [1]. Maximally stimulated brown fat can produce 300 watts/kg of heat compared to 1 watt/kg in all other tissues. UCP1 is only present in small amounts in the fetus and in precocious mammals, such as sheep and humans; it is rapidly activated around the time of birth following the substantial rise in endocrine stimulatory factors. Brown adipose tissue is then lost and/or replaced with white adipose tissue with age but may still contain small depots of beige adipocytes that have the potential to be reactivated. In humans brown adipose tissue is retained into adulthood, retains the capacity to have a significant role in energy balance, and is currently a primary target organ in obesity prevention strategies. Thermogenesis in brown fat humans is environmentally regulated and can be stimulated by cold exposure and diet, responses that may be further modulated by photoperiod. Increased understanding of the primary factors that regulate both the appearance and the disappearance of UCP1 in early life may therefore enable sustainable strategies in order to prevent excess white adipose tissue deposition through the life cycle.

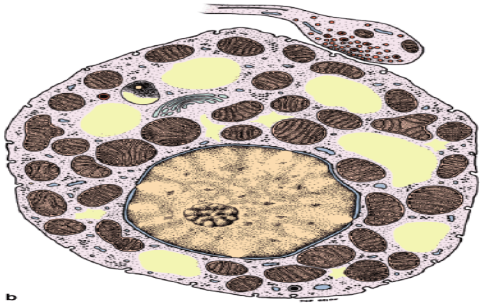
Keywords: BAT, UCP, White fat, obesity, brown adipose tissue; HFD: high fat diet; SNS: sympathetic nervous activity; WAT: white adipose tissue.

Introduction

The iron, along with lots of blood tiny blood vessels, gives this fat its brownish appearance. Brown fat is usually found in the front and back of the neck and upper back. The purpose of brown fat is to burn calories in order to generate heat. That's why brown fat is often referred to as the "good" fat, since it helps us burn, not store, calories. Brown fat is derived from muscle tissue and is found primarily in hibernating animals and newborns. After life as an infant, the quantity of brown fat significantly decreases. Adults who have comparatively more brown fat tend to be younger and slender and have normal blood sugar levels. It is generated by exercising, which can convert white-yellow fat to a more metabolically active brown fat; getting enough high-quality sleep, as proper melatonin production influences the production of brown fat; and exposing yourself to the cold regularly, such as exercising outdoors in the wintertime or in a cold room. Lowering the temperature in your living and working spaces is another tip[2]. White Fat is composed of a single lipid droplet and has far less mitochondria and blood vessels, thus resulting in its lighter white or yellow appearance. White fat is the predominant form of fat in the body, originating from connective tissue. White fat has many purposes. It provides the largest energy reserve in the body. It's a thermal insulator and cushion for our internal organs, and cushions during external interactions with our environment (that's code for a soft landing when we fall on our behind!). It is a major endocrine organ, producing one form of estrogen as well as leptin, a hormone that helps regulate appetite and hunger.[3] it's also got receptors for insulin, growth hormone, adrenaline, and cortisol (stress hormone). So, it's a myth that fat cells just sit there and do nothing all day long. In women, excess fat accumulates around the hips, thighs, buttocks, and breasts until perimenopause (the 40s), when fat is redistributed to the abdomen as well. Men tend to gather excess fat primarily in the belly region most of their lives[4]. An excess of white fat inside the belly (visceral fat) is associated with metabolic syndrome—a group of symptoms that signal an increased risk for heart disease, diabetes, and cancer. Location of body fat really counts! Excess white fat throughout the body is associated with an increased risk of breast, colon, esophageal, gall bladder, and pancreatic cancer. It's also associated with sleep apnea, and physical disabilities such as knee arthritis. Here's how much white fat a "normal-weight" person would carry throughout a lifetime: Men's body fat range is 15 to 25 percent; women's is 15 to 30 percent. Your generic 154-pound person would carry about 20 pounds of fat. One pound of stored fat contains roughly 4,000 calories, so 20 pounds has 80,000 calories of energy storage. If you required 2,000 calories to live per day, you'd last about 40 days on a desert island. These numbers aren't meant to be perfect or exact, but instead, give you a broad, general idea[5]. As a species, white fat is very important to our survival. It's a matter of how much and where it's located. You want to control your visceral fat level (keeping your waist circumference to less than 35 inches if you're a woman and to less than 40 inches if you're a man) and keep your total body fat within the normal ranges for each gender. Does white fat interact with brown fat? New research shows that when people overeat, they not only increase their total amount of white fat, but the overconsumption results in their brown fat becoming dysfunctional and thus unable to burn calories. Starting today, make it a point to achieve two major goals[6]: Optimize your brown fat function and manage your white fat load—by doing precisely the same thing. That is, eat whole foods in moderation, stay active, practice stress resilience, and lead a mindful lifestyle. The study of brown adipose tissue (BAT) biology has always been an exciting and

