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To cite this article: Haijun Dong, Man Qin, Peng Wang, Shufan Li & Xing Wang (05 Oct 2023): Regulatory effects and mechanisms of exercise on activation of brown adipose tissue (BAT) and browning of white adipose tissue (WAT), Adipocyte, DOI: [10.1080/21623945.2023.2266147](https://doi.org/10.1080/21623945.2023.2266147)

To link to this article: <https://doi.org/10.1080/21623945.2023.2266147>



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Accepted author version posted online: 05 Oct 2023.



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Publisher: Taylor & Francis & Informa UK Limited, trading as Taylor & Francis Group

Journal: *Adipocyte*

DOI: 10.1080/21623945.2023.2266147

Regulatory effects and mechanisms of exercise on activation of brown adipose tissue (BAT) and browning of white adipose tissue (WAT)

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Abstract: Exercise is a universally acknowledged and healthy way to reducing body weight. However, the roles and mechanisms of exercise on metabolism of adipose tissue remain largely unclear. Adipose tissues include white adipose tissue (WAT), brown adipose tissue (BAT) and beige adipose tissue (BeAT). The main function of WAT is to store energy, while the BAT and BeAT can generate heat and consume energy. Therefore, promotion of BAT activation and WAT browning contributes to body weight loss. To date, many studies have suggested that exercise exerts the potential regulatory effects on BAT activation and WAT browning. In the present review, we compile the evidence for the regulatory effects of exercise on BAT activation and WAT browning and summarize the possible mechanisms whereby exercise modulates BAT activation and WAT browning, including activating

sympathetic nervous system (SNS) and promoting the secretion of exerkinins, with special focus on exerkinins. These data might provide reference for prevention or treatment of obesity and the related metabolic disease through exercise.

Key words: Obesity; BAT activation; WAT browning; Exercise; Exerkinins;

1 Introduction

In 2016, the number of obese adults reached 671 million^[1], and the obesity rate of children in China and the United States was 1/5^[2] and 1/3^[3] respectively. It is estimated that by 2025, the number of overweight children will reach 268 million, and the number of overweight children in China will reach 48.5 million^[4]. In addition to a variety of metabolic diseases, obese people may also have psychological problems such as depression^[5]. In addition, the direct cost of obesity treatment in the UK is up to 5 million pounds, and the cost of obesity-related chronic diseases is up to 1 billion pounds^[6].

Exercise can activate the sympathetic nerve, accelerate the decomposition of fat, and promote the utilization and consumption of energy in skeletal muscle, thus reducing the amount of fat deposition^[7]; The Browning of brown adipose tissue (BAT) and white adipose tissue (WAT) can be affected by exercise^[8], thus promoting the transformation of energy-storing WAT into energy-consuming and heat-producing beige adipose tissue (BeAT), and increasing the heat production of BAT and BeAT, so that the energy consumption of the body can increase and the amount of fat deposition will reduce. It has been widely recognized that exercise is beneficial to weight loss. Studies published in the Lancet^[9] and Nature^[10] have shown that effect of weight loss

can be achieved by increasing energy consumption through increasing physical activity. The latest META-study in China also shows that exercise is beneficial to weight loss and the improvement of the body composition for overweight and obese college students^[11]. It should be noted that the non-thermogenic mechanisms of exercise also contribute greatly to weight loss and will not be reviewed here.

Exercise plays a vital role in the regulation for BAT activation and the Browning of WAT^[12]. Therefore, by comprehensively and systematically searching relevant literature and summarizing relevant research progress on the regulation and mechanism of exercise on BAT activation and the Browning of WAT, we explore some possible targets for exercise prevention and treatment of overweight and obese people, thus making up for the weak link in the current research on the regulation mechanism of exercise on human body fat, and providing reference for the prevention or treatment of obesity and related metabolic diseases by exercise.

2 Research method

By combining subject words with free words, two researchers searched English databases: The Cochrane Library, PubMed, Web of Science, Embase and Chinese databases: CNKI, CBMdisc, VIP and Wang Fang Data by computer. The English search words are "exercise", "overweight", "obesity", "fat", "white fat", "brown fat", etc. The retrieval time was from the establishment of the database to December 31, 2022, and then the relevant literature was combed, in order to clarify the regulatory effects of exercise on brown fat and white fat.

