Am J Physiol Endocrinol Metab 325: E610–E620, 2023.
First published October 11, 2023; doi:10.1152/ajpendo.00160.2023

american physiological society

AMERICAN JOURNAL OF PHYSIOLOGY
ENDOCRINOLOGY AND METABOLISM

REVIEW

Physical activity and batokines

Gabriela Ueta Ortiz[1] and Ellen Cristini de Freitas[1,2]

[1]*Department of Health Sciences, Ribeirao Preto Medical School, University of São Paulo—FMRP USP, São Paulo, Brazil and*
[2]*School of Physical Education and Sport of Ribeirão Preto, University of São Paulo, São Paulo, Brazil*

Abstract

Brown and beige adipose tissue share similar functionality, being both tissues specialized in producing heat through nonshivering thermogenesis and also playing endocrine roles through the release of their secretion factors called batokines. This review elucidates the influence of physical exercise, and myokines released in response, on the regulation of thermogenic and secretory functions of these adipose tissues and discusses the similarity of batokines actions with physical exercise in the remodeling of adipose tissue. This adipose tissue remodeling promoted by autocrine and paracrine batokines or physical exercise seems to optimize its functionality associated with better health outcomes.

adipose tissue remodeling; batokines; brown adipose tissue; myokines; physical exercise

INTRODUCTION

Mammals have two main types of adipose tissue: white adipose tissue (WAT) and brown adipose tissue (BAT) (1). Although WAT serves as an energy storage tissue due to its high triglyceride content within a large fat droplet and its relatively low number of mitochondria, BAT is a tissue with a smaller amount of triglycerides arranged in several small fat droplets but with a greater number of mitochondria that present uncoupling protein 1 (UCP-1), which is considered the main marker of BAT and is partly responsible for its thermogenic function (1–3).

A third adipose tissue type called beige adipose tissue shares functional and morphological similarities with BAT and can be activated from white adipocytes when exposed to specific stimuli like cold temperatures and physical exercise to perform similar functions to brown adipocytes (1, 4). Although BAT and beige adipose tissue present differences, such as originating in different cell lineages (5), this review will focus on their similar functionalities. Thus, herein we will refer to these tissues collectively as BAT.

The activation of such adipose tissues has been proposed as a therapeutic target in treating obesity and associated diseases because of their thermogenic functions (1). When activated, these tissues increase the oxidation of energy substrates to sustain thermogenesis, leading to greater utilization of fatty acids and glucose, decreasing insulin resistance, and promoting energy homeostasis (4, 6).However, the scientific literature has recently shown that the metabolic effects promoted by BAT are not limited to thermogenesis.(7) Like WAT and skeletal muscle, BAT also releases its secretion factors, known as batokines (7). These molecules, which can be peptides, lipids, or miRNA, can act in an autocrine and paracrine manner, supporting tissue expansion and enhanced activation, or in an endocrine manner, reaching several target tissues, such as the liver, heart, skeletal muscle, and WAT (8).

In these tissues, they play important roles in preventing hepatic steatosis, reducing insulin resistance, providing cardioprotective effects, promoting muscle development, and inducing the browning of WAT, among other metabolic benefits (8).

Evidence in animals and humans demonstrates that physical exercise can activate thermogenic tissues by two possible mechanisms of action: *1*) through β-adrenergic activation and *2*) through signaling myokines released by skeletal muscle in response to exercise, such as irisin, interleukin 6 (IL6), meteorin-like protein (METRNL), lactate, and vascular endothelial growth factor A (VEGFA) (9).

The activation of thermogenic tissues through physical exercise involves the recruitment of mature adipocytes and other cell types residing in these tissues as well, such as progenitor cells, stem cells, endothelial, neural, hematopoietic, and immune cells, which collectively promote adipose tissue remodeling, leading to increased thermogenic and/or secretory activity (10).

The autocrine and paracrine action batokines act likewise on the resident cells of adipose tissue, promoting angiogenesis, nerve outgrowth, modulation of the immune system cell profile, and adipocyte biogenesis. (7) This remodeling creates a microenvironment that favors the expansion and activation of brown or beige adipose tissue (10), as illustrated in Fig. 1. Some notable cytokines include neuregulin 4 (NRG4), nerve growth factor (NGF), bone morphogenetic protein 8 b (BMP8b), VEGFA, chemokine ligand 14 (CXCL14), and IL6 (11).

