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BROWN ADIPOSE TISSUE: MAIN STAGES OF RESEARCH AND POTENTIAL ROLE IN ENERGY BALANCE AND OBESITY

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ABSTRACT

Obesity and diabetes mellitus are worldwide epidemics driven by the disruption in energy balance. In recent years, it was discovered that functional brown adipose tissue (BAT), once thought to exist mainly in infants, is present in adults, and can be detected during cold stimulation, and is associated with decreased adiposity. Brown fat pads were shown to be highly vascularized and metabolically active and on stimulation, they caused enhanced energy expenditure and increased glucose and fatty acid uptake. These observations drew attention to the possibility that nonshivering thermogenesis medited by activation of BAT might be important in human energy balance and a potential tool to counter obesity. Recent investigations have revealed significant advances in the understanding of the role of BAT-mediated thermogenesis, uncovering essential knowledge on the origin, differentiation, activation, and regulation of BAT in both murine models and humans. In addition to classic BAT depots, transformation of white adipocytes into brown-like adipocytes, and the development of “beige” cells from distinct precursors, were demonstrated in different animal models and resulted in increased thermogenic activity. This review will summarize the evolution of research on BAT in humans, in light of the renewed scientific interest and growing body of evidence showing that recruitment and activation of BAT and browning of white adipose tis- sue can affect energy expenditure and may be a future feasible target in the treatment of metabolic diseases.

Keywords: brown adipose tissue, obesity, energy balance, UCP1.

Introduction. Obesity is a major public health problem and a global epidemic that contributes to the development of dyslipidymia, type 2 diabetes and cardiovascular diseases [42]. Treating patients with obesity requires serious efforts in lifestyle changes. Other methods, such as medication and bariatric surgery, are only suitable for a limited group of people. Therefore, a significant effort is aimed at developing the latest therapeutic tools to combat obesity. One possible solution would be to increase energy consumption through the activation of brown adipose tissue.

Brown adipose tissue (BAT) is a unique adipose tissue, its main function is to generate heat by dissipating chemical energy. Until recently, it was believed that among people BAT is present only in newborns [4]. However, at present there is a belief that BAT is also active in adults and can be a therapeutic way against obesity. An obstacle to achieving these goals is the small number of BAT in adults, especially in older people.

The purpose of this article is to review the topics of current research on BAT and its impact on energy balance, obesity and metabolic diseases.

The epidemic of obesity and energy balance. According to the WHO, the number of people with obesity has increased by more than 2 times worldwide, including among children [11, 32, 42]. Currently, obesity is the main cause of pathologies, disability, premature mortality [2].

Obesity is a frequent result of an imbalance between energy intake and consumption, which consists of a basal metabolic level and physical work, which includes physical activity and non-physical adaptive thermogenesis [14, 25]. The main factors contributing to the imbalance are a decrease in physical activity with an increase in the energy consumption of high-calorie foods and drinks [6]. An important factor that can play a role in the energy balance and the development of obesity is the temperature of the environment [15].

However, it is not easy to influence the energy balance by intensive lifestyle changes in people with obesity. Caloric restriction is accompanied by unpleasant sensations of hunger and compensation, leading to a decrease in the basal metabolic rate and a decrease in physical activity [22, 35].Due to the limited efficacy of drugs, bariatric surgery has improved significantly in recent years. It has been shown to improve metabolic dysfunction, reduce the levels of inflammatory cytokines [12], and help improve glycemic control in patients with obesity and diabetes [21]. However, these procedures are invasive, have potential complications and are a therapeutic option for a small number of patients with severe obesity and concomitant diseases. Therefore, methods to increase energy costs are still needed for obese patients. For example, the use of BAT features, a unique feature of which is to stimulate lipid metabolism to activate thermogenesis, which thus increases energy consumption.

BAT consists of brown adipocytes, characterized by a large number of mitochondria. BAT mitochondria are unique in expressing the release of protein 1 (UCP1) in the inner mitochondrial membrane. When activated, this protein separates the electron transfer in the respiratory chain from the formation of adenosine triphosphate and, thus, converts chemical energy, which mainly originates from fatty acids, into thermal energy, leading to thermogenesis. It should be emphasized that UCP1 is present only in BAT and is not characteristic of white adipose tissue. BAT is physiologically active in newborns. Its evolutionary function is to generate heat when no other means of producing it has been developed. After puberty, the number and activity of BAT decreases rapidly. However, in adults, BAT is found in the supraclavicular and cervical areas, around the spinal cord and the paravertebral and periaortic areas.