3. Structural and functional characteristics of different adipose tissue and cells

The uneven energy intake and consumption will lead to fat accumulation and precipitation, which will result in obesity^[13]. Studies have found that the precursors of mammalian nerve sheath or mesoderm can produce adipocytes, in which the nerve sheath can differentiate directly into mature adipocytes^[14], and the precursors of mesoderm can differentiate into precursor cells with different functions, and then differentiate into different types of adipocytes or muscle cells^[15]. The plasticity of adipose organs can occur through the proliferation and differentiation of stem cells. In addition, under certain stimulation, mature adipose cells can promote the change of phenotype and function by reprogramming the genome, thus promoting the plasticity of adipose organs^[16].

The fat tissue in the body can be divided into three types (Figure 1). Adult WAT is mainly distributed in the abdomen and subcutaneous parts, and the morphology is dominated by large unilocular cells, whose main function is to store excess energy in the body. There is a large fat drop in the cells, but there are few mitochondria in the cells^[17]. Adipocytes of obese people have functional abnormalities and acquire more features of white fat cells, such as the enlarged lipid droplets, enlarged endoplasmic reticulum, cholesterol crystals and some degraded mitochondria, surrounded by more and more collagen fibers, thus storing excess fat in the body^[18].

BAT cells are thermogenic adipocytes containing a large number of mitochondria and small lipid droplets^[19]. In infancy, BAT is mainly distributed in the interscapular region, accounting for 1%-5% of the body weight. However, in adulthood, BAT is mainly distributed in the clavicle, neck, paravertebral, mediastinum and perirenal

region^[20]. There are a large number of sympathetic nerve fibers on the surface of BAT cells, and there are a large number of mitochondria, cytochrome and multi-chamber small lipid droplets inside the cells. In addition, there are also a large number of capillaries around the cells^[21]. Van Marken Lichtenbelt WD et al. confirmed that the number of BAT in overweight and obese people was significantly less than that in normal people, and obesity was closely related to the reduction of BAT tissue number^[22]. 0.05kg of activated BAT can increase resting energy consumption by 5% per day and reduce fat by 4-4.7 kg per year^[23]. The activation of BAT can reduce fat storage and body weight^[24], and conversely, the reduction of BAT activity leads to an increase in total fat content and body mass index^[25].

The beige or brite adipocyte contains small lipid droplets with multiple chambers. What's more, the number of mitochondria are increased and the volume of mitochondria are larger, and the cells also have the thermogenic function similar to BAT^{[26], [27], [28]}. Uncoupling protein 1 (UCP1) exists in beige fat and white fat. The expression of UCP1 is low when it is unstimulated, while the expression of UCP1 increases when it is stimulated. UCP1 in beige fat can mediate heat production of beige fat by uncoupling oxidized phosphoric acid to promote lipolysis and reduce body weight^[29]. Beige adipose cells will gradually change into white adipose cells after stimulation^[30].

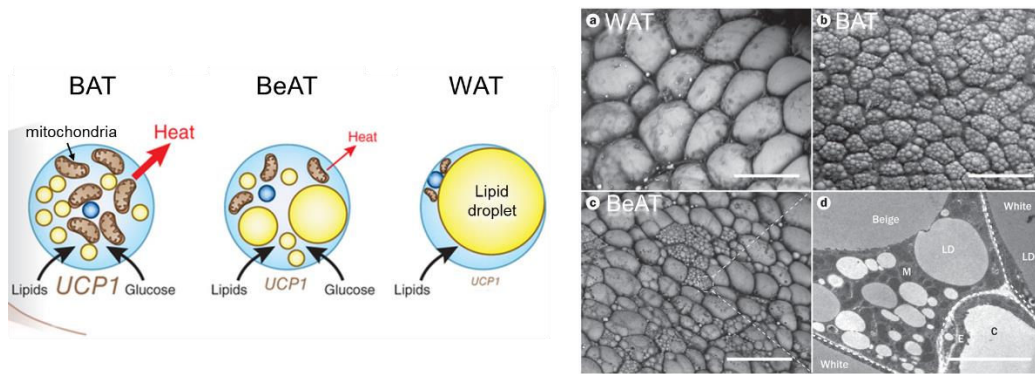


Figure 1. The structure and function of different types of adipose tissue/adipocytes

A: Structure and function model diagram^[31]; B: SEM image^[32]. (BAT: Browning of brown adipose tissue; BeAT: Beige adipose tissue; WAT: white adipose tissue; LD: lipid droplets; M:mitochondria)

4. The effect of exercise on brown fat to improve obesity

4.1 Exercise reduces fat by increasing BAT activity

The sympathetic nervous system can regulate BAT activity, and it is a classical regulator of BAT activity. Studies have shown that exercise can stimulate the sympathetic nerve and excite it, thus increasing the level of norepinephrine (NE) in the circulatory system^[33]. Norepinephrine released by the sympathetic nerve binds to beta adrenergic receptors in BAT to activate the CAMP-dependent protein kinase A (PKA) signaling pathway. The activation of PKA can promote lipolysis and increase the expression of UCP1, thus promoting the activation and thermogenesis of BAT^[34].

