A.V. Efremova

THE ROLE OF BROWN ADIPOSE TISSUE IN ANIMAL AND HUMAN METABOLISM. NEW APPROACHES TO THE STUDY

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This review presents the main and latest stages of the study of brown adipose tissue in humans and animals, as well as the potential role of this tissue in their energy metabolism.

Keywords: brown adipose tissue, obesity, thermogenesis, UCP-1, energy metabolism.

Introduction. The first description of brown adipose tissue (BAT) dates back to 1551, when the German scientist Gessner in his atlas of anatomy described this tissue as "nec pinguitudo nec caro", which means "neither fat nor flesh" [1]. However, as an organ producing heat for mammalian thermoregulation, it was recognized only less than half a century ago [2]. Since the second half of the XX century, it was believed that BAT is present only in newborns and over the course of one year this tissue is reduced [2,3].

However, few studies have suggested the presence of BAT in the body of adults [1,4-9], and only with the widespread use of positron emission tomography with 18-fluorodeoxyglucose (18FDG-PET), a method of functional imaging evaluating areas of increased metabolic activity, have become more often used in the observation of certain types of cancer. Due to this diagnosis, BAT was detected in at least one subgroup of the adult human population [2,10-14]. This surprising discovery aroused great interest among researchers in this field and supported the hypothesis that the presence or absence of brown adipose tissue may be the cause of such common non-communicable diseases as obesity and type II diabetes, and can also be used as a potential therapeutic strategy, since non-contractile thermogenesis contributes to the expenditure of excess energy in the human body.

Function and structure of brown adipose tissue. The main function of brown adipose tissue is thermoregulation through non-contractile thermogenesis [1]. This thermogenesis occurs due to a unique and specific enzyme called UCP-1 (uncoupling protein-1), which disables the production of ATP energy in mitochondria, generating heat instead [1,15]. UCP1 is a unique protein that promotes proton leakage through the inner membrane of mitochondria, reducing the transmembrane electrochemical gradient of protons, and thus thus provides non-contractile thermogenesis by generating heat [1,15]. UCP-1 is a marker of thermogenic adipocytes (not only classic brown, but also recently discovered beige adipocytes), and it is believed that this is the only protein physiologically capable of causing non-contractile thermogenesis, since mice with UCP-1 knockout can produce heat only with chills [2,16].

BAT is activated by sympathetic noradrenergic receptors, mainly through beta-3 adrenoreceptors [2]. Cold is the main physiological stimulator for this noradrenergic activation, since mammals need to maintain thermoneutrality, but it has long been assumed that it can also be activated by food [2,16,17].

Microscopic examination of BAT shows cells with many fat droplets and numerous mitochondria positively expressing UCP-1 [2,18,19]. Classical white adipocytes have one large fat vacuole and a smaller number of mitochondria, which indicates their energy storage function [19].

Recent studies have shown that with a relatively small mass of BAT in the mammalian body, its activation can increase the energy consumption of the animal fourfold, since tissue perfusion increases [15,19-21]. To generate heat, not only fat stored in lipid droplets is used, but also free fatty acids and glucose from the systemic circulation, which exponentially increases the thermogenic potential [15]. This is of particular importance for winter-sleeping animals because there is an urgent need to increase body temperature after micro-arousals that occur during hibernation [2,19,20]. During hibernation, metabolism proceeds under hypothermic conditions, and the animal's body should achieve thermoregulation as soon as possible during microarousal or after the end of the hibernation period [2, 19]. Only thermogenic tissue with high capacity is able to provide adequate short-term thermoregulation [22]

In addition to winter-sleeping animals, the important role of brown adipose tissue is well known for small mammals (rodents), in which the body surface area is larger in proportion to the internal volume [2,22,23]. This large area increases heat loss to the environment and requires more energy used by the BAT to maintain thermoregulation. For example, infants have a high area/volume ratio, and it has long been proven that BAT is present in the human body at an early age [2,21]. However, with a gradual decrease in the surface area relative to the internal volume, the energy costs of thermoregulation decrease, and therefore it was believed that BAT undergoes gradual involution until it completely disappears in early childhood [21]. However, the invention, and then the introduction into practice of 18FDG-PET, changed this point of view, since it was hypothesized that at least a small part of people still have BAT in adulthood, since the detection of metabolic activity in some of the surveyed sites increases the likelihood of the existence of unnoticed thermogenic fat [15,21].