Correspondence: G. U. Ortiz (gabriela.ortiz@usp.br); E. C. de Freitas (ellenfreitas@usp.br).
Submitted 24 May 2023 / Revised 28 September 2023 / Accepted 2 October 2023

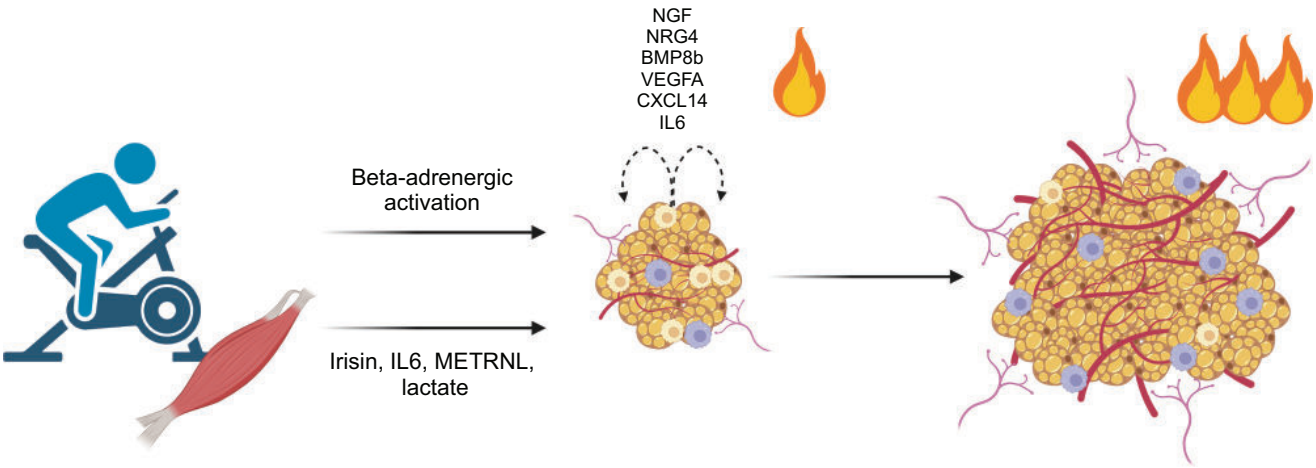

Figure 1. Physical exercise through β-adrenergic activation or the release of myokines activates thermogenic tissues (brown or beige recruitment), which in turn release their secretion factors (batokines), which, through autocrine and paracrine actions, remodel the tissue, promoting angiogenesis, growth of sympathetic innervation, and modulation of immune system cells profile, creating a favorable microenvironment for greater activation and expansion of the tissue and, consequently, greater thermogenic activity. Created with BioRender.com.

Although the evidence for the activation of thermogenesis in BAT by physical exercise is not entirely conclusive, the secretory function of these tissues has already been demonstrated in thermoneutral conditions (12, 13). Therefore, some authors suggest that this tissue does not necessarily need to perform thermogenesis to promote positive health impacts since batokines have great potential in promoting metabolic health, mainly in controlling obesity and type 2 diabetes (8, 10, 11).

Most evidence on exercise's potential to recruit thermogenic adipocytes focuses on increased genes and proteins expression related to thermogenic function and lipid or glucose oxidation markers (14–17). At the same time, few human studies have investigated its secretory function in response to exercise (13).

This review overviews physical exercise's influence on thermogenic tissues' secretory function. In addition, we gather clinical studies exploring physical exercise's effects on the thermogenic function in these tissues and describe the role of exercise and batokines in remodeling white and brown adipose tissue.

THE ROLE OF THERMOGENESIS IN METABOLIC HEALTH

Due to its primary thermogenic function, when activated, BAT increases the oxidation of energy substrates to sustain thermogenesis, leading to greater oxidation of fatty acids and glucose, reduced insulin resistance, and an increase in energy expenditure (4).

It is estimated that only 50 g of BAT can account for ~20% of the daily energy expenditure when fully activated (18) although the contribution of BAT thermogenesis to energy expenditure shows high individual variability, and it appears to be lower in individuals with higher body mass index (BMI) (19).

Thermogenesis is primarily mediated by the UCP-1 proteins, which are present in the inner membrane of mitochondria. These proteins interrupt the process of oxidative phosphorylation, allowing the leakage of hydrogen ions from the intermembrane space to the mitochondrial matrix, generating heat (20). Therefore, it is a process where chemical energy is expended to produce thermal energy (20).

There is a strong correlation between the prevalence of BAT activation and body mass index (18). Despite the robust correlation, it is important to highlight the possibility that the relationship may be influenced by confounding effects that need to be better elucidated. Although there are challenges in understanding, which factor is the cause and which is the effect, there is consistent evidence that BAT thermogenesis contributes to energy homeostasis (21–24).

Hamann et al. (21) developed a transgenic mouse model with toxin annihilating UCP-1-positive cells. When these mice were fed a high-fat diet, they experienced positive energy balance and gained fat. At the same time, animals with activated thermogenic tissue were protected against weight gain, even when fed the same diet.

