Brown Fat and Its Thermoregulatory Role in the Human Neonate

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Abstract

Brown fat is a unique thermogenic organ. Though small in quantity and diffuse in distribution, it plays a vital role in body temperature regulation and energy balance in both animals and humans by its adaptive heat producing capacity. Several factors affect the functional capabilities of brown adipose tissue including nutritional status and maturity of the different organ systems of the body especially in the newborn infants. Recent findings using molecular techniques have provided better understanding of the regulation of brown fat activity that may have some implications for therapeutic purposes particularly in treating obesity. An overview of the brown fat and its relevance to newborn babies is presented in this article. (**JPBS 2010;Volume 23 No.2:5-10**)

Key Words: *Brown adipose tissue, Thermogenesis, Energy balance, Malnutrition, Premature infants*

The widespread white adipose tissue (WAT) and several smaller depots of brown adipose tissue (BAT) are the two types of fat in the human body. They are generally referred to as white fat (WF) and brown fat (BF) respectively. WAT and BAT have distinct physiological role and are closely interrelated but differ in their distribution and histological features.[1,2] BAT is a remarkable lipid containing connective tissue found in almost all mammalian species. It is present in various locations of the body depending up on the age and the species the animal.[1,3] BAT is well recognized as an organ with thermogenic function almost 50 years ago.[3,4] Its role in metabolic efficiency was recorded at a later date.[5] It also secretes some chemical substances such as Resistin, Angiotensin and others in smaller amounts that are produced by WAT as well.[3] Some of the new studies have shown that men, older people, people with high blood sugar and obese people have lesser BAT than their respective controls.[6,7] These observations may indicate some physiologic importance of BAT as a factor in maintaining the lean or obese phenotype that may be associated with other comorbidities.

How does BAT differ from WAT?

The major differences between WAT and BAT can be summarized as follows: White fat is present throughout life in the subcutaneous and visceral areas. It is formed in the foetus during the third trimester of pregnancy. Cell size varies from 25-200 μ, each cell contains a single fat globule (unilocular), few mitochondria, peripheral nucleus giving a characteristic 'signet-ring' appearance. It has sympathetic nerve supply more to vessels than the cells and lesser vasculature to the tissue. It does not contain uncoupling protein 1 (UCP1). It produces more ATP and is not involved in thermoregulatory heat production. Its functions include that of storage of energy, insulation and padding the visceral organs around the fat.

The brown fat distributed in specific locations in humans is found in plenty in newborn infants. It has a characteristic color that varies from dark red to tan due to rich blood supply and dense mitochondria that contain high levels of cytochrome. BAT is also formed during the third trimester of intrauterine life. The cell size ranges from 50-60μ and each cell has many fat globules (multilocular) that have an important role in heat production. It has a central round nucleus. BAT has profuse sympathetic innervation to both cells and blood vessels and also has a rich blood supply. The presence of a very special UCP1 is the hall mark of BAT. The main function of BAT is regulatory heat production which is also known as facultative or adaptive thermogenesis that plays a vital role in thermoregulation and energy balance that will be referred later.

Where is BAT present?

Brown fat contributes little to the body weight in infants and much less in adults. It is located between the scapulas (interscapular BAT – IBAT), at the nape of the neck, along the great vessels in the thorax and abdomen and also scattered in other locations in the body.[8,9] Though, human adults were assumed to have less or no functional brown fat with advancing age due to the loss of mitochondria,[10] ^{18}F-flurodeoxyglucose positron emission tomography (^{18}F FDG PET) and other studies have shown that an active and functional BAT still persists in the upper chest and neck regions and several other parts of the body in a majority of the subjects.[6,7,9,11] The largest depot of the tissue was found in supraclavicular and neck regions. The other areas

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include paravertebral, mediastinal, para-aortic, suprarenal, perirenal, apex of the heart and so on. But the most interesting finding from these recent studies was that in the adult humans brown fat was not seen in the interscapular area (IBAT) unlike in the neonates and infants that confirm the results of earlier reports.[12,13]

Evidence for the existence of BAT

Many techniques such as light microscopy to more sophisticated positron emission tomography and computed tomography (PET-CT) scanning and others such as measurement of noradrenaline stimulated oxygen consumption, infrared thermography, immuno-histochemistry, enzyme histochemistry, radioimmunoassay, thermocouples for temperature measurements, blood flow measurements, molecular biotechniques, excision studies, pharmacological studies and so on have been of great help in providing ample evidence for the existence of BAT in both animals and humans.

