An Overview about Energy Expenditure and Advantage of activating Brown adipose tissue

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Abstract

Background: Brown adipose tissue (BAT) is recognized as the major site of sympathetically activated nonshivering thermogenesis during cold exposure and after spontaneous hyperphagia, thereby controling whole-body energy expenditure and body fat. Energy expenditure (EE) consists of basal metabolic rate (BMR), physical exercise and thermogenesis. Generally, BMR represents 65% to 75% of total energy expenditure which is determined by fat-free mass. In minimal activity it represents two thirds of total daily EE, in maximum activity it represents half of total daily EE RMR is controlled by the hypothalamus through neuroendocrine systems. As for thermogenesis, the brain, mainly the hypothalamus and the brain stem are responsible for the control of BAT thermogenesis through sympathetic projections.

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Introduction

Energy expenditure (EE) consists of basal metabolic rate (BMR), physical exercise and thermogenesis. Generally, BMR represents 65% to 75% of total energy expenditure which is determined by fat-free mass and**.** The thermic effect (thermogenesis) represents 5-15% of daily EE while, the rest represents physical exercise as fideting. For maintain stable body weight is requiring balance between food intake and energy expenditure. Under normal condition, food is used for producing energy in resting metabolic rate (RMR), physical activity and thermogenesis. RMR refers to amount of energy that body used to maintain the basic cellular metabolic activities which differ according to body size, fat mass, age and gender **(1)**.

In minimal activity it represents two thirds of total daily EE, in maximum activity it represents half of total daily EE. RMR is controlled by the hypothalamus through neuroendocrine systems. As for thermogenesis, the brain, mainly the hypothalamus and the brain stem are responsible for the control of BAT thermogenesis through sympathetic projections. It was showed that large and rapid shifts in substrate oxidation rates can be measured by a whole- room calorimeter without affecting total energy expenditure **(1)**.

Formation of adipose tissue

It has been assumed that mesenchyme produces a population of progenitor's cells that develops into brown and white adipocytes under control of specific effectors. Also, there was a study suggested that the development feature of BAT and WAT and its evolution refers to them as a distinct tissue with separate origins. BAT appears during fetal development earlier than WAT reaching its maximum size till WAT develops at mid gestation in humans or after birth in rodents and gradually increases in its size throughout life **(2)**.

Brown adipose tissue (BAT):

Adipose tissue is considering well vascularized tissue in which playing an important role in providing tissue with appropriate oxygen **(3).** There are two types of adipose tissue in humans and rodents which are white adipose tissue (WAT) and brown adipose tissue (BAT).

Difference between WAT and BAT (White et al., 2019):

Histologically:

BAT has small fat droplets, numerous mitochondria that contain cytochrome pigment, which is responsible for the brownish color also containing uncoupling protein 1 (UCP1) in their inner membrane. UCP1 only expressed in brown adipocytes and innervated by sympathetic nervous system which important for activation of BAT thermogenesis. While WAT has large lipid droplets, limited mitochondria and innervated by sympathetic and parasympathetic nervous system.

Functionally:

WAT is considered an energy store in the form of triglyceride (TG) and release energy during fasting or physical activity. While BAT considers thermogenic tissue that function is to generate heat in response to cold exposure.

Location:

- WAT present in multiple location in the body and has two major types:
  a) Visceral white adipose tissue (vWAT)

Located surrounding the internal organ and associated with insulin resistance, increased occurrence of atherosclerosis, mortality and risk for type 2 diabetes.

b) Subcutaneous WAT (scWAT)

Located peripherally and associated with increase insulin resistance. Decreased incidence of artherosclerosis. Studies have been showing differences in scWAT and vWAT as transplantation of scWAT into the visceral cavity improves glucose metabolism in the whole body, but transplantation of vWAT has no effect.

- BAT is present in rodent and human in different body parts, In rodent present in interscapular, periaortic, axillary, subscapular and perirenal region. While, in human present in neck, supraclavicular, mediastinal, paraspinal and suprarenal area **(4)**.