Observational studies provide evidence suggesting an important role of BAT activation beyond energy regulation (22, 23). Becher et al. (23) conducted a retrospective analysis of various positron emission tomography/computed tomography (FDG-PET/CT) scans to detect BAT, and the amount of this tissue was independently associated with lower odds of cardiovascular diseases such as coronary artery disease, hypertension, heart failure, and dyslipidemias.

Despite reducing activity in obese individuals, some human studies have observed metabolic improvements with BAT activation through cold exposure in this population. Hanssen et al. (24) conducted a study on overweight men exposed to cold. The authors observed an increased glucose uptake by BAT using FDG-PET/CT and clinically relevant improvements in insulin sensitivity.

In addition to cold exposure, β-adrenergic receptor agonist drugs also demonstrated the same effect in obese men, improving glycated hemoglobin, oral glucose tolerance, insulin sensitivity, and promoting the browning of subcutaneous adipose tissue (25).

The pharmacological approach using adrenergic agonists, although proven effective in thermogenic tissue activation

(25), does not provide selectivity only to β-3-adrenergic adipocyte receptors, leading to side effects such as tachycardia, making its long-term safety debatable (26, 27).

Exposure to cold, although effective, is not efficient due to its lack of sustainability, as the withdrawal of the stimulus seems to interrupt the thermogenic activity of BAT (28).

Considering the information mentioned above, it becomes relevant to deepen our understanding of interventions with the potential to activate BAT safely and sustainably. In this review, we present a comprehensive discussion on the role of physical exercise as an intervention for BAT activation.

THERMOGENIC TISSUES ACTIVATION IN RESPONSE TO EXERCISE-INDUCED MYOKINES

Physical exercise promotes systemic health benefits. In part, these benefits are mediated by secretion factors released by the muscle in response to physical exercise, called myokines (9, 29). In addition to acting in an autocrine and paracrine manner in skeletal muscle, these proteins are released into the blood in response to muscle contractile activity, reaching multiple organs, including adipose tissue (9, 29).

In WAT, myokines promote the development of beige adipocytes, a process called WAT browning, in which white adipocytes temporarily acquire the phenotype and functionality of a brown adipocyte. This topic is currently under extensive study in the scientific literature (30–34).

The adipose tissue browning involves morphological changes in white adipocytes, including developing more mitochondria rich in UCP-1 and lower lipid content, arranged in multiple fat droplets (35). This process also leads to gene expression changes, with increased expression of thermogenic genes like peroxisome proliferator-activated receptors γ (PPARγ), transcriptional coactivator peroxisome proliferator-activated receptor-gamma coactivator 1 α (PGC-1 α), PR domain containing 16 (PRDM16), cell death CIDE-A (CIDEA), and UCP-1 (36, 37).

Boström et al. (30) identified, in mice, that by activating the PGC-1 α in skeletal muscle, the expression of a membrane protein called FNDC5 is increased, and when cleaved, it gives origin to a hormone called irisin. The plasma levels of this hormone seem to be increased in humans and mice in response to exercise, and it also appears to have actions on WAT browning (30).

Rao et al. (31) observed the same effect on WAT for the myokine METRNL, which seems to induce thermogenic and anti-inflammatory genes in WAT through the stimulation of interleukin 4 (IL4), that modulates the activation of anti-inflammatory macrophages in WAT, a process that favors the development of a beige phenotype.

Similarly, Knudsen et al. (32) identified that the increase in UCP-1 expression in the WAT of mice in response to exercise is dependent on the myokine IL6, as Carrière et al. (33) also observed thermogenic gene upregulation (UCP-1, CIDEA) in response to lactate, a metabolite released into plasma in response to high-intensity exercise.

Animals treated with an intramuscular infusion of lactate at concentrations similar to those released in response to exercise showed adaptations in the WAT that resemble thermogenic tissue characteristics (38). These adaptations included the upregulation of proteins involved in lipolysis, such as the protein kinase activated by adenosine monophosphate (AMPK) and hormone-sensitive lipase (HSL) (38). In addition, there was an increase in mitochondrial biomarkers like PGC-1 α, through activation of protein kinase A (PKA), and an increase in β-3-adrenergic receptors (38).

THERMOGENIC TISSUE ACTIVATION IN RESPONSE TO β-ADRENERGIC STIMULATION DURING EXERCISE

In addition to stimulating myokines and metabolites, physical exercise can also activate thermogenic tissues via β-adrenergic activation (4). This mechanism of action is mediated by noradrenaline, which binds to β-3-adrenergic receptors in the adipocyte and stimulates cyclic adenosine monophosphate (cAMP), which phosphorylates PKA and signals the regulation of UCP-1 gene expression, as well as leading to the lipolysis of stored triglycerides to sustain thermogenesis (39).