vibrant arena not least because although this tissue is present in comparatively small amounts, it can have a pivotal role in energy balance. BAT is characterized as possessing large amounts of the unique uncoupling protein (UCP) 1 which when activated enables the free-flow of protons across the inner mitochondrial membrane, resulting in the rapid dissipation of chemical energy as heat. [7]Consequently, when maximally activated, BAT can generate up to 300 W/kg of tissue compared with 1 W/kg from most other tissues. This process is regulated primarily by the unmasking of GDP-binding sites located within UCP1 and represents the initial response necessary to ensure rapid heat generation. The primary energy source for this process comes from nonesterified fatty acids that are released from lipid at the same time as UCP1 is activated, usually through activation of the sympathetic nervous system. Despite the control of BAT being well documented from a range of investigations in both small and large mammals, it has only been over the past decade following the discovery of the presence of thermogenically active BAT in adult humans that its potential role in a range of homothetic processes has been suggested[8]. Brown adipose tissue has been the subject of a number of recent reviews which have included a developmental perspective and the potential role it can have on metabolic flux and have largely focused on studies in humans and rodents. The current paper will therefore focus on potential insights that can be gained from also using large animal models of development together with the use of new imaging techniques such as thermal imaging to assess BAT function. Ultimately this may enable a life-course approach to the study of BAT biology in order to provide sustainable interventions aimed at preventing the pronounced loss of BAT with age.

