SCIENTIFIC REVIEWS AND LECTURES

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ACTIVATION OF BROWN ADIPOSE TISSUE IN THE HUMAN BODY

This literature review presents current data on the influence of physiological factors such as cold, nutrition, and fasting on the activation of brown adipose tissue in the adult body, since the activation of this tissue stimulates human metabolism and can be a potential therapeutic method in the fight against obesity and concomitant diseases.

Keywords: cold, brown adipose tissue, thermogenesis, insulin, positron emission tomography, postprandial, obesity.

Introduction. Obesity is a major public health problem in this decade, reaching epidemic proportions not only in high-income countries, but also in middle-income countries.

According to the WHO, the number of obese people has more than doubled worldwide [37]. So, from 1980 to the present time, overweight and obesity are more frequent causes of death in 65% of people than underweight [10]. Obesity was found in approximately 1/3 of the adult population, the same number of people were found to be overweight [37].

Brown adipose tissue (BAT) is a unique adipose tissue whose main function is to generate heat by dissipating chemical energy. This tissue has been extensively studied in the past in small mammals and until recently it was believed that in humans, BAT is present only in newborns [6]. In addition, many studies have shown that BAT thermogenesis increases energy expenditure in mammals, affects excess lipids and fat accumulation. Active BAT is controlled by the sympathetic nervous system, in which the adrenergic response initiates the absorption of energy in fatty acids and carbohydrates in the BAT and stimulates thermogenetic activity. This activity is associated in particular with the hypothalamus and is regulated by a wide range of transcription factors and regulators. Currently, it is believed that BAT is active not only in small mammals and newborns, but also in adults. By scanning including recognizing and measuring the mass and activity of BAT in humans, current research has expanded the understanding of the prevalence, clinical correlations, activators and regulators of BAT systems. These findings prove the ability of BAT to be metabolically active in adults, and it is possible that this tissue could be a potential therapeutic option in the fight against obesity and metabolic disease. Cold activation of brown adipose tissue

In the human body, during fasting and at room temperature, the functions of brown adipose tissue are neutral in metabolic activity and are comparable to white adipose tissue [19, 32]. Cold is one of the most effective natural and physiological activators of human BAT [32]. In persons with active BAT during acute exposure in the cold, the temperature of the skin does not decrease in the supraclavicular region, in this area is the most significant depot of BAT in humans [35]. A number of studies have shown that the effect of cold increases energy expenditure at rest in the human body [14, 22, 27, 32], especially in individuals with high metabolic BAT activity in the cold [35].

A non-invasive combined PET/CT (positron emission tomography / computed tomography) imaging technique is used to determine tissue-specific BAT activity in humans in vivo. The physiological and metabolic functions of BAT can be determined using various indicators. The most commonly used BAT assay is quantitative tissue-specific glucose uptake or semi-quantitative 18FDG (18F-fluoro-D-deoxyglucose) uptake. The 18FDG indicator is a glucose analogue and its uptake provides an overall assessment of the metabolic activity of a tissue.

Acute exposure to cold increases the probability of detecting the metabolic activity of BAT, so in people with normal weight, this probability can be 60-90% [14,19]. In the absence of exposure to cold, increased metabolic activity of BAT can be detected only in 0,6-25% of patients [8, 12]. With regular daily exposure to the cold in the study group, the level of metabolic activity of BAT was increased [2, 9, 36], which was characteristic of natural seasonal acclimatization during the thermal winter.

Oxidative metabolism with active brown adipose tissue

Oxidative metabolism in BAT can be measured indirectly using 11C-acetate-PET or radio guides, as well as directly by measuring oxygen absorption in BAT using ^{15}O-O^2-PET [19, 22, 30]. Indicators of oxidative metabolism are more descriptive indicators of thermogenesis and oxidation of the mitochondrial substrate than the absorption of the substrate itself, since exposure to cold significantly activates oxidative metabolism [22]. Also, the perfusion of BAT significantly increases during cold weather, approximately twofold [19], which further confirms the increased oxidative role of brown adipose tissue when exposed to cold.

Thus, it was revealed that oxygen consumption was 50% higher in subjects with functionally active BAT - their tissue oxygen consumption was also high at rest compared to the control group with non-functional BAT [15]. In general, the oxygen uptake of BAT doubles during acute cold exposure along with double perfusion [30], and oxygen consumption and perfusion are interrelated. Taken together, they indicate the activation of thermogenesis in human FAT during exposure to cold.

Tissue-specific oxygen consumption can also be used to estimate the energy expenditure in BAT, which is strongly associated with the absorption of fatty acids by brown tissue both at cold and at room

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temperature [30]. Fatty acid absorption in FAT is measured using PET and 18F-fluoro-TIA-heptadecanoic acid (18F-FTHA), a palmitate analog that can enter either the intracellular lipid pool or directly into the mitochondria. During cold weather, activated BAT uses both glucose and fatty acids, but if intracellular triglyceride lipolysis is inhibited by nicotinic acid during cold weather, oxidative metabolism in BAT slows down and muscle tremors increase [4]. The importance of intracellular lipolysis for oxidative metabolism in BAT is additionally confirmed by the data that the radiodensity of BAT does not change with the introduction of nicotinic acid [4].