Regarding the activation of BAT in response to exercise, fewer studies in humans are available in the literature than in animals. Although it is possible to find similar outcomes as in animal studies based on existing evidence, the findings from human studies exhibit considerable diversity. This variability could be attributed to heterogeneity in research methodologies, the characteristics of the studied populations, variations in the type, intensity, and duration of the exercise programs, as well as different approaches employed to evaluate tissue browning.

Table 1 summarizes studies investigating the effect of different physical exercise protocols on thermogenic outcomes in BAT and WAT browning in diverse populations. Although the compilation of evidence demonstrates that exercise is a possible tool to promote the beige phenotype in WAT, further human studies are needed to better elucidate this issue in different exercise modalities and populations. Despite the limitations and conflicting results on the activation of thermogenesis in BAT, the literature has already demonstrated that physical exercise can activate another function in this tissue, which will be described below.

PHYSICAL EXERCISE AND BATOKINE SECRETION

Although some animal and human studies fail to find any exercise-influenced thermogenic activity in BAT (45, 46), emerging evidence demonstrates that effects on its secretory function do not follow the same pattern. Recently, a lipokine (a secretion factor of the lipid class) called 12,13-diHOME was discovered, a metabolite of linoleic acid released by BAT in response to physical exercise, which acts mainly on skeletal muscle, increasing the oxidation of fatty acids in this tissue (13).

Stanford et al. (13) performed liquid chromatography-mass spectrometry (LC-MS) and identified that an acute bout of physical exercise increased plasma levels of 12,13-diHOME in humans, independent of gender, age, BMI, or fitness level.

This finding was obtained from two different cohorts with diverse populations that underwent moderate to intense aerobic exercise to evaluate circulating levels of a panel of 88 lipids. Among all these lipids, only 12,13-diHOME levels

Table 1. *Clinical trials involving the effects of different physical exercise protocols on BAT outcomes and on WAT browning*

Physical Exercise Protocol	Population	Effects on BAT	Effects on WAT	Reference
Three times a week/ combined exercise/16 wk	Overweight and T2D individuals	Increased thermogenic activity	Increased expression of thermogenic genes	Bonfante et al. (15)
Three times a week/aerobic training 60 min per session/12 wk	Sedentary adults, eutrophic, overweight, or obese	NA	Increased expression of thermogenic genes	Otero-díaz et al. (16)
Six sessions/high-intensity interval training or continuous moderate intensity training/2 wk	Healthy eutrophic middle-aged men	Decrease in glucose oxidation rate	NA	Motiani et al. (40)
150 min per week of aerobic training and 80 min per week of resistance training/24 wk	Sedentary adults eutrophic and overweight	No change in BAT volume or glucose oxidation rate	NA	Martinez-Tellez et al. (41)
Five times a week/exercise combined with caloric restriction (∼200 kcal/day)/16 wk	Overweight and obese women	NA	No change in beige biomarkers in WAT	Nakhuda et al. (42)
Three times a week/combined exercise/12 wk	Sedentary, overweight, and obese middle-aged men	NA	No change in beige adipocyte morphology and biomarkers in WAT	Stinkens et al. (43)
Three times a week/combined exercise associated or not with taurine supplementation/8 wk	Sedentary obese adults women	NA	Increased expression of beige adipocyte biomarker genes in WAT	De Carvalho et al. (17)
Four times a week/combined exercise/12 wk	Healthy or prediabetic, eutrophic or overweight adult men	NA	Slightly increased expression of beige biomarker genes in WAT	Norheim et al. (44)

BAT, brown adipose tissue; NA, not available; T2D, type 2 diabetes; WAT, white adipose tissue.

increased immediately after exercise and returned to baseline 1 h later (13).

To identify the tissue of origin of this lipokine, a study was carried out in mice submitted to physical exercise. The results showed expressively lower plasma levels of 12,13-diHOME in animals with the inguinal BAT removed through surgery than in animals with conserved BAT, showing that this lipokine is a batokine released by BAT in response to exercise (13).

Batokines are secretion factors released by BAT, which can be proteins, lipids, or miRNAs (47). They have recently been described in the literature, and their functions include autocrine and paracrine as well as systemic actions, contributing to increased energy expenditure and glucose homeostasis, pointed out as allies in the fight against obesity and associated diseases (47).More details on their effects will be discussed in subsequent sections of this review.