New stages in the study of brown adipose tissue in adults. 18 FDG-PET is a functional study characterized by the ability to detect metabolically active sites absorbing 18-fluorodeoxyglucose (18FDG), a glucose radioisotope [19,24,25]. It began to be used in the 90s, mainly in the diagnosis of oncology, to detect tumors and metastases, which usually have a high metabolic rate and, consequently, high glucose uptake. With 18 FDG-PET scans, organs such as the heart and brain are also constantly detected, as these organs are known to have a pronounced glucose intake, even during fasting [24,25].

PET studies revealed bilateral symmetrical absorption regions of 18 FDG

EFREMOVA Agrafena Vladimirovna – Ph.D. of Biology, Arctic Medical Centre of the Yakut Research Center of Complex Medical Problems, a.efremova01@mail.ru

in the supraclavicular, cervical and parasternal regions, which could not be interpreted as tumors due to the described characteristics [7,24,26]. Highly active areas were anatomically located in areas of fat weakening on computed tomography, which indicates the presence of metabolically active fat. A high proportion of images with such characteristics on 18FDG-PET in individuals diagnosed with pheochromocytoma, in whom catecholamine-producing tumors are known as intense noradrenergic activation, aroused suspicion that these areas were actually unrecognized brown adipose tissue that proliferated under the influence of chronic noradrenergic stimuli [7,27,28].

The interest of endocrinologists and specialists in metabolism increased in 2007 after the publication of an article in which convincing evidence was presented that, from a functional point of view, these areas detected by 18FDG-PET scanning are brown adipose tissue [15]. However, just two years later, after the publication of three articles, the scientific community recognized that at least some adults have brown adipose tissue [12,13,14]. Brief research results are presented in the table (Table 1).

Cypess and his colleagues analyzed 3,640 18FDG-PET scans performed to detect neoplasms and found absorption sites indicating the presence of BAT in 7.5% of women and 3.1% of men [12]. Indicators such as age, body mass index (in the elderly), outdoor temperature and fasting glucose levels were inversely proportional to positive PET results, and the use of beta blockers was associated with a lower probability of detecting absorption sites. However, after multivariate analysis, glucose concentration and BMI lost their statistical significance, but BMI continued to have a significant negative association with absorption in older people.

A scientific group led by Van Marken Lichtenbelt conducted 18FDG-PET in 24 people after exposure at low temperatures (16 C° for two hours), in light clothing and without body chills [13]. According to the study, 96% of positive results were revealed, and an inverse proportional relationship was obtained between the level of absorption (kilobecquerels) and BMI (conditional amount of body fat). Only one obese subject had negative absorption after exposure to cold. Also, adipose tissue samples obtained from areas with positive uptake of 18FDH had high immunoreactivity to the UCP-1 protein, which indicated the presence of metabolically active BAT.

In a recent paper published in the aforementioned publication, Virtanen and co-authors analyzed tissue biopsies from PET-positive areas visualized in three young people and found positive expression of UCP-1, confirming the presence of brown adipose tissue [14]. Considering that only 10% of the energy used by BWT is glucose and 90% is fatty acids, the Finnish group calculated by mathematical analysis based on the absorption of FDG in these people an increase in energy consumption by 7%, which corresponds to a weight loss of 4.1 kg per year.

None of the studies were aimed at assessing the causal relationship between BMI and the presence or absence of BAT, which leads to countless hypotheses. One hypothesis is that because obese people have more fat protection, they may feel less cold, which in turn means that they need less activation of BAT. Another version that requires further study is that the absence of brown adipose tissue may be, at least in part, due to weight gain and a decrease in blood glucose levels in a certain subgroup of people.

The role of brown adipose tissue in human metabolism. After the appearance of the first 18FDG-PET images, it was hypothesized that the BAT is a residual organ, like other organs that often do not involute during embryo development. Data from Van Marken Lichtenbelt studies demonstrated almost 100% absorption during cold stimulation and made this hypothesis less likely [13].

The total mass of brown adipose tissue in humans does not exceed 60-100 grams, which is only a small part of the mass of white adipose tissue, even in people with low body weight [21]. However, as already noted, BAT perfusion increases significantly with noradrenergic stimulation, which leads to high peripheral absorption of glucose and fatty acids, which makes BAT an energy-intensive tissue, as well as an important regulator of glucose homeostasis [2,20,21,29,30]. This tissue has an insulin-dependent ability to absorb glucose and promotes the clearance of free fatty acids, which is closely related to insulin resistance [24].