The X-ray density of tissue is measured by computed tomography (CT), which is measured in Hounsfield units (HU) for tissue as an indirect measure of triglyceride content. It was shown that after a 3-hour exposure to the cold, the subjects were found to have an increased level of HU, reflecting the degree of oxidation of one third of the intracellular lipid pool [22].

In mild cold (- $4C^0$), a high consumption of fatty acids in BAT was observed [3]. In addition, other methods such as magnetic resonance imaging (MRI) and proton spectroscopy (PS) can be used to assess the content of lipid profile and triglycerides in tissue. The content of triglycerides in BAT, measured using PS, is significantly lower in subjects with functionally active BAT compared to subjects with inactive BAT and is associated with the sensitivity of the whole organism to insulin [25].

Interestingly, when exposed to cold for 2 to 3 hours, lipid oxidation predominates [30], while prolonged exposure to cold (5 to 8 hours) in patients with functionally active BAT and increased insulin sensitivity increases glucose consumption [7].

Insulin-stimulated glucose uptake in brown adipose tissue. Despite the fact that cold is a powerful activator of BAT function, people do not currently spend significant time in the cold. A number of authors have found that nutrition and physical activity directly affect the activation of this tissue [5, 26].

Food intake is a complex chain of reactions in which the first signals of metabolic changes and the body's preparation for food intake and nutrient utilization occur even before the meal begins. The head phase of appetite and eating begins with the thought of food or the smell of food, accelerating the secretion of saliva. During this phase, a number of hormonal signals are transmitted, and among others, early release of insulin and peak insulin concentration are recognized [28].

Insulin also plays an important role after meals, in the postprandial state. After the first phase of increasing insulin, the concentration is gradually increased to facilitate digestion. Typically, in healthy people, the fasting plasma insulin level is approximately 3-10 IU/L (20-60 pmol / L), and in the postprandial state, the insulin level rises to 70-100 IU / L (420-600 pmol / L).

The postprandial level reflects the fasting level; the higher the fasting insulin concentration, the higher the postprandial concentration. Knowledge of postprandial insulin concentrations is used in an experimental setting, and the stimulation of insulin produced by the euglycemic hyperinsulinemic clamp is aimed at achieving an insulin concentration of 70-100 IU/L similar to postprandial clamping levels. During this type of insulin stimulation, the uptake of tissue-specific substrate can be measured by PET, and especially the rate of glucose uptake increases [17]. In part, the clamping stimulation of insulin can be viewed as mimicking the postprandial state, at least in terms of plasma insulin concentration.

Like cold, insulin activates the sympathetic nervous system (SNS), and through SNS activation, insulin can increase BAT thermogenesis. However, during steady state hyperinsulinemic clamping, BAT perfusion does not increase in the same way as when exposed to cold [19], suggesting that insulin may not have a direct effect on BAT thermogenesis. It is noteworthy that the steady state in hyperinsulinemic clamping is usually achieved 45-60 minutes after the start of the insulin infusion, and the acute effect of insulin may have already passed.Thus, BAT can be considered an insulin sensitive tissue type. Despite the fact that BAT is a small tissue in size and the contribution of this tissue to glucose consumption and to the sensitivity of the whole body to insulin is small, the rate of glucose uptake by insulin in BAT correlates with the M-value, a measure of the sensitivity of the whole body to insulin [19].

The effect of cold and insulin stimulation on BAT metabolism is somewhat different. Both stimulations increase the absorption of glucose by BAT and energy expenditure throughout the body [19], while the concentration of glucose in the blood plasma remains unchanged. However, with cold sympathetic activation results in high plasma fatty acid concentrations, and with insulin stimulation, a decrease to low fatty acid concentrations is observed. So, when exposed to cold, lipolysis predominates in adipocytes of white adipose tissue, and with insulin stimulation, it is suppressed by a high concentration of insulin. This is due to high plasma norepinephrine levels during cold periods, but such changes in norepinephrine concentration cannot be detected during insulin stimulation. Plasma insulin concentration is evidently high during hyperinsulinemic clamping, but during cold exposure, insulin levels decrease in all subjects, even those with higher fasting levels (obese and insulin-resistant subjects) [19]. The levels of thyroid hormones, thyroxine (T4) and especially triiodothyronine (T3), decrease during exposure to cold in patients with functionally active BAT [19]. No changes in the content of thyroid hormones were detected with insulin stimulation.Activation of brown adipose tissue through food intake and fasting

Food-induced thermogenesis refers to the production of heat that occurs in response to food intake. Thermogenesis reflects tissue respiration, in which mitochondria play a key role. Thus, tissues with a higher content and function of mitochondria have a greater contribution to thermogenesis of the whole organism.

The role of human BAT, which contains a large number of mitochondria, has been the focus of this debate, and it has been questioned whether BAT thermogenesis has any role in energy balance, especially in obesity. In the 1980s, results from studies in mice [26] prompted researchers to hypothesize that thermogenesis induced by fasting or food intake may explain why some people gain weight more easily than others [13]. However, the question of whether food-induced thermogenesis plays a role in human metabolism remains poorly understood.