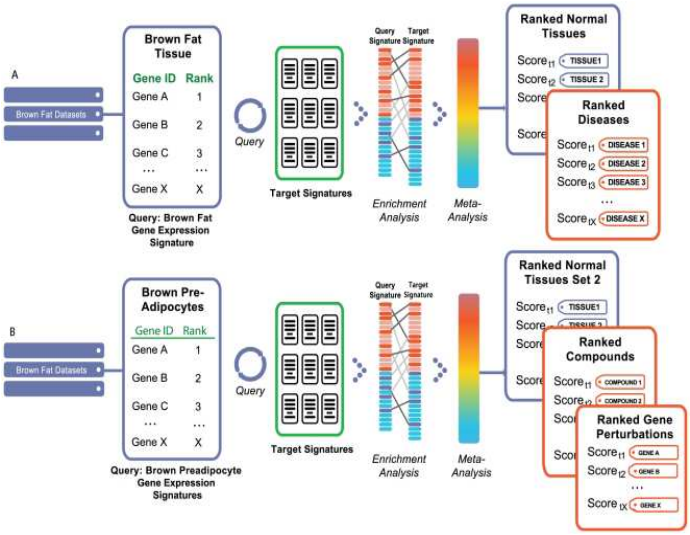


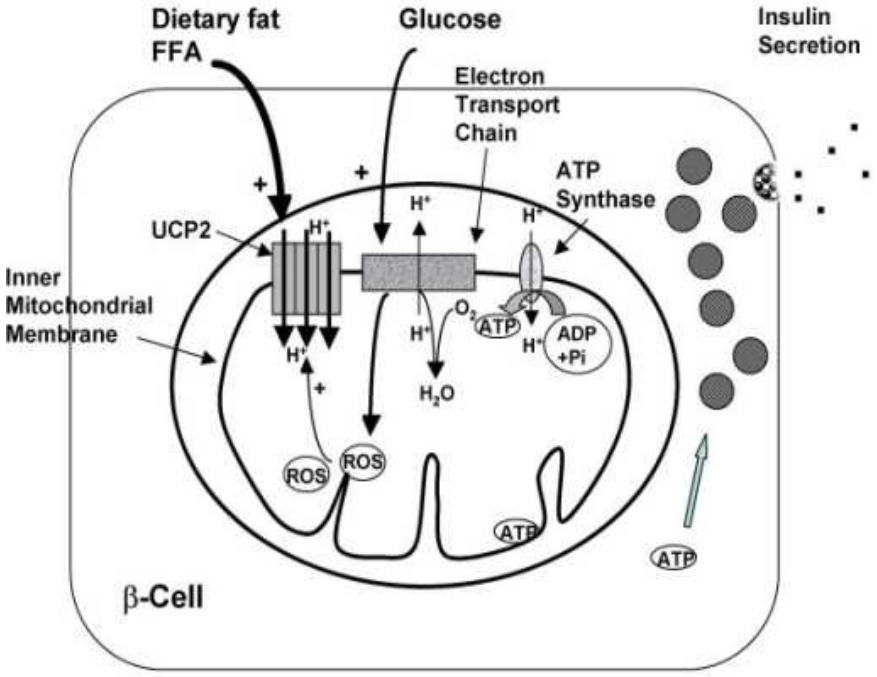


Observation

In small animal models defective BAT function is closely associated with increased white fat deposition, but in humans although increased body mass index is accompanied with decreased BAT, whether this is a cause or consequence remains to be established. The precise contribution of BAT to daily heat production is a contentious issue; it has been calculated that only small amounts of BAT may make a substantial difference to daily energy expenditure with ~60 g of BAT estimated to contribute up to 20% of daily heat production in adult humans. In many genetic studies of obesity, however, the potential role of BAT is largely ignored, even in rodent studies that would be expected to impact on BAT function. The developmental regulation of BAT and the extent to which its subsequent loss into adulthood can either be delayed and/or reversed are all factors that could make a significant contribution to overall energy balance. Ideally, these processes need to be considered in view of contemporary lifestyles as a substantial[9] majority of

humans now live in an urbanized environment, have a sedentary lifestyle, and tend to consume food in a "grazing pattern" through the day rather than have fixed and more modest sized meals 2-3 times a day .All of these factors would be predicted to compromise BAT function and thus contribute to excess white fat deposition although this remains to be fully established[10]. It is also likely that diurnal variations in BAT temperature in addition to more acute changes in response to environmental challenges such as variations in day length will all impact on the ability of BAT to produce heat and therefore energy balance. The recent rediscovery of BAT in adult humans was the consequence of publications from nuclear medicine describing the symmetrical and differential tissue uptake of ^{18}F-fluorodeoxyglucose (FDG) during positron emission tomography (PET) scans undertaken for diagnosis and monitoring of malignant disease. Utilized as an intravenously administered radioactive glucose analogue, FDG is taken up but not metabolized by tissues, and can therefore be used to identify any organ with significant glycolytic activity[11]. As a highly metabolic tissue, BAT exhibits comparable "FDG trapping" accounting for this additional uptake in apparent nontumour sites. Concomitant computed tomography (CT) fusion and guided biopsy of these regions have allowed the localization of BAT in humans. A number of studies have thus shown that when patients have had some degree of cold exposure prior to undergoing PET-CT, then BAT is readily detectable .it can be rapidly activated by cold exposure , the amount decreases with age and body mass index , and it is more likely to be detected in female than male patients . There is, however, considerable variation in potential BAT function which adds to the difficulty in assessing its potential role in overall energy balance regulation .It is not only the distribution of BAT that has been reassessed but also its developmental origin and precursor cell types, Rodent studies have thus established that brown adipocytes are derived from a myogenic lineage, separate entirely from white adipose tissue. Consequently, there are at least three different categories of adipocyte, that is, brown, white, and Brown. Furthermore the relative distribution of these individual or