Recently a subtype of adipocyte has been discovered in both rodents and humans called beige or brite (brown in white) which have functions overlapping WAT & BAT. Brite has the same morphological structure as BAT, but differs in its expression and positive for UCP1. In cold environment BAT provides extra thermogenesis condition which increase glucose uptake in BAT and improve whole body insulin sensitivity. So, cold exposure increases BAT activity and energy expenditure, so BAT is considering main site of non-shivering thermogenesis in mammals while WAT is the main depot at which energy stored **(5).**

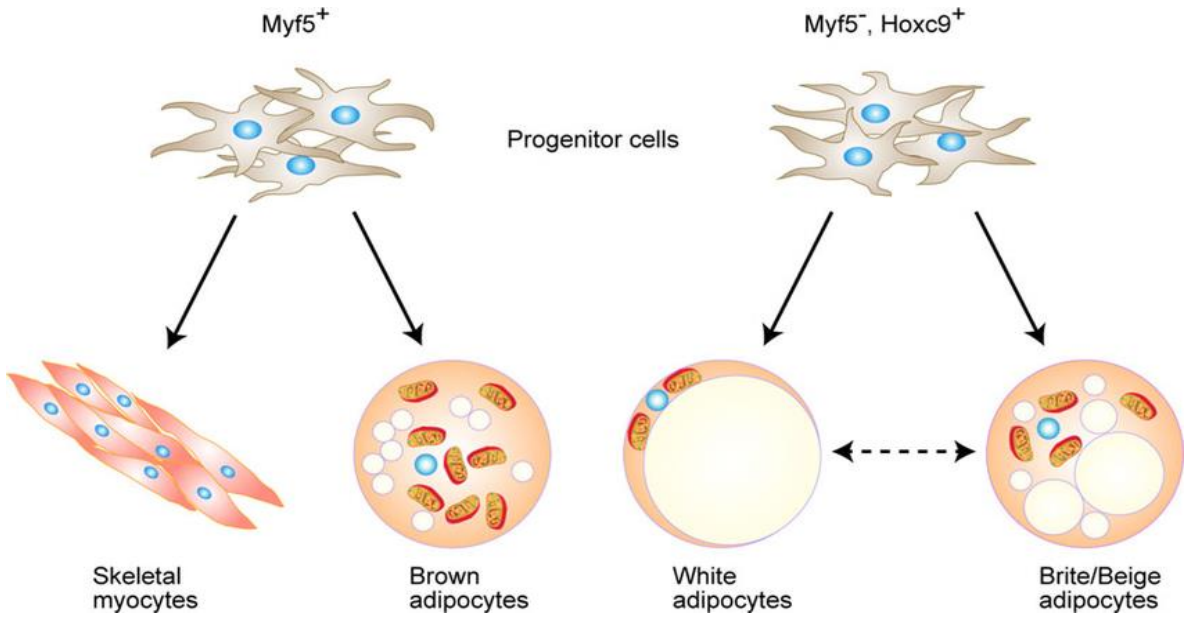

Figure (1): Origins of adipocytes. Modified from **(6)**.

Table (1): showing compressions between white, brown and brite adipose tissue **(7)**.

	WAT	**BAT**	**Brite**
Origin	Myf5- cells	Myf5+ cells	Myf5- cells
Function	Energy storage and endocrine tissue	Thermogenesis and endocrine tissue	Adaptive thermogenesis
Phenotype	White-fat phenotype	Brown-fat phenotype	White-fat phenotype
Mitochondria	Low	Abundant	Present
UCP-1 expression	Absent	Present	Present
Protein markers	LPL, leptin, adiponectin	PGC1α, PRDM16	CD137, PRDM16, Tmem26

Pharmacological induction	PPAR agonists, renin angiotensin system blockers, among others	Sympathomimetic drugs, thyroid hormones, thiazolidinediones, hormones like FGF21 and irisin, among others	Adrenergic receptor agonist, thyroid hormones, PPARα agonist, FGF21, irisin, BMP7, BMP8, AMPK activator, leptin, insulin, among others
Nutritional induction	n-3 PUFA, polyphenols, vitamin D, vitamin E, vitamin A, carotenoids, among others	PUFA, especially n-3 PUFA, bile acids, among others	Amino acid restriction, capsaicin, bile acids, n-3 PUFA, retinoic acid, among others

Advantage of activating BAT:

In lipid metabolism:

Some researchers have discovered that fatty acids (FAs) are the main fuel to UCP1 mediated BAT thermogenesis **(4)**. Recently it was discovered that prolonged activation of the β3-adregenic receptor (β3-AR) increases β-oxidation of fatty acid and lipolysis in both WAT and BAT **(8)**. The prolonged activation of BAT enhancing phosphorylation of adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL), which induces intracellular lipolysis which eventually leads to release of FAs from lipid droplets.