The earliest identification of BAT in the human neonate was reported by Hatai in 1902.[14] Further work on the existence of brown fat particularly in the human neonates was done during 1920-1960. Histologically detectable BAT in human infants and adults in a number of locations is well established.[8,13,15] Heim *et al.*[16] have shown histological changes in BAT in infants exposed to different temperatures from 22 – 35^{o}C. In the first decade of life active brown fat seems to be widely distributed in all areas of the body, and with advancing age, BAT starts disappearing and is seen only in deeply situated areas as late as 8th decade of life.[8,13] IBAT depots may not be quantitatively important for thermogenesis in adult humans as there was no histological evidence for its presence.[8.13] This view is supported by recent findings using PET-CT techniques as mentioned earlier.[6,7,9] Whereas, all other internal sites contain at least isolated or islands of BAT.[8,9,13]

Several clinical conditions provide more convincing evidence for the functional capability of BAT. One condition that supports the BAT thermogenic

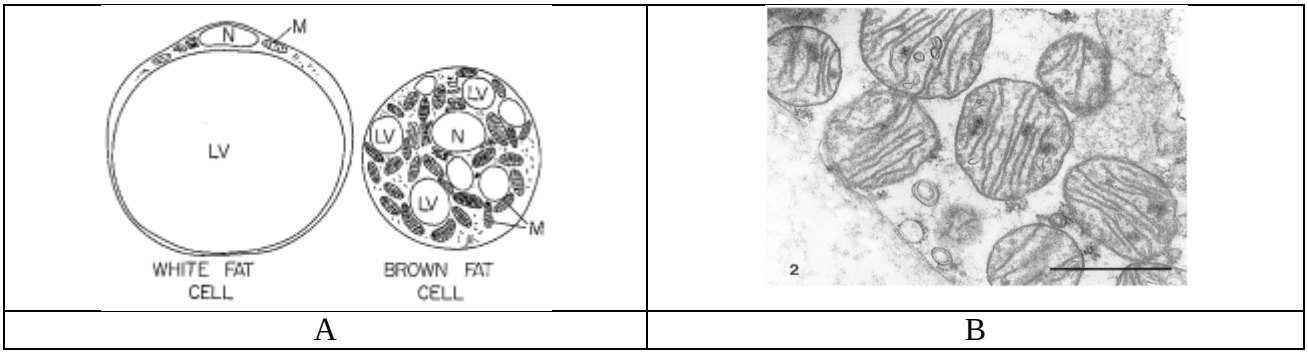


Figure 1. (A) Schematic representation of a White fat cell and Brown fat cell. LV = Lipid vacuole, M = Mitochondria, N = Nucleus. (B) Mitochondria in a brown fat cell.