The identification of batokines in science is a recent discovery, and the factors that stimulate their secretion are still under investigation. Some stimuli identified in the literature capable of producing the secretion of batokines include exposure to cold, β-adrenergic activation, ingestion of nutraceuticals such as capsinoids, and high levels of thyroid hormones (48, 49). Although 12,13-diHOME is the only batokine with evidence of being secreted in response to physical exercise in an in vivo environment (13), some in vitro studies suggest that irisin and lactate, factors released by skeletal muscle in response to physical exercise and with actions on WAT browning, also stimulate the secretion of batokines (50, 51).

A study was conducted with human subcutaneous and neck region adipocyte precursors, anatomical regions where adipocytes with beige gene signatures can develop or be found (52), to evaluate the effect of irisin, a myokine secreted in response to physical exercise, on the differentiation to thermogenic adipocytes and the secretome produced (50). In the results, it was not possible to observe increased expression of thermogenic genes; however, during adipocyte differentiation, there was significant secretion of chemokine ligand 1(CXCL1), a batokine with angiogenic functions, suggesting that irisin has a regulatory role in the secretory function of thermogenic adipose tissue (50).

Jeanson et al. (51) conducted an in vitro study to investigate the effects of lactate on mature adipocytes differentiated from the stromal vascular fraction of WAT in animals. Besides observing an increase in UCP-1 expression, a well-known effect of lactate on WAT browning, the study also revealed a rapid increase in the expression and secretion of fibroblast growth factor 21 (FGF21), a batokine with both autocrine and systemic actions (51). This increase in FGF21 was found to be mediated through the signaling of p38 mitogen-activated protein kinase (p38-MAPK), a class of activated proteins associated with cellular stress and involved in cell differentiation processes. In addition to lactate, this study suggested that other exercise metabolites, such as pyruvate and ketone bodies, may promote the same effect (51).

The liver mostly secretes the FGF21 protein; however, emerging evidence suggests that it is also secreted by skeletal muscle, WAT, and BAT, thus, categorizing it as a batokine (53). Like other batokines, it has been associated with positive metabolic effects in several target tissues, such as the liver, central nervous system, and adipose tissue, contributing systemically to the regulation of energy and glucose homeostasis through actions such as increased glucose oxidation and

thermogenesis by BAT, stimulating the oxidation of hepatic fatty acids and acting on the hypothalamus to reduce sugar consumption (54).

The evidence above suggests that physical exercise can modulate the secretory activity of thermogenic tissues, potentially providing additional benefits for metabolic health by stimulating batokine secretion. Although studies in this area are promising, further advances are still necessary to validate the hypotheses raised in the in vivo environment. Moreover, comprehensive evaluations are needed to investigate the behavior of myokines and metabolites released in response to exercise on the secretory function of thermogenic tissues, considering the intricate complexity of the organism.

PHYSICAL EXERCISE AND ADIPOSE TISSUE REMODELING

Adipose tissue remodeling in obesity is related to adipocyte hypertrophy, low tissue vascularization, and the proinflammatory profile of immune system cells, conferring the dysfunctionality of adipose tissue observed in the obesity phenotype. Alternatively, the remodeling that the practice of physical exercise can provide refers to alterations in the morphology of adipocytes, with lower lipid content, higher mitochondria content, greater vascularization, and immune system cells with a predominantly anti-inflammatory profile, providing a favorable microenvironment for the activation of beige adipocytes (10, 55, 56).

BAT activity and the brown phenotype in WAT are maintained by nerve stimulation of the central nervous system, and therefore, developing sympathetic innervation in these tissues is crucial for thermogenic tissue functionality (57–60).

Several studies have identified that the activity of the central nervous system and catecholamine levels are increased during physical exercise (4, 61, 62), promoting actions in white adipose tissue, such as browning of white adipocytes (14, 63), and stimulating lipolysis of triglycerides through binding with adipocyte β-adrenergic receptors (64).

In a recent animal study, it was observed that moderate physical exercise promoted an increase in the content of β-3-adrenergic receptors and sympathetic activity in BAT (65). However, the role of physical exercise in promoting the growth of sympathetic innervation in human adipose tissue is still unclear, as no studies directly investigated this topic in the literature.

In addition to sympathetic innervation, adequate tissue perfusion is required to sustain thermogenic tissue metabolic activity by providing oxygen and energetic substrates (56). Unlike the outcome related to the growth of sympathetic nerves, there is consistent evidence in the literature regarding angiogenesis promoted by physical exercise in adipose tissue (66–68). Kolahdouzi et al. (66) observed that physical exercise was able to reverse the dysfunctionality of WAT caused by diet-induced obesity in rats, increasing capillary density and expression of type 2 macrophages to levels even higher than those of animals with a control diet.

Macrophage polarization from type 1 (M1) to type 2 (M2) in adipose tissue also appears to be a factor influencing the ability of WAT to acquire a brown phenotype. Similar to the investigation conducted by Kolahdouzi et al., other studies have also observed this outcome in response to exercise (69).