In addition to activating the sympathetic nervous system, exercise promotes the secretion of a series of Exerkines that regulate BAT activity^[35]. Exerkines have been widely studied such as Myokines, Hepatokines, heart and brain secretion factors.

Muscle cells and BAT come from the same source, and exercise can actively promote

the expression of myogenic cytokines Irisin^[36] and β -amino-isobutyric acid (BAIBA)^[37], and the activation of BAT can also be realized through Irisin and Sirt1 signaling pathways. In addition, exercise also has a positive effect on the expression of brain-derived neurotrophic factors in the hypothalamus, so that it can enhance the activity of mitochondria, thus achieving the enhancement of BAT activity^[38]. Long-term participation in sports can also increase the recruitment of BAT precursor cells and improve the activity and density of BAT^[39].

Previous studies have found that high-intensity physical activities can increase the density of BAT^[40]. Compared with sedentary and inactive males, the endurance training athletes will have a reduced glucose uptake of BAT when they are exposed to low temperature, reflecting that the BAT activity is lower than that of inactive individuals. Moreover, compared with sedentary and inactive males, there was no difference in the expression of peroxisome proliferator-activated receptor- γ costimulator factor 1 α (PGC-1 α) in BAT^[41]. In addition, compared with non-athletes, female athletes tend to get a decreased volume and activity of BAT^[42]. These findings indicate that different exercise programs or other stimuli may have different effects on BAT activity and other indicators^[43].

4.2 Exercise reduces fat by increasing heat production of BAT

In terms of heat production capacity, BAT has a more heat production capacity than liver and muscle^[44]. Heat production is achieved by uncoupling fatty acid oxidation and ATP production through UCP1 on the inner membrane of mitochondria, causing energy to dissipate in the form of heat^[45]. Exercise can enhance the expression of

UCP1 and genes related to mitochondria biogenesis, thus inducing the improved heat production capacity of BAT^[46] and elevated basal metabolic rate^[47]. Previous studies have shown that the expression of heat marker genes UCP1^[29] and PGC-1 α ^[30] in BAT can be improved by running on the treadmill for 8 weeks in male mice and swimming for 6 weeks in rats. PGC-1 α , as an important activator of UCP-1, can assist the activation of nuclear receptors such as peroxisome proliferator-activated receptor γ (PPAR- γ). Thus, UCP-1 gene transcription and post-transcriptional processing can be activated to induce high expression of UCP-1 in brown fat cells^[48]. At the same time, the activity and secretion of PGC-1 α in BAT are enhanced during physical activities, which can improve the level of UCP-1^[49].

Exercise also has a positive effect on the ability of human liver to secrete fibroblast growth factor 21 (FGF21)^[50]. UCP1 expression and BAT thermogenesis are induced through endogenous, peripheral and endocrine pathways^[51]. Veniant et al.^[52] have found that FGF21 injection in mice can increase the weight of BAT and the expression of UCP1 in BAT. In addition, the secretion of FGF21 from brown adipocytes will increase when the mice are activated by thermogenesis. Slusher et al.^[53] also have found that exercise can increase the level of FGF21 in plasma and maintain it for as long as 6 hours after exercise. Xu et al.^[54] have found that whether mice are fed a high-fat diet or are fed a standard diet, 8 weeks of treadmill exercise can increase the transformation of pre-brown cells into brown cells, and the expression of specific genes of brown cells is up-regulated. In rodents, 6-week swimming training can not only increase the mass and total protein content of mouse

brown adipose cells, but can also promote the mitochondrial activity and respiratory enhancement of mouse brown adipose tissue^[55].