During a diagnostic 18FDG-PET scan for tumor detection, the goal is to reduce the accumulation of the indicator by other metabolically active tissues. Such tissues include, in particular, skeletal muscle and brown adipose tissue. The accumulation of 18FDG tracer in BAT in diagnostic scans has been successfully reduced with beta-blockers [23], but equally effective results can be achieved by keeping the patient warm before and during the scan. In addition to premedication and controlled ambient temperature during scans, fatty foods have been used to reduce the uptake of 18PDHv BAT [34]. One group of patients (n = 741) prepared for a high-fat, very low-carb, protein-free diet scan, and another group of patients (n = 1229) was on an empty stomach. The high-fat group had a lower incidence of high uptake of 18FDG in BAT [34].

Thus, food composition can influence substrate preference in FAT, and the Randle cycle appears to function in FAT as well, in addition to other tissues such as myocardium and skeletal muscle [16]. Provided that a healthy person is given a high-calorie, carbohydrate-rich food, the postprandial uptake of 18FDG in BAT is higher than in subcutaneous or visceral adipose tissue [33], but it is not known whether the uptake of 18FDG after a meal is increased compared to the fasting state prior to a meal. In general, postprandial uptake of 18FDH remains lower than during acute cold exposure [33].

With oral glucose after 3,5 hours at ambient temperatures of 20 °C and 25 ° C, the insulin response appears to be higher at 20 ° C, based on the higher ratio of insulin to glucose at 2 hours of GTT (glucose tolerance test) [24]. At a temperature of 20 °C, the concentration of insulin in the blood of the subjects decreases, since the lipolysis process is activated by catecholamines, the glucose load can cause a pronounced and compensatory release of insulin in favor of glucose oxidation after exposure to moderate cold. However, insulin concentrations at various temperatures have not been shown, nor have the levels of catecholamines or fatty acids been measured, and therefore the previous assumption remains validated under controlled conditions.

Thus, postprandial FAT substrate uptake may be influenced by food composition, although postprandial insulin levels can be expected to be sufficient to increase glucose uptake by this tissue. Since glucose uptake is not an ideal indicator of thermogenesis, postprandial oxidative metabolism may provide a better understanding of food-induced thermogenesis. Thus, eating food with a caloric content within the normal range, with a predominance of carbohydrates, increases blood supply and oxygen absorption in the BAT as well as during cold exposure [29].Prolonged fasting for 54 h leads to a decrease in the cold-induced rate of glucose uptake in the BAT, which is approximately half the rate measured under normal ambient temperature [15]. In addition, obesity reduces the likelihood of detecting metabolically active BAT, and only 30% of obese patients have shown a significant increase in cold-induced absorption of glucose in BAT [20]. The metabolic activity of BAT in obesity is impaired, and insulin-stimulated glucose uptake is less than half of the absorption measured in subjects with normal weight [20]. It is possible that the brown adipocytes of obese subjects are transdifferentiated into white adipocytes completely filled with triglyceride, or isolation by thick subcutaneous adipose tissue in obesity is effective enough to prevent a similar degree of FAT activation than in lean subjects. On the other hand, some people may be prone to obesity due to poorly functioning BAT.

Recruiting BAT (browning) to other fat depots, such as visceral white fat depots or perirenal white fat depots, may be beneficial in the fight against obesity. Patients with morbid obesity have a lower content of uncoupling protein 1 (UCP1) in intraperitoneal adipose tissue than lean subjects [18]. Weight loss predominantly targets intra-abdominal fat, and thus UCP1 expression and function can be increased following weight loss at these depots. Routine weight loss through diet and exercise for 5 months results in a 12% reduction in baseline weight, while cold-induced metabolic activity of BAT tends to be higher than before weight loss [20].

It was found that in patients with severe obesity, bariatric surgery leads to a noticeable weight loss (by about 30% of the initial weight), and one year after surgery, the metabolic activity of BAT in these patients increases [31].

Conclusion. Modern studies on the physiology of brown adipose tissue have shown that the effect of cold increases energy expenditure at rest in the human body, especially in persons with a high metabolic activity of this tissue, which contributes to a decrease in body weight. The activation of brown adipose tissue most effectively occurs during exposure to cold, but in the modern world we spend less time in natural cold conditions, therefore nutritional factors can serve as inhibitors for the activation of this tissue. Short-term regulation of the functional activity of brown adipose tissue by nutritional factors is possible mainly due to insulin. Insulin helps to reduce the absorption of glucose in brown adipose tissue by 5 times under fasting conditions.The activation of brown adipose tissue most effectively occurs during exposure to cold, but in the modern world we spend less time in natural cold conditions, therefore nutritional factors can serve as inhibitors for the activation of this tissue. Short-term regulation of the functional activity of brown adipose tissue by nutritional factors is possible mainly due to insulin. Insulin helps to reduce the absorption of glucose in brown adipose tissue by 5 times under fasting conditions.

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