mixed cell types varies significantly between each fat depot in the body which may reflect their differential responsiveness to external challenges such as cold exposure, Moreover, at least in mice, genetic variability affects beige, but not BAT, development, suggesting that their regulation is very different during early life[12]. To date, however, the precise role of beige adipocytes in overall energy balance remains to be established as the relative abundance of UCP1 in these cells is substantially lower than "classic" BAT, although studies from knockout mice indicate a plethora of regulatory factors. In fetal sheep, the animal model in which this process has been most intensively studied, adipocytes are clearly visible from mid-gestation when they have a multilocular appearance but do not express UCP1 .They then mature up to term when they are characterized as containing a mixture of unilocular and multilocular cells. of which the former are lipid filled, whereas the latter are rich in mitochondria and express UCP1 .The extent to which this is a pure form of BAT as opposed to a mix of beige and white adipocytes remains to be fully clarified although it is now clear that there are at least four distinct stages of adipose tissue development in early life[19]. By mid-gestation when adipose tissue first becomes visible to the naked eye, it has a dense histological cellular structure[25]. Then, close to term, as the depot increases in size, cells with the appearance of both white and brown adipocytes are visible with the latter surrounding the larger, single lipid droplet filled (white) cells .Following birth, a pronounced reduction in the number of white adipocytes occurs coincidently with maximal UCP1 abundance. Finally, a gradual disappearance of brown adipocytes occurs through the postnatal period, culminating in only white adipocytes being discernable by one month of age[13].

The primary phases of fetal/postnatal adipose tissue development, together with the primary regulatory factors, are summarized in Table -1 and include the following.

Table 1: Summary of the main developmental changes in adipose tissue during early life.

Stage of development	Proliferative phase	Preparatory phase	Thermogenic phase	Lipogenic phase
Primary adipose tissue characteristics	Preadipocyte	Brown adipose tissue	Brown adipose tissue	White adipose tissue
Function	Cellular multiplication necessary to form adipose tissue depot	Acquisition of large amounts of uncoupling protein 1	Rapid activation of uncoupling protein 1 in order to prevent hypothermia	Lipid deposition and storage
Most abundant gene	Antigen identified by monoclonal antibody ki-67	Long form of prolactin receptor	Uncoupling protein 1	Leptin

The plethora of endocrine changes which occur at birth following intense stimulation of the hypothalamic-pituitary-thyroid and adrenal axes is essential for the rapid activation of nonshivering thermogenesis. This process has been extensively studied in the newborn sheep for which impaired BAT thermogenesis not only compromises the onset of breathing but also results in hypothermia that is ultimately life-threatening[24]. A large number of endocrine factors have the potential to activate BAT around the time of birth and include catecholamines, thyroid hormones, cortisol, leptin, and prolactin[27]. The secretion and plasma concentrations of a majority of these hormones then decline over the first few days and weeks of life. as shivering replaces nonshivering thermogenesis as the dominant response to cold exposure . (Figure-1). It thus appears that it is only possible to very transiently promote the reappearance of BAT during the postnatal period at least in a precocial species.