4.3 Exercise regulates chronic inflammatory response caused by obesity through BAT

In addition, exercise can also down-regulate macrophage expression gene 1 in BAT, monocyte to macrophage transformation gene, chemokine ligand 28, interleukin-6 (IL-6) receptor α and other inflammatory and pro-inflammatory related genes that are up-regulated by obesity. It also promotes BAT to play a role in improving health problems caused by obesity by regulating Janus kinase/signal transduction and transcriptional activator (JAK-STAT), transforming growth factor- β and insulin signaling pathways^[56]. In exercise-regulated BAT participating in inflammatory response, the downstream gene of JAK-STAT, namely cytokine signaling inhibitory factor-3 (SOC-3), can participate in the occurrence of leptin resistance, and through exercise, Transforming growth factor- β (TGF- β) is activated and up-regulated under the action of inflammatory mediators and reactive oxygen species (ROS), thus playing a role in regulating the involvement of inflammatory cells (IL, NF- κ B) in immune response^[57]. In addition, NF- κ B in macrophages can be activated by saturated fatty acids to relieve obesity^[58]. Experimental studies have also proved that after 8-week swimming intervention, inflammatory factors and inflammatory response in obese mice can be significantly reduced^[59].

4.4 Exercise relieves obesity by regulating glucose and lipid metabolism through BAT

Brown adipose tissue also has a large number of mitochondria, which can also accelerate the consumption of free fatty acids through UCP1, so as to accelerate the consumption of excess energy in the body^{[60], [61], [62]}. Exercise stimulates the sympathetic nerve and induces mature BAT cells to release hormones, which can activate G-protein to activate adenylate cyclase (AC), and promote the activation of cAMP, PKA and p38 mitogen activated protein kinase (MAPK) on lipopolysaccharide stimulating enzymes after binding with β -adrenergic receptor. At the same time, the enhanced metabolism of sugar of BAT can also be related to the increased release of norepinephrine through exercise^[63]. In addition, strength training can promote the intake of glucose in BAT and reduce blood sugar, thus relieving obesity^[64]. In addition, exercise is able to significantly lower the total abundance of triglyceride (TG) in BAT, and significantly lower the expression of genes related to phospholipid metabolism and fatty acid biosynthesis, thus promoting the metabolism of glucose and lipid in vivo and relieving obesity^[65].

5 Exercise acts on the Browning of white fat, thus relieving obesity

5.1 The effect of exercise on the Browning of white fat

The Browning of WAT has been widely applied in metabolic research, among which the reduction of oxidative stress in WAT is considered to be one of the methods to prevent and improve metabolic related diseases^[66]. Moreover, most studies have shown that the Browning of WAT is the main reason for the increase in total energy consumption of obese people. Therefore, the Browning of WAT through various means has become a new strategy to relieve obesity and related metabolic diseases^[67].

White fat turns brown under certain stimulation, presents UCP1 positive multilocular cells in the region, and can express UCP1 and other thermogenic genes when stimulated by the outside world, which is conducive to the whole body energy consumption and plays a similar role to BAT^[72]. Studies have found that exercise can promote the Browning of WAT and the expression of related marker genes. After exercise training, the enzyme activities of superoxide dismutase and catalase in white fat cells can be enhanced, thus speeding up the Browning process of white fat and relieving obesity^[68].

Studies have found that whether in animals or humans, aerobic exercise can increase the expression of PGC1- α in skeletal muscle cells and cause changes conducive to weight loss such as mitochondria, muscle fibers and angiogenesis^[69]. Treadmill running or autonomous wheel running can increase the expression of UCP1 in subcutaneous groin WAT^{[70], [71]} and peritoneal WAT in mice^[72]. In addition, exercise can also increase the expression of PGC-1 α in subcutaneous groin WAT and epididymis WAT^{[73], [74]}. What's more, the 12-week aerobic combined resistance training can increase the expression of UCP1 in subcutaneous WAT^[41], the 6-week endurance training can increase the expression of PGC-1 α in subcutaneous WAT^[75], and high-intensity physical activity can increase the expression of PGC-1 α in abdominal subcutaneous WAT^[76]. It has also been found that autonomous wheel running for 4 weeks and 11 days can increase the expression of specific markers of beige fat cells in the white adipose tissue of mice, increase fat consumption, and reduce the degree of obesity^[31].

5.2 The mechanism of exercise on the Browning of white fat

5.2.1 Exercise can induce muscle factors to promote the Browning of white fat

The Browning of white fat is influenced by RNA and other various factors^[77]. A transcription factor containing PRDM16 (PR domain-containing 16) can activate the uncoupling respiration of brown fat cells when the progenitor cells of white fat cells are expressed, enhancing the effect of mitochondria and regulating the expression of PGC-1 α and uncoupling protein 1, thus promoting the Browning of white fat^[78]. Moreover, PPAR γ and PGC-1 α are also the core transcription factors of the Browning of WAT, and some proteins and intestinal flora are also conducive to the Browning of WAT^[79]. Experiments on Rodent have shown that brown-like cells that can be induced to transform mainly appear in subcutaneous WAT^[80], and exercise can induce the release of growth factors and hormones.