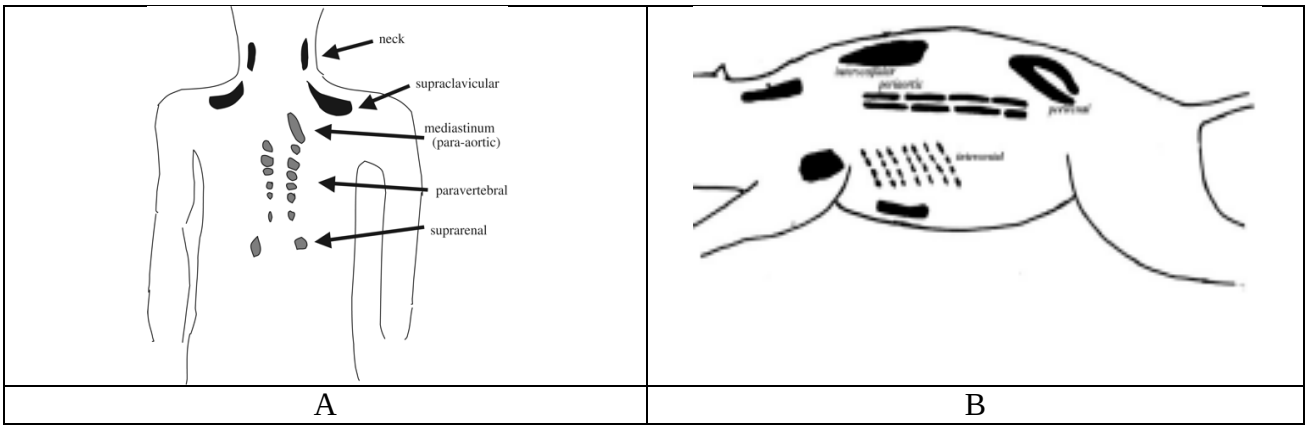


Figure 2. Locations of BAT in (A) the human and (B) the rat.

function is sudden cot-death which is a problem amongst the small infants. Lean and Jennings[17] reported two cases of cot-deaths with no other pathology other than high core temperature of > 40^{o}C. In humans, noradrenaline secreting tumors of phaeochromocytoma is associated with abundant brown fat in the perirenal fat. The unique protein UCP1 that was identified about 30 years ago in BAT[18] is significantly increased in phaeochromocytoma.[19] Hibernoma, a rare benign tumor of BAT, is another condition that shows the presence of

functional BAT in humans characterized by increased accumulation of FDG in PET.[20,21] There are also reports that have shown increased BAT lipid contents suggestive of reduced heat production that correlates well with clinical characteristics of hypothyroidism.

BAT thermogenesis and its control

Konrad Gessner was the first to recognize BAT in 1551 as 'Embryonal fat' in hibernating marmots. At different time points in its history of more than 450 years, BAT has been considered to play a role either as a 'glandular organ' or a 'hibernating gland' or an 'endocrine' gland. The 'thermogenic' function of BAT and its 'consequences' was clearly established only after a great deal of research carried out in late 1960s in small laboratory animals.[3,4,22] BAT has a major thermoregulatory role, i) during cold exposure by generating heat without shivering and hence referred to as cold induced thermogenesis (CIT) or nonshivering thermogenesis (NST) ii) during arousal from hibernation iii) during entry into febrile state and iv) postnatal period after birth.

BAT also produces heat after food intake termed as diet induced thermogenesis (DIT) that is recently referred to as 'metaboloregulatory thermogenesis' to indicate the same phenomenon.[3,23,24,25] Many experiments in animals on brown fat and its thermogenic response to overfeeding has strengthened the view that BAT could also be of importance in energy balance, body weight regulation and in the etiology of obesity in humans.[3,5,13,24] Muralidhara and Desautels[26] have shown that in diet-induced obese mice brown fat thermogenic function was reduced during fasting which recovered following nutritional rehabilitation, and this response was independent on the animal's prior energy reserves. The same authors[27] have also shown that ethanol consumption in mice did not involve BAT functional alterations, though produced energy deposits as extra fat. Desautels and his coworkers[28] reported an important and indirect role for basal metabolic rate (BMR) and weight loss and excess histamine produced by the mast cells of BAT in its thermogenic response. The physiological regulation of heat production in BAT involves a complex neuroendocrine mechanism[29] and is thus affected by several factors. The evidence for this comes further from the observation that in animals reared in thermoneutral conditions, the tissue subsequently involutes and heat producing capacity is lost whereas cold exposure and feeding may activate heat production and prevent the involution of brown fat.[30] Propranolol also blocks the BAT function as referred recently.[9] Blood flow and sympathetic nerve discharge increase after food intake so that heat production is increased.[5,22,24] BAT thermogenesis, both CIT/NST and DIT are controlled by the hypothalamus via sympathetic nervous system involving norepinephrine (NE) as the neurotransmitter. UCP1 as another mediator also plays a vital role in all these cases.[23,31] Variations in brown fat sympathetic activity affect the expression of UCPs thereby altering the efficiency of its function.[32] NE is also important in preventing the death of brown fat cells. Thus, the life of brown fat cells is primarily under the adrenergic control.