Some studies have tried to estimate the increase in energy consumption after the activation of BAT, and data were obtained on fluctuations from 5 to 77% compared to the basal level [21]. As described earlier, Virtanen and co-authors suggested an increase in basal metabolism by 7% [14]. Orava and co-authors found a similar increase of 8% after exposure to cold, but when the analysis was carried out only in 18FDG-PET-positive people, the increase increased to 22% [29]. Quellett and colleagues decided to measure energy consumption by indirect calorimetry, before and after exposure to cold in a shirt soaked with water at a temperature of 18 °C [31]. The percentage increase in this study reached 77% after exposure to cold. A scientific group led by Yoneshiro divided the positive and nega-

Table 1

Summary of the results of three articles of the New England Journal of Medicine in 2009, which confirmed to the scientific community the presence of brown adipose tissue in adults

Van Marken Lichtenbelt and cols.	Virtanen and cols.	Cypess and cols.
Active BAT was detected with FDG-PET in 96% of people after acute exposure to cold	Cold-induced absorption of PET-FDG was 15 times higher in paracervical and supraclavicular adipose tissue in five subjects	Positive scan results were noted in 7.5% of women and 3.1% of men
Significantly lower activity in overweight and obese individuals (the only subject with a negative PET result was obese)	Mathematical analysis showed a decrease in body weight by 4.1 kg during 1 year in patients with active brown adipose tissue	The probability of detecting active BAT is inversely proportional to the outdoor temperature, years, and BMI in the elderly
Higher activity has a significant direct positive correlation with resting metabolic rate and negatively correlates with BMI and body fat mass of the studied	Biopsy samples of three subjects were collected, which demonstrated levels of messenger RNA and UCP-1 protein, as well as other markers of brown fat (such as PGC1a, DIO2, PRDM16 and ADRB3), and morphological assessment showed an abundance of multilocal adipocytes	The probability of detection is inversely proportional to fasting glycemia in univariate analysis, but is not significant in multivariate analysis

tive results of PET-FDG in relation to the activation of BWT and found a stimulated 25% increase in energy consumption in the positive group, which corresponds to 358 kcal [31]. However, the hypothesis about adipostats asserts that an increase in energy consumption must necessarily lead to a parallel increase in energy consumption in order to avoid weight fluctuations [33,34]. In order to better understand what happens to the energy balance in a situation of increased energy consumption due to thermogenesis, it is necessary to evaluate animal studies, since there are not so many studies in this area in the human body.

Cannon and Nedergaard found an increase in oxygen and energy consumption in animals exposed to lower temperatures, while the increase in nutrition was proportional to oxygen consumption, but animals living in the cold did not gain weight [32]. However, several authors, based on different results in different experiments, still believe that any increase in energy consumption will be easily compensated by an increase in food intake, and that isolated activation of BAT will not lead to weight loss [16,23,35,36]. Ravussin and co-authors put forward an original assumption that the activation of BAT in combination with an anorexigenic drug can cause weight loss synergy due to the dissociation of increased energy consumption with food consumption, however, the results of his studies combining acute intermittent exposure to cold with AM251, an antagonist of endocannabinoid receptors, showed neither synergy nor weight loss in the group exposed to cold and not receiving this substance [36].

Yoneshiro and co-authors, who analyzed the differences between BAT-positive and BAT-negative people based on their uptake of 18FDG-PET, reported that BAT-positive people did not gain weight with age [37]. On the other hand, the BAT-negative subjects had a high body mass index, a high percentage of body fat and abdominal fat mass, which confirms the assumption that the activation of BAT contributes to weight control and prevents the development of obesity.

Gadea and colleagues described a case of a rare BAT tumor called a hibernoma in a 68-year-old woman who lost 10 kg of weight in 6 months during this disease [37]. Within a year after the operation, the woman gained 15 kg, but after resection there was no decrease in energy consumption and an increase in food intake was observed. The description of this case suggests, although obviously with all the limitations of the evaluation of a single case, that BAT is capable of causing weight loss, at least when it is present in large quantities and stimulated. Another situation that deserves mention is hyperthyroidism. Thus, Lahesmaa and co-authors have found that hyperthyroidism, which often leads to significant weight loss, is associated with a threefold increase in the absorption of glucose by BAT, increased energy consumption and high consumption of lipids as an energy substrate [38]. The relationship between BAT and thyroid hormones has been known for several decades and has been described by many authors [2,39].