Exercise can not only activate the sympathetic nervous system, but can also induce the body to produce various factors to regulate the Browning of WAT^[46]. Skeletal muscle produces a variety of muscle factors and can produce more when someone is doing exercise. In skeletal muscle, the expression of fibronectin type III domain containing protein 5 (FNDC5) is enhanced by the activation of PGC-1 α . After the cleavage of FNDC5, it is secreted into the blood as Irisin, which promotes the expression of UCP1 and induces the Browning of WAT both in vivo and in vitro. FNDC5 in skeletal muscle and Irisin in blood are both increased after exercise, and the expression of Browning marker gene UCP1 is also increased after exercise^[41]. In addition, the activation of PGC-1 α can promote the synthesis and secretion of BAIBA

and Mtrn-like. Studies have shown that BAIBA can promote the expression of WAT thermogenicity genes and promote the Browning of WAT^[57], and the activation of M2 macrophages can be promoted by Mtrn-like. Moreover, the expression of genes related to the Browning of WAT and thermogenesis can be induced by the release of norepinephrine^[61]. IL- interleukin-6 is produced by immune and non-immune cells in skeletal muscle and can reach its highest concentration immediately after exercise^[51]. IL-6 can regulate various metabolic processes such as glucose uptake, lipolysis and fatty acid oxidation^[27]. Studies have shown that IL-6 is not only involved in burn-induced Browning of WAT^[52], but also plays an important role in exercise-induced Browning of WAT^[53]. Knudsen et al. have found that repeated exercise can increase the level of IL-6 in plasma and further promote the expression level of UCP1 in groin WAT^[53]. Moreover, in WAT, IL-6 can induce the production of M2 macrophages and promote the Browning of WAT through the production of local norepinephrine^[54].

5.2.2 Exercise induces adipose, liver, heart and brain factors to promote the Browning of white fat

The potential mechanisms for the regulation of BAT activation and WAT browning by exercise (Figure 2). It has been widely documented that exercise can regulate the release of adipokines, thus promoting thermogenesis^[81-83]. The exercise-regulated adipokines include leptin, adiponectin, resistin, and apelin etc. Exercise can increase the release of adiponectin and apelin and decrease the secretion of leptin and resistin. However, exercise can induce increase in leptin sensitivity through AMPK signaling

pathway. Furthermore, exercise-elevated adiponectin and apelin can lead to mitochondrial biogenesis, increased brown fat and thermogenesis, and decreased white fat. It should be noted that the exercise-regulated metabolites^[84] and exosomes^[85,86] are also involved in exercise-induced adipose thermogenesis and will not be reviewed here.

FGF21 is a member of the fibroblast growth factor family, which is mainly expressed and secreted in the liver, and it is also secreted in skeletal muscle, WAT and BAT. Studies have found that exercise can promote the secretion of FGF21 in muscle tissue, increase the content of FGF21 in serum^[87], regulate plasma and lipids, regulate glucose metabolism, enhance glucose utilization and consumption rate, and reduce blood sugar, etc.^[88]. In addition, exercise can promote the Browning of WAT, increase energy consumption, and reduce the degree of obesity^[46]. Follistatin, a member of the TGF- β superfamily, is secreted mainly by the liver, and it is also secreted by skeletal muscle, WAT and BAT. Studies have shown that exercise can also significantly increase the level of Follistatin in plasma that is considered as a systolic liver factor^[72], which can increase the expression of FNDC5 and the secretion of Irisin, and induce the Browning of WAT in mice^[71].

Cardio-secreted factors NPs include atrial natriuretic peptide (ANP) and B-type NP (BNP), whose primary function is to regulate blood pressure^[89]. Studies have shown that exercise promotes myocardial secretion of NPs, and is involved in regulating WAT lipolysis^[90] and fat oxidation in human skeletal muscle^[91]. In adipocytes, ANP and BNP can promote UCP1 expression^[92]. In addition, Thomsen et al. have found

that in healthy young adults (20-28 years old), serum proANP (a marker of ANP secretion) level is positively correlated with VO₂max during exercise and negatively correlated with respiratory exchange rate (RER), suggesting that exercise can promote cardiac NPs secretion, thus promoting BAT activation and WAT Browning and enhancing the metabolic function of the body^[93].