In several human studies, both aerobic and resistance exercise have demonstrated significant angiogenic potential in individuals with insulin resistance and hypertension, as well as in healthy individuals (70–72). This effect seems to be associated with an increase in the angiogenic capacity of endothelial progenitor cells (70–72). The same effect has already been observed in animal BAT (73).

Furthermore, physical exercise appears to be a significant factor contributing to the healthy expansion of white adipose tissue in a situation of chronic caloric surplus. This finding can be attributed to the promotion of angiogenesis, and mitochondrial biogenesis, while also preventing adipocyte hypertrophy, which makes the tissue dysfunctional and is associated with chronic low-grade inflammation, insulin resistance, type 2 diabetes, and other metabolic disorders (56, 74).

Just like physical exercise, the autocrine and paracrine actions of batokines also exert the effect of remodeling thermogenic adipose tissue to promote an environment that favors its greater activation and consequently optimizes its thermogenic and secretory functions. These actions will be discussed in the following topic.

BATOKINES AND ADIPOSE TISSUE REMODELING

As previously described, for thermogenesis to occur in BAT, it is required not only the activity of mature UCP-1-positive thermogenic adipocytes but also the provision of adequate blood supply to the tissue. This blood supply enables the arrival of the energy substrates and oxygen essential to sustain thermogenesis efficiently (10).

Other crucial factors for BAT thermogenesis and WAT browning involve the tissue's sympathetic innervation and the presence of immune system cells residing in the tissue that can influence its functionality depending on its phenotype (10).

In light of this, the actions of autocrine and paracrine batokines are targeted toward the endothelial, neuronal, or immune cells within the thermogenic tissue, stimulating the growth of peripheral nerves, angiogenesis, and modulating resident immune cells, optimizing its thermogenic activity and for this reason are important therapeutic targets for BAT restoration in humans who have lost or have insignificant amounts of this tissue, such as obese or older individuals (10)

Batokines Neurite Outgrowth Effects

Some proteins, such as NGF and NRG4, stimulate neurite outgrowth, promoting the growth and differentiation of sympathetic neurons in the tissue. These proteins are considered important BAT markers, with a regulatory function of BAT sympathetic innervation in response to cold (75, 76). NRG4 serum levels are decreased in pathological conditions such as type 2 diabetes, metabolic syndrome, and coronary artery disease in humans (77).

Batokines Angiogenic Effects

In addition to promoting sympathetic innervation, BAT also secretes batokines with angiogenic capabilities, such as

VEGFA. The VEGFA protein promotes the activation, proliferation, and differentiation of vascular endothelial cells, acting as a trigger for angiogenesis within adipose tissue (78).

Park et al. (79) further observed that VEGFA significantly induced the browning of white adipocytes. In the same study, transplantation of adipose tissue exhibiting high VEGFA expression into mice with diet-induced obesity resulted in a notable decrease in the inflammatory response.

Other studies also observed the action of VEGFA in promoting the browning of adipose tissue, increasing the expression of UCP-1 and PGC-1 α in this tissue (78, 80). Furthermore, VEGFA can promote angiogenesis in the BAT itself, stimulating its activation (81).

BMP8b belongs to the bone morphogenetic protein family and is secreted by mature brown adipocytes in response to β-adrenergic activation or other nonadrenergic stimuli, such as estrogen. It appears to play a dual role: first, in promoting tissue vascularization by stimulating angiogenic factors, and second, indirectly promoting tissue innervation by stimulating the endogenous production of NRG4 (47, 82).

Batokines Immunomodulation Effects

The profile of cytokines and immune system cells residing within the adipose tissue seems to interfere with its functionality (83). In obesity, the infiltration of inflammatory cytokines into BAT appears to impair the activation of thermogenesis, negatively impacting its functionality (81) which confers some similarity between BAT and WAT.

A chemokine from the CXC family, CXCL14, was identified as a batokine capable of recruiting M2 macrophages to the BAT itself, modulating the inflammatory phenotype (84). As demonstrated by Cereijo et al. (84), CXCL14 secreted by BAT, in addition to activating it, also promoted the browning of WAT, reflecting improvement in glucose homeostasis in diet-induced obese mice.

Other BAT secretion factors, such as METRNL and adiponectin, also seem to modulate the profile of tissue-resident macrophages through different mechanisms of action, favoring an anti-inflammatory profile and stimulating the differentiation of white adipocytes into beige (31, 85).

Growth differentiation factor 15 (GDF15), another batokine that modulates the local inflammatory phenotype, is secreted by BAT in response to exposure to cold and can suppress the expression of proinflammatory genes in the tissue (86).