Diet-induced thermogenesis and metabolic inefficiency. The components of daily energy consumption are the basal metabolic rate, energy costs for physical activity and the thermal effect of food [40]. Food thermogenesis is classically regarded as the energy costs of digesting and storing calories. However, several decades ago, a hypothesis was put forward about another concept of thermogenesis caused by diet and associated with energy expenditure, which is closely related to BWT, although it was insufficiently recognized, and only a few researchers tried to follow this path until recently [16,17].

In 1979, Rothwell and Stock demonstrated in a fundamental study published in the journal Nature that rats chronically fed a "cafeteria diet" consisting of a diet with high energy value, rich in fats and carbohydrates and poor in proteins, had a disproportionate increase in energy consumption, which could not be explained only by the energy value of food [17]. The rats gained less weight than predicted, and it was suggested that they spent part of the incoming energy in the form of heat. In accordance with these findings, higher rectal and interscapular temperatures were observed in rats in the postprandial period. Tissue analysis of these rats confirmed an increase in the mass of brown adipose tissue by 260% compared to control rats fed a standard diet, which suggests that the energy consumed came from replenishment and activation of brown adipose tissue.

Despite the impact of the study, diet-induced thermogenesis has been almost forgotten, at least by human physiologists. However, in 1999 Stock put together a series of studies on overeating, the purpose of which was to evaluate interindividual reactions to weight gain based on possible differences between percentages of fat mass and fat-free mass [39]. Using the law of thermodynamics, Stock calculated that it takes from 30 to 45 kJ/kg to increase body weight by one kilogram. However, some people needed values up to 100 kJ/kg to gain one kilogram. The only possibility, according to the author, is that such a large spread is due to the inefficiency of metabolism and thermogenesis. Recently, Wijers and colleagues found a linear correlation between energy costs for weight gain of 1 kg and energy costs caused by cold, suggesting that the same mechanism is involved in thermogenesis caused by cold, which leads to metabolic inefficiency, possibly caused by the influence of BAT activity [40].

A recent study in which postprandial 18FDG-PET was evaluated, with all the resulting reservations regarding interpretation due to postprandial glucose uptake

Table 2

Prevalence of positive uptake of PET-FDG in different population groups from different countries

Ambient temperature	Acute exposure to cold
USA (Cohade, and others) – 13,7% (winter), 4,% (the rest of the year)	Netherlands (von Marken Lichtenbelt, and others) – 97%
USA (Yeung, and others) – 3,7% (neck fat)	Finland (Virtanen, and others) – 100%
USA (Cypess, and others) – 7,5% (women), 3,1% (men)	Japan (Saito, and others) – 53%
England (Au-Yong, and others) – 7,2% (winter), 2,5% (summer)	Japan (Yoneshiro, and others) – 46%
Canada (Ouellet, and others) – 6,8%	
Australia (Lee, and others) - 8,5%	
Germany (Stefan, and others) – 3,05%	

by muscles, showed that, compared with thermoneutrality, after a hypercaloric and hyperprotein diet, glucose uptake of BAT is observed, similar to that which occurs after cold activation [41]. However, another similar study questioned the significance of thermogenesis caused by diet, demonstrating that chronically overfed people (200% overfed) did not increase the absorption of glucose by BAT when comparing the results of 18FDG-PET scans before and after the period of overfeeding [42]. Scanning for 18 FDG-PET in overeating patients was performed four hours after meals using a low-carb diet. The timing and composition of the diet could distort the results.

It was also noted that in persons with constitutional thinness, even under thermoneutral conditions, glucose uptake in the BAT was 16.7 times higher compared to persons with normal weight [43]. On the contrary, in women with anorexia nervosa who have a weight similar to that of people with constitutional thinness, the glucose uptake of BAT was practically zero, which suggests that the role of BAT is metabolically ineffective in this rare but interesting subgroup of people.

Although it is difficult to imagine the evolutionary advantage of metabolic inefficiency, since it is generally believed that obesity is the result of an economical phenotype adapted to energy storage in food shortage conditions, a possible explanation may be that it is active with a low-protein diet, and thermogenesis is important for the animal to constantly look for protein sources [2,16]. In fact, it has been demonstrated in humans that low-protein diets are associated with greater metabolic inefficiency, and high-protein diets lead to high thermogenesis, and the latter is mainly due to the high rate of digestion, metabolism and storage of this macronutrient [44].

Despite the fact that this concept is highly controversial and refuted by some researchers, the idea that brown adipose tissue contributes to the expenditure of excess calories in the form of heat and makes it difficult for some people to gain weight deserves further study and may lead to the development of drugs that activate these mechanisms.