Brain-derived neurotrophic factor (BDNF) is a neurotrophic factor expressed mainly in the hippocampus region of the brain. BDNF can promote the plasticity of synapse and play an important regulatory role in human memory^[94]. In addition, BDNF also plays an important role in energy homeostasis^[95]. Previous studies have found that exercise affects the secretion of BDNF and thus promotes the Browning of WAT, partly through regulating the expression of PGC-1 α and Irisin^[96]. On the contrary, inhibiting the BDNF can inhibit the exercise-induced Browning of WAT^[97], promote fat consumption and achieve weight loss^[98].

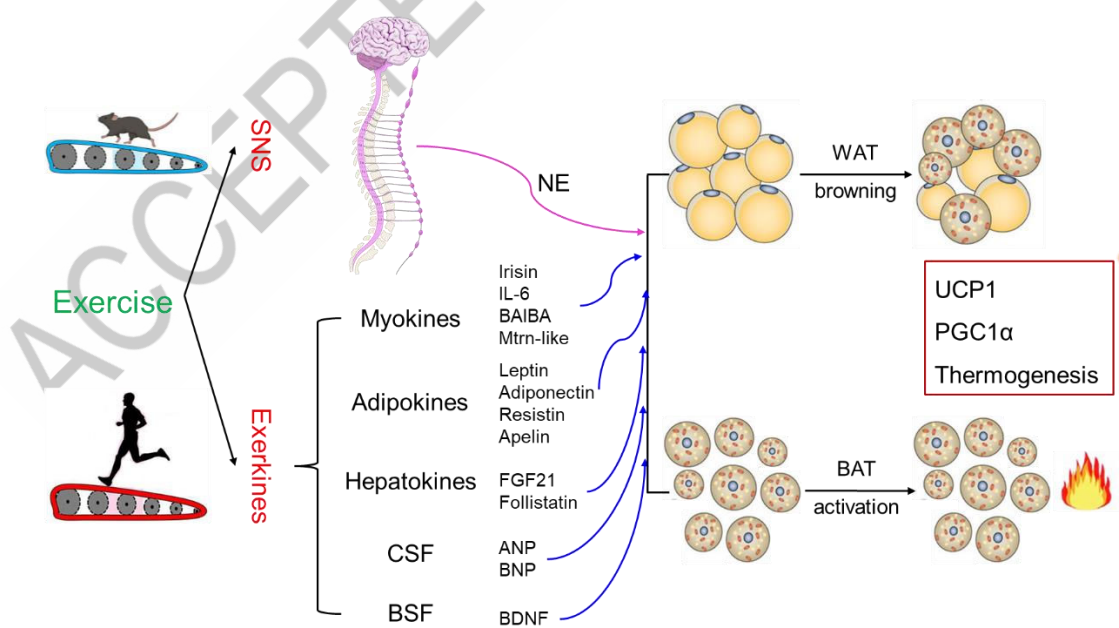


Figure 2. The potential mechanisms for the regulation of BAT activation and WAT

browning by exercise

(SNS: Sympathetic nervous system, CSF: Cardiac Secretory Factor, BSF: Brain secretion factor, NE: norepinephrine; IL-6: interleukin-6; BAIBA: β -amino-isobutyric acid; FGF21: fiber growth factor 21; ANP: atrial natriuretic peptide, BNP: B-type natriuretic peptide, BDNF: Brain-derived neurotrophic factor)

6 Conclusion

Obesity has become a worldwide epidemic, and it affects both physical and mental health. Exercise can not only activate the sympathetic nerve, enhance the activity of brown fat, but also improve heat production, and regulate the metabolism of sugar and lipid. What's more, exercise can reduce the chronic inflammatory response caused by obesity and promote the Browning of white fat. Last but not least, exercise can promote the Browning of white fat through a variety of muscle factors, liver factors and brain secretion factors, increase heat production, increase fat consumption, and achieve the effect of weight loss.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the first author on reasonable request.

Competing interests

The authors declare no conflict of interest.

Funding

Key Laboratory Project of Shanghai Science and Technology Commission (Grant No.11DZ2261100).

Authors' contributions

DHJ contributed to the conception and design of the study. DHJ and QM organized the database. DHJ wrote the first draft of the manuscript. WP and LSF wrote sections of the manuscript. WX review and editing. All authors contributed to manuscript revision, read, and approved the submitted version.

Acknowledgements

Not applicable.