Study of brown adipose tissue in adults. For the first time, physiologically active BAT in humans was described several decades ago, and the question of the clinical significance of BAT in adults was raised in the 1970s [29, 37]. In 1981, it was stated that working in the cold could contribute to the activation and increase in the mass of BAT [37]. Several studies have shown that catecholamines stimulate BAT thermogenesis and negatively correlate with obesity [17, 18].However, until recent years, BAT was considered a tissue without significant physiological significance in healthy adults. Scientific interest in the physiology of brown adipose tissue occurred in the 1990s — during FDG-PET scans, physiologically active BAT were found in the upper surface of the neck [26]. In 2002, Hani and colleagues found that BAT probably increased under the influence of cold stress on sympathetic activity [13]. A few years later, Nedergaard and colleagues put forward “unexpected evidence of BAT activity in adults,” its potential in human metabolism and physiology, and a possible role in the fight against obesity [31].Until recently, the results of FDG-PET showed the presence of active BAT only in a small proportion of adults. So, in 2009, Cypress et al. demonstrated

the presence of BAT depot in the front of the neck and chest in 7.5% of women and 3% of men (without stimulating the activity of BIT) [7]. However, the scientific team Lichtenbelt found active BAT in 23 of 24 healthy men during mild exposure to cold. This activity has a negative correlation with BMI, supporting the possibility of applying regulation of BAT activity in people with obesity [38]. Saito’s research also demonstrated cold-induced FDG-PET / CT in 27 of 32 healthy young volunteers [36].All these studies prove the presence of BAT in a more significant proportion of adults than in earlier studies that were carried out in thermoneutral conditions.The next step was to confirm that BAT is actually metabolically active in humans and contributes to cold-induced non-contractile thermogenesis. A number of studies have shown that cold activates BAT more than 2 times, increasing the rate of perfusion in tissue, which is associated with energy metabolism during cold exposure and confirms active thermogenesis [8, 43]. The scientific group Qellet found that cold activation of BAT is also associated with high oxidative metabolism in the tissue. Researchers have shown an increase in the consumption of triglycerides as energy sources during BAT thermogenesis [34].

However, another study shows that despite the high glucose uptake in BAT, active BAT does not significantly contribute to energy expenditure [33]. Low activity of BAT depot may reflect low density of brown adipocytes - therefore, to increase energy expenditure, their excess will be needed.BAT and human interactions

The main question is whether the presence, mass or activity of BAT affects the development of obesity. It is preliminary shown that we are dealing with an increase in body weight; overexpression of transgenic mice with UCP1 protection against obesity; and adrenergic stimulation of β3-adrenergic receptors, leading to the appearance of brown adipocytes in white tissue, accompanied by increased expression of UCP1 and a decrease in body weight [36, 38, 45].Recent studies have shown a negative correlation between BAT activity and various obesity parameters, such as BMI, fat percentage and fat composition [9,13, 33, 39, 41]. After weight loss by bariarthric surgery, a significantly high non-contractile thermogenesis was observed in BAT-positive patients compared with BAT negative group [44].

Other clinical correlations

At present, a clear decrease in the activity of BAT, which is associated with the age of the subjects [5, 13, 30, 33, 34], has been proven. Several studies have shown that BAT predominates more in women than in men [5,27,30,41].

The relationship between the detection of BAT and ambient temperature is also well understood. Activation of BAT was most often recorded during the cold season [27], and seasonal variations, the external temperature, apparently, are associated with the presence of BAT [13, 28.41]. In the work of Hyuang Y.C, it was shown that the prevalence of active BAT decreases by 1% with each increase in the external environment by 5 ° C, and the prevalence of BAT is rarely found in tropical zones [46].

Conclusion. Recent studies suggest that BAT-mediated thermogenesis may play a major role in the energy balance. Activation of BAT can have therapeutic potential in treating patients with obesity, diabetes and metabolic syndrome, providing new treatment options.

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