Biochemistry of heat production in BAT

The function of BAT is to transfer energy from food to heat. The mitochondria in a eukaryotic cell utilize fuels to produce energy in the form of ATP. In the brown fat mitochondria, inward proton conductance that generates ATP (oxidative phosphorylation) takes place as usual, but in addition there is a second proton conductance (proton run back) that does not generate ATP. This alternative route or 'short-circuit' conductance depends on a 32-kDa uncoupling protein (UCP), now called UCP1 present in the inner membrane of the mitochondria. This protein causes uncoupling of metabolism and generation of ATP, so that more heat is produced[32].

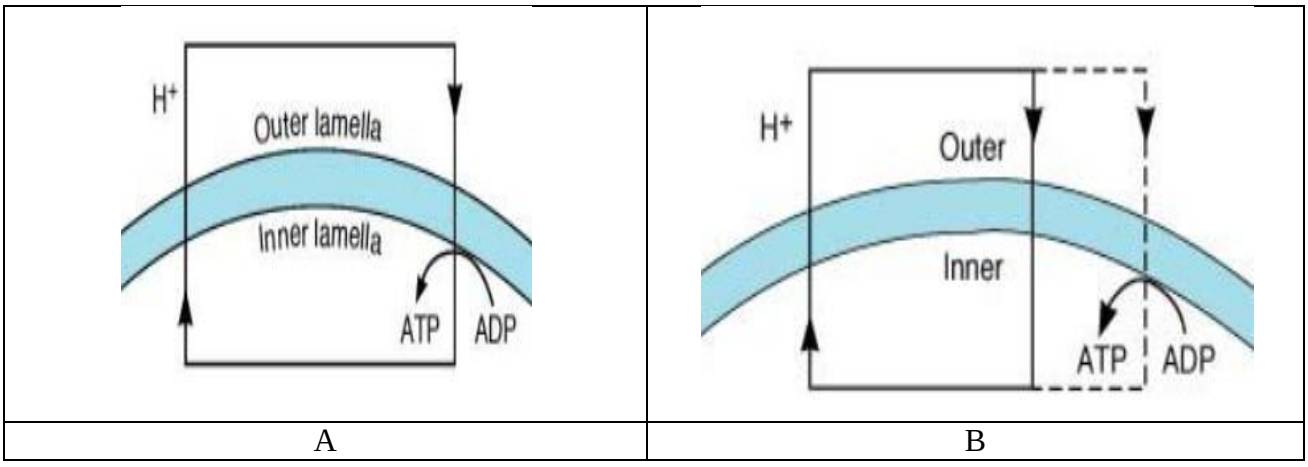


Figure 3. (A). Schematic representation of ATP production using the electron transport system. (B). Additional inward proton 'leak' in the BAT cell that does not generate ATP.

BAT and thermoregulation in the newborn

Normally, newborns have relatively large deposits of brown fat containing UCP1 in the tissue and have been shown to increase oxygen consumption without shivering or involvement of other muscular activity.[13] Aherne and Hull[33] examined BAT in 394 infants who died before the age of 4 weeks and the premature babies who were at risk of thermoregulatory deficiency, and proposed that this may be due to the lack of well developed BAT and WAT. Thus, the wide distribution of BAT in early years of life may be related to the immaturity of the body temperature regulating mechanisms in the new born children.