Lastly and possibly most importantly, IL-6 is also recognized as a batokine, perhaps the most extensively studied. One of its actions takes place locally as a consequence of BAT activation in response to a β-adrenergic stimulus, also acting on the recruitment of M2 macrophages and promoting the modulation of the profile of immune cells in the tissue, which directly impacts its activation capacity (87).

Batokines Thermogenic Effects

Although thermogenesis in adipose tissue can be controlled by β-adrenergic activation (88), the influence of batokines appears capable of promoting this phenomenon independently of this stimulus (89).

The newly discovered adipose tissue signaling protein batokine (Adissp), highly expressed in BAT, appears to bind to specific receptors on the adipocyte in a paracrine manner, activating the PKA pathway and promoting the transcription of glycolytic and thermogenic genes in thermoneutral conditions and a β-3-adrenergic receptors independent manner (61). These changes in gene expressions were accompanied by improvements in glucose homeostasis (89).

These data suggest that the secretion of batokines may be an alternative to exposure to cold or β-adrenergic agonists to promote the browning of adipocytes and their thermogenic activity (Fig. 2).

Data regarding the effects of physical exercise and autocrine/paracrine batokines point to a similarity in their roles in adipose tissue remodeling, consequently contributing to its functionality.

Dysfunctional adipose tissue is associated with the development of metabolic diseases (56), thus awakening great interest in the investigation of factors that trigger the secretion of batokines since their local effects within adipose tissue resemble the effects of physical exercise, potentially influencing tissue remodeling and functionality (Fig. 3).

CHALLENGES AND FUTURE PERSPECTIVES

Although the relevance of BAT activation has been demonstrated, there are still several gaps to be addressed in this field of research. These include the investigation of different pathways that drive BAT activation and pursuing new approaches to stimulate this tissue in an effective, sustainable, and safe manner. The scientific community is actively exploring this topic. Some animal studies have shown the role of microbiota metabolites inducing BAT thermogenesis (90, 91), whereas others have observed the potential of some thyroid hormones and nutraceuticals (48, 92, 93).

But the evidence is still limited to in vitro and animal models. The progress in this scientific area depends on conducting research involving human subjects and striving to observe whether these novel approaches to activate BAT will be accompanied by clinically relevant effects. These efforts should be the central focus of future studies, including more clinical research to strengthen the role of physical exercise in BAT activation, aiming to gather comparable studies in a systematic review to obtain a robust estimative of its effects.

A significant concern to consider when evaluating the metabolic health impacts of BAT activation is the restricted duration of its effects. It has been suggested that the interruption of exposure to external stimuli may reduce the activation of BAT. This decrease is more pronounced in obese individuals, whereas lean subjects may maintain higher heat production after 1 h of rewarming, as demonstrated by Claessens-van Ooijen et al. (19)

Similarly, the BAT-secreted 12,13-diHOME levels in response to exercise returned to baseline after 1 h. After 3 h, the levels remained elevated only in active young individuals compared with older and sedentary individuals (13).

The information about how long physical exercise could maintain the thermogenic or secretory function of BAT activity still needs to be further explored in the literature. It would be valuable in determining this intervention's optimal volume and frequency to achieve the desired outcomes. In addition, it is important to investigate whether there are any differences in the effects of exercise on diverse populations.

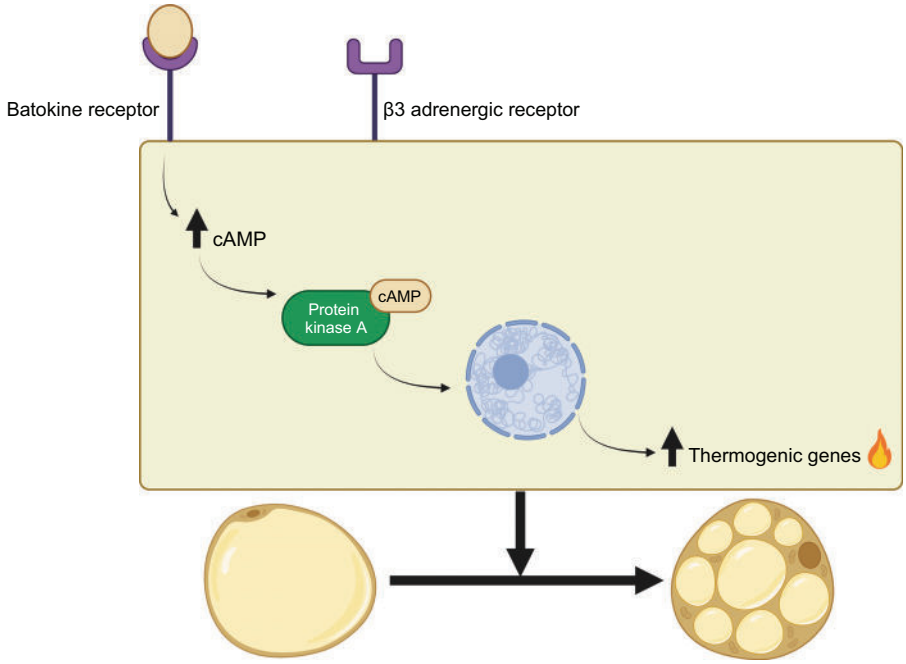

Figure 2. Batokines promote thermogenic genes transcription in a β-3-adrenergic independent manner. Created with BioRender.com.