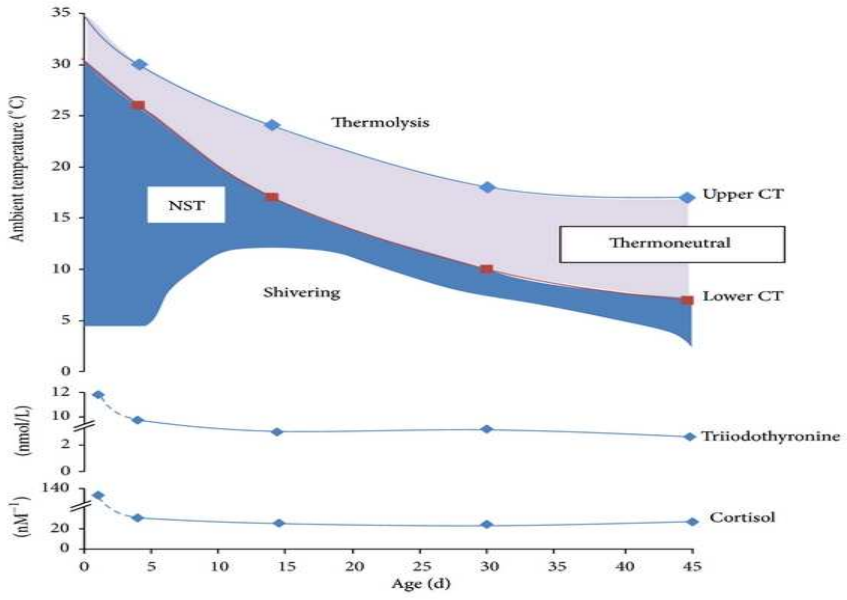


Figure 1: Summary of the metabolic and endocrine changes that occur from birth to 45 days of postnatal life in the sheep as brown adipose tissue is lost and shivering replaces nonshivering thermogenesis (NST) as the primary response to cool exposure[19].

Discussion

The onset of nonshivering thermogenesis in BAT is a prerequisite for effective adaptation to the cold challenge of the extra uterine environment in a majority of mammals but especially in species that are precocial and do not benefit from huddling with their littermates in order to maintain body temperature [14]. This of course includes humans for whom comparatively large amounts of BAT are present in the newborn, located predominantly around the internal organs, together with interscapular and supraclavicular regions (including discrete depots surrounding the carotid artery and jugular vein)[12]. BAT usually comprises only 2%–4% of birth weight which is not surprising given the high energy costs of fat deposition together with its thermogenic capacity being maximal at birth[23]. Term human infants are also characterized as possessing substantial amounts of subcutaneous white adipose tissue that has an additional insulatory role. There are fundamental differences in the maturation of BAT in the perinatal period between species which reflect both maturity and body composition at birth and can be summarized as follows[15].Altricial offspring, such as mice and rats, which are born after a short gestation with an immature hypothalamic-pituitary-adrenal (HPA) axis, maintain their body temperature by the pups huddling together in their nest, rather than by active heat production through nonshivering thermogenesis. Consequently their BAT matures postnatally in parallel with maturation of the HPA, and maternal-offspring behavioral interactions have a primary role in postnatal temperature control, Precocial offspring such as sheep and humans that are born after a long gestation demonstrate maturation of the HPA prior to birth and are able to rapidly switch on nonshivering thermogenesis following cold exposure to the extra-uterine environment[25]. A failure to switch on BAT, such as following preterm birth, thus impairs heat production and results in hypothermia[22] .One notable exception to the above categories is the pig that lacks BAT as its UCP1 gene is nonfunctional having been disrupted by several mutations , Consequently pigs are entirely dependent on shivering thermogenesis in order to maintain body temperature following cold exposure at birth[21] .This is coincident with the initial appearance of fetal adipose tissue and characterized by rapid cellular multiplication. [16]This process is primarily regulated by the rapid appearance of endocrine stimulatory factors which act to maximize both the amount and thermogenic potential of UCP1 .Notably, gene expression for the long form of the prolactin receptor (PRLR) peaks prior to birth, which is in accordance with of its critical role in promoting thermogenesis demonstrated in studies in both small and large mammals[17]. The direct contribution that BAT makes to overall energy balance is clearly indicated by the very high rates of oxygen consumption that are seen in the newborn and are seldom matched in later life. This high rate of heat production occurs in the absence of any visible signs of shivering and is dependent on the magnitude of thermal challenge and nutritional status[28]. It is also closely linked to functional measurements of BAT such as its thermogenic index. Interestingly, however, in view of the common origin of brown adipocytes and skeletal, a close link between functional BAT and muscle volume has recently been suggested in children and adolescents[26]. The capacity for heat production within the supraclavicular region is high in children and then declines into adulthood. This process, or adaptation, is in accord with the suggestion that ultimately BAT within the supraclavicular region becomes beige.