Following Bruck's earliest work,[34] much work has been done on human neonates to show that BAT is largely responsible for heat production in cold exposure. A study on malnourished children of 4-16 months age has shown that they had low basal metabolic rate, slow pulse rate, low body temperature and at low respiratory quotient (RQ). Metabolic response of malnourished babies to cold exposure at 25^{o}C was insufficient to produce an increase in total oxygen consumption and also failure to raise the body temperature. Furthermore, IBAT atrophy was also seen in these children.[15] Similar thermoregulatory deficiencies have been reported in children with low birth weights.[35,36] A study by Muralidhara and Shetty[37] has shown similar results in young malnourished Wistar rats that exhibited thermoregulatory insufficiency in the form of reduced CIT/NST, reduced BMR and low body temperature.

Therefore, brown fat thermogenesis is of great importance in the new born babies to avoid hypothermia, especially in the premature neonates and malnourished children. The new born child needs to adapt to low environmental temperature in the initial hours after birth by increasing metabolic heat generation. Premature babies have smaller body size and hence produce less heat. Furthermore, they are not able to generate heat by shivering, unable to move away from cold stress, do not have much BAT to assist metabolic heat production as it is laid down only in the 3rd trimester of intrauterine life, do not have much insulation as white fat is also laid down during the last trimester of pregnancy, cannot control vasodilatation and vasoconstriction adequately due to incomplete development of nervous system. BAT seems to be the major means of metabolic heat production until the second year of life in the new born. Premature babies can be helped only to prevent heat loss and not heat generation. Therefore, the consequences of hypothermia in such children are many which include neonatal cold injury, high metabolic rate and increased oxygen consumption leading to hypoglycemia, jaundice and kernicterus, increased susceptibility to infection and poor weight gain. Most of these complications are related to the dysfunctions of immature organ systems in the premature/malnourished babies.

Recent advances in human BAT research

The cumulative information from both animal and human experiments has enhanced the knowledge of BAT functions and its control to a great extent. But there have always been questions raised on the relevance of the experimental results of animals and its application to humans. Some argue that there is no reason to believe that the experimental results of rodents on brown fat functions are not applicable to humans just because they are large mammals. And, considering the total mass of BAT in adult humans, its physiological importance in whole body energy homeostasis was overlooked or considered negligible too until now. However, it must be remembered that though, BAT thermogenesis may contribute to 1-2% of energy balance and thereby to body weight regulation, a rough estimate of a defect of this order of thermogenic capacity could lead to weight gain at about 1-2 kg/year in humans[13]. Recent studies support this view and suggest that BAT activity could have a significant impact on daily energy expenditure by dissipating energy as heat and can thus counteract weight gain. Therefore, therapeutic interventions or activation of BAT may be an effective approach for limiting obesity. Molecular biotechnology has greatly assisted in better understanding of the factors and their mechanisms in the regulation of BAT functions. During the last few years, research work related to transcriptional control of BAT development, differentiation and functions has kindled more hopes in that direction. The prime regulator of BAT formation and function PRDM16 (a zinc-finger protein selectively expressed in BAT) can simultaneously induce BAT gene expression while suppressing WAT gene expression. It is suggested that PRDM16 and other associated co-regulators – PPARγ coactivator-1α (PGGC -1α) and C-terminal binding protein (CtBP1/2) which controls the switch from WAT to BAT are potential targets for the development of obesity related therapeutics[38,39]. Recent report on a bone growth messenger protein named bone morphogenetic protein 7 (BMP 7), claims that it can be another important regulator of BAT functions[40]. This protein is reported to play an important role in BAT cell differentiation, induction of PRDM16 and UCP gene expression. These new findings may suggest BAT as one of the possible effectors of pharmacological protection for human excessive adipose tissue deposition, diabetes mellitus, hypertension and arteriosclerosis and also to overcome the thermoregulatory insufficiencies. Although new findings are stimulating and look rational, the possible counter effects on cardiovascular system, central nervous system and others such as increased appetite, increased heat generation due to heightened BAT activity must be kept in mind before any decisive actions are taken.

Conflict of interest : None to declare

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