Also, it is always relevant to highlight the complexity of obesity and its associated diseases. Given their multifaceted nature, BAT activation may complement other interventions to counteract obesity rather than being used as a standalone strategy. Furthermore, an important limitation of the applicability of increasing energy expenditure through BAT activation to promote a caloric deficit and weight control is the possibility of triggering adaptive mechanisms to restore homeostasis and preserve fat tissue (94).

Another limitation in studying BAT is the lack of adequate tools and methods for its quantification. Although FDG-PET/CT is commonly used to detect BAT in scientific research (18, 22), it relies on glucose oxidation activity, potentially leading to underestimating the total BAT mass since it can also oxidize other substrates.

Moreover, the tools currently available for identifying beige adipocytes in WAT, such as biopsies (17), present challenges due to their high cost and invasive nature. Advancing research efforts to explore more accessible methods for

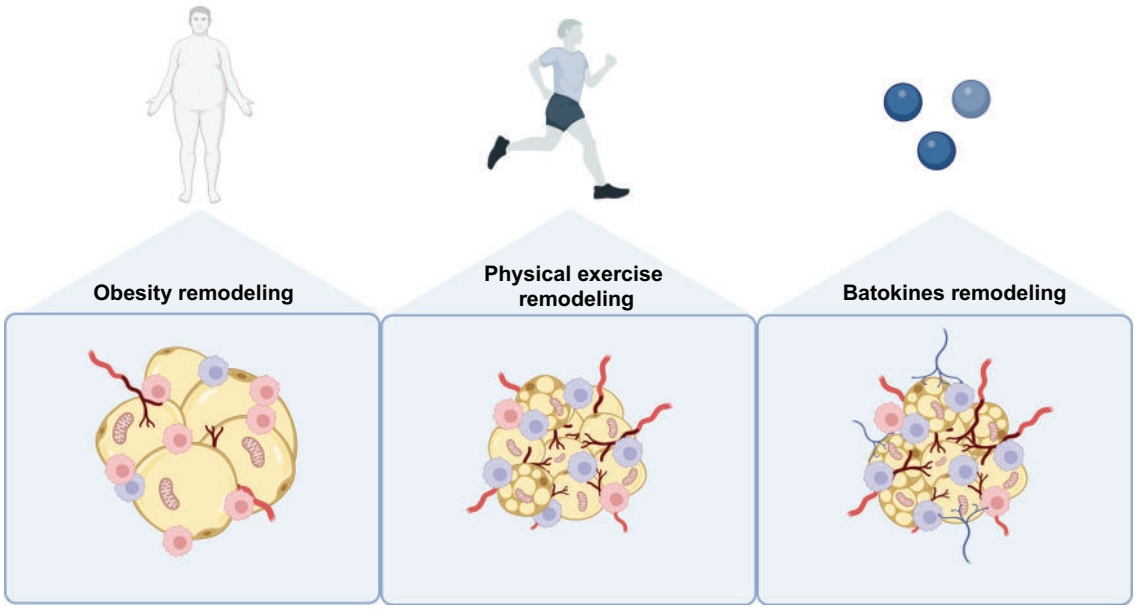

Figure 3. Different types of adipose tissue remodeling. Obesity is marked by dysfunctional tissue remodeling, with high infiltration of proinflammatory cytokines, poor vascularity, and hypertrophied adipocytes, creating a chronic low-grade inflammatory environment that predisposes to metabolic diseases. On the other hand, physical exercise and the action of autocrine and paracrine batokines share similar effects in the remodeling of adipose tissue, providing greater vascularization, polarization of type 2 macrophages, increase in mitochondrial content, browning of white adipose tissue and higher oxidative rates. Created with BioRender.com.

detecting and quantifying these tissues, such as blood biomarkers, would be a significant advancement in this field.

Regarding batokines, science still has a great deal of work ahead to fill the several gaps in this topic. It is crucial to elucidate whether BAT is the source of 12,13-diHOME secreted in response to exercise in humans and which other batokines are stimulated by physical exercise or its associated myokines. Furthermore, modern techniques