Summary and conclusion

To date, all studies investigating the reactivation of BAT have been conducted on rodents in which it is becoming increasingly apparent that different control mechanisms

and sensitivities exist between brown and white fat depots[21]. Another protein recently suggested representing a therapeutic target to promote BAT function was the mediator of cell signal transduction. When this was specifically knocked out in adipocytes a global reduction in UCP1 was observed, that is, in brown, white, and beige depots.

Target function, based on brown fat function in the knock out	Effect on brown adipose tissue	Effect of white adipose tissue	Phenotype	Primary mechanism	Reference
Inhibitory					
Bone morphogenetic protein (BMP8B) knockout	Normal but reduced thermogenic activity, most apparent during cold exposure	Not examined	Lower body temperature, increased body mass, and an adaptation amplified with consumption of an HFD	Modulates SNS activity within BAT	21
Scaffold protein p62, adipocyte specific knockout	Reduced activity and responsiveness to norepinephrine	Reduced UCP1 within inguinal	Increased body weight and fat mass and an adaptation reduced when fed an HFD	Acts specifically on mitochondrial function in brown adipocytes and thus thermogenesis	9
Stimulatory					
Phosphatase and tensin homolog, conditional knockdown	Increased adipocyte cell size	Increased adipocyte cell size	Despite similar body mass, WAT distribution disorder is apparent	Both brown and white cells may have Myf5+ origins	7
SERTA domain containing 2 (TRIP-Br2) knock out	Increased thermogenic activity and cold responsiveness	Decreased adipocyte cell size	Improved glucose homeostasis and ability to maintain body temperature during cold exposure	Modulates fat storage through inhibition of lipolysis, thermogenesis, and oxidative metabolism	14
Retinaldehyde dehydrogenase 1a, knockout	None	Increased UCP1 with a greater	Improved glucose homeostasis	Inhibits the browning of WAT	27

		response in perigonadal compared with inguinal	and ability to maintain body temperature during cold exposure		

Table 2: Summary of recent targets for gene manipulation studies designed to impact on brown fat function in adult rodents maintained in a fixed thermal and photoperiodic environment

Despite elegant studies demonstrating even more potential therapeutic targets to promote UCP1 abundance, it should be noted that they are all conducted in mice maintained within a comparatively cool environmental temperature of 21–23°C and kept under a fixed 12 h light and 12 h day photoperiod. These experimental constraints may ultimately limit the translational relevance of these important findings which in humans the pronounced effects of age, lifestyle, and environment on energy balance are substantial.

In addition to the thermal, nutritional, and related environmental stimuli, BAT is influenced by a range of other factors including genotype[18]. These can have a profound effect on postnatal survival in sheep but its influence in humans is less obvious. In a small Japanese cohort in whom three different polymorphisms were identified, the distribution of BAT positive subjects was only associated with individual genotypes when groups were subdivided with age. Genotype can influence BAT function and the use of thermal imaging offers the potential to assess this relationship in large populations of known genetic constitution.

Consequently, as comparable noninvasive and safe methods for detecting BAT on a population-wide basis are established, significant progress on the interaction between genotype, age, diet, and environment can be made[19]. These types of study are a real possibility and predicted to open up a range of new horizons in adipose tissue biology over the next decade. This could mean that a more direct relationship between body weight regulation and BAT function is finally established throughout the life cycle in humans[20].

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