In rodents, cold exposure could decrease plasma triglycerides (TG) level and improve hyperlipidemia, as norepinephrine (NE) is released from the sympathetic nervous system and binds to the β3-adrenergic receptor on brown and beige adipocytes. This results in activation of adenylyl cyclase to produce cyclic adenosine monophosphate (cAMP) that activates protein kinase A (PKA). PKA phosphorylates and activates cAMP response element-binding protein (CREB) resulting in enhanced transcription of uncoupling protein-1 (*Ucp-1*) and peroxisome proliferator-activated receptor-gamma co-activator (*Pgc-1α*). In addition, activation of PKA enhances the activity of lipolytic enzymes that are associated with the intracellular lipid droplets, leading to release of fatty acids (FA) that enter the mitochondria for β-oxidation. The produced acetyl-CoA is used in the citric acid cycle where reducing equivalents are formed that donate electrons to the electron transport chain. UCP-1 is a proton channel that uncouples respiration, which results in the generation of heat instead of ATP **(9)**.

Upon prolonged activation of brown and beige adipocytes, intracellular lipid droplets become depleted and are replenished via the uptake of TG-derived FA, mainly via selective dilapidation of TG-rich lipoproteins (TRLs) through the hydrolyzing action of lipoprotein lipase (LPL). The released FA are taken up by cluster of differentiation 36 (CD36) and FA transport proteins (FATP) and stored in the lipid droplets as TG. Furthermore, glucose is taken up as well via glucose transporter (GLUT) 1 and 4 and used for, among others, de novo lipogenesis. ATGL indicates adipose triglyceride lipase; DAG, diacylglycerol; HSL, hormone-sensitive lipase; MAG, monoacylglycerol; and MGL, monoglyceride lipase **(10)**.Although short or prolonged cold exposure led to reduction in plasma TG in humans. Similarly, metformin treatment also decreases plasma TG level by increasing BAT activity. Therefore triglyceride hydrolysis and re-synthesis are critical factors for BAT medicated lipid metabolism. So acute cold exposure for 6 weeks elevates FAs uptake in BAT, not

muscle or WAT. The activation of BAT is considering a therapeutic strategy for treatment of obesity and hypertriglyceridemia **(11)**.

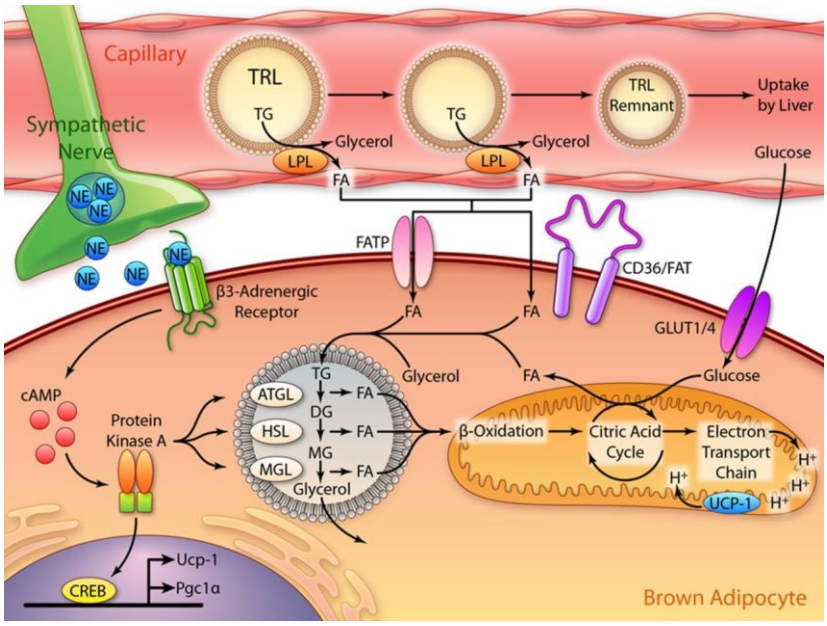

Figure (2): Activated brown adipose tissue (BAT) takes up triglyceride (TG)–derived fatty acids after lipolysis **(10)**.