The prevalence of brown adipose tissue. Concepts of recruitment and activation. As noted earlier, in 2009 Cypress and colleagues found that 7.5% of women and 3.1% of men were BAT-positive at ambient temperature [12]. Similar results were obtained in previous studies conducted under similar conditions, with slight variations [23]. Van Marken Lichtenbelt and co-authors identified 96% of BAT-positive individuals (only one obese man was BAT-negative) after acute cold exposure [13], however, in the Japanese population this number decreased to 40% [31]. There are no published studies on this topic in Brazil, but unpublished data indicate an even lower level. Table 2 shows the differences in the absorption of BAT in different populations, at ambient temperature and after exposure too cold [12,13,14,21,24,31]. What could be the reason for such differences in similar experiments?

To better understand this difference, we need to go back to physiology and research on mice. If an animal lives in conditions of complete thermoneutrality and is exposed to the harsh effects of cold, its first reaction is chills to protect the internal temperature of the body [2]. At this moment, the animal does not have brown adipose tissue ready to activate and maintain the basic body temperature. As the duration of exposure to cold, the animal begins to gain weight of BAT and activate it, reducing shivering. When the recruitment of this tissue reaches its maximum, the animal ceases to tremble, and all heat production occurs due to the activation of BAT, hence the mitochondrial cleavage of UCP-1. After returning to thermoneutrality, the animal retains the recruited BAT, inactive, but ready to activate in case of a new exposure to cold. This is demonstrated by the administration of norepinephrine before and after recruitment. The increase in energy consumption after recruitment is significant, which proves that the BAT has been recruited and is ready for activity, unlike what happens earlier, when the BAT is not recruited for rapid activation after acute stimulation with norepinephrine.

This is a fundamental concept, since it helps explain why there is such a population spread in the uptake of 18FDG-PET - daily chronic exposure to cold is likely to recruit BAT, which may become more active after an acute decrease in ambient temperature. This hypothesis was confirmed by the studies of two scientific groups, which found a significant activation of BAT after chronic and daily exposure to cold, as well as an increase in energy consumption during acute exposure to cold after chronic stimulation compared with acute exposure to cold at the beginning of the experiment [45,46].

Based on this hypothesis, a higher percentage of BAT-positive individuals was identified in the winter season. Another interesting theory that helps explain this difference is that photoperiodism can also interfere with the set of BAT. With the reduction of daylight hours, on the eve of winter, BAT can be slowly recruited in order to have a sufficient level ready for the onset of cold weather, and to prevent the dependence of the body's thermoneutrality on shivering. Melatonin plays a significant role in this process, so in an animal study during hibernation, a higher content of BWT mass was shown in animals that received melatonin [47], and in a recent study, a high body temperature was observed in mice receiving a melatonin supplement in the amount of 10 mg/kg, which was detected using infrared thermography [48].

New imaging techniques for detecting brown adipose tissue. In the study of BAT, there may be difficulties partly related to detection methods. Thus, 18FDG-PET was fundamental for the identification of BAT in adults, but it is an expensive method that uses ionizing radiation and the method depends on the activation of this tissue for detection [16]. Since only 10% of BAT absorption occurs due to glucose, the sensitivity of the method using mainly glucose absorption may be low [15].

Therefore, new imaging methods are proposed to replace 18FDG-PET in scientific research and in clinical practice [47]. Validation studies of magnetic resonance have already been conducted on animals, with promising results and good opportunities for detecting depots of brown adipocytes in white adipose tissue [48]. Experimental studies have also been conducted on humans and have shown good sensitivity with the additional advantage of detecting even inactive tissue [49,50].

Another available research option is infrared thermography (IT), a non-invasive and simple method that evaluates body temperature in various tissues by image (this method has long been used in civil engineering and in medical conditions such as anastomosis and cancer) [51,52]. The possibility of obtaining results using IT makes this method promising and useful, as evidenced by a study by Lee and colleagues, which describes an increase in temperature in the corresponding areas of BWT after exposure to cold and eating in humans [53]. Studies in children using infrared thermography have also shown promising results [54]. Borga and co-authors presented a new version of the study using dual-energy computed tomography (DCT) [47].

In conclusion, it should be noted that the study of brown adipose tissue has been greatly developed after the discovery of 18FDG-PET in adults, becoming an intensive area of research not only in general biology, but also in medicine.

Most of them are recent discoveries and therefore need further study and justification.

Activation of BAT mediated thermogenesis may have therapeutic potential in the treatment of patients with obesity, diabetes and metabolic syndrome, providing new therapy options.

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