In glucose metabolism:

Clinical studies showed that BAT using a large amount of glucose as they have found improved in glucose uptake and postprandial insulin sensitivity in associated with increased BAT volume and function during intermittent cold exposure **(4)**. More recently during acute cold exposure they have found increasing in BAT activity and peripheral glucose uptake and insulin sensitivity up to 20%. Currently it's difficult to find the relation between BAT to the whole-body glucose metabolism, however there is evidence that BAT represents a physiologically relevant site of insulin-mediated glucose disposal. Glucose uptake by BAT arranged by insulin dependent and insulin-independent manner. In addition, BAT shares in glucose uptake to the whole-body glucose metabolism. In humans' cold exposure increases insulin sensitivity and activates supraclavicular BAT **(12)**.

Contribution of active BAT to whole body energy expenditure:

In rodents, BAT shares up to 60%of resting energy expenditure (REE) during cold acclimation **(4)**. It's estimated that BAT mass ranges from ~30 to 300 g in human which could contribute to 20% of daily REE **(13)**.

The amount of active BAT in adult humans is rather heterogeneous due to different experimental conditions. For example, acute cold exposure leads to increased energy expenditure of 0.8 kcal d-1 g-1 of BAT. On the other hand, fully activated BAT could account for increasing energy expenditure of 1.5 kcal d-1 g-1 of BAT. Therefore, an average of 1 kcal d-1 g-1 of BAT is assumed to generate 50 kcal/d and might decrease 2 kg of fat mass yearly if adult human has average 50 g of BAT. The browning of WAT also improves thermogenic function by glucose and fat to produce heat, resulting in a reduction of adiposity **(14)**.

Activators of BAT:

For preventing obesity and its related disease it's urgent to find specific BAT activators as BAT has important role in glucose and lipid metabolism.

Cold exposure:

Cold exposure is known as a safe way to activate BAT. Physiologically, cold exposure stimulates sympathetic nervous system which increases norepinephrine turnover, thereby increasing thermogenic function of BAT. Mechanistically, norepinephrine enhances transcriptional factor mediated UPC1 expression by activating PKA and p38-MAPK signaling pathways **(**. Interestingly, it was reported that PET-CT positive biopsies from supraclavicular area displays more similar gene signatures with beige cells rather than classical brown adipocytes in adult human. More recently it has been demonstrated that cold exposure activates eosinophils and type 2 cytokines that stimulates M2 macrophages to secret catecholamines and finally induces WAT browning. It has been reported that acute mild cold exposure activates BAT and increases total energy expenditure in humans **(15)**.

Exercise:

Exercise increases metabolic activity of BAT and activation of thermogenic programs as well as browning in the visceral fat. Researchers found that in day 7 of aerobic exercise has upregulates mitochondrial UCP1 expression in BAT and reducing body weight in mic**e** also affecting subcutaneous WAT after 12 weeks of training. So, exercise might activate and recruit BAT through activation of sympathetic nervous system (SNS) **(16)**.

Natural components:

Oral administration of capsinoids that derived from chili pepper has been shown to increase acute energy expenditure and BAT activity in adult humans **(15)**. Berberine (BBR) treatment showed increased energy expenditure and BAT activity in obese rodent model. Also researchers discovered that the mulberry extract (ME) and mulberry wine extract (MWE) which contain large amount of anthocyanin such as cyaniding 3-glucoside (C3G) and rutin, increase mitochondrial function during the brown adipogenesis **(17)**. Kaempferia parviflora extract (KPE) administration significantly decreases body weight gain and intraabdominal fat accumulation, which suggested that KPE increases energy expenditure by BAT activation **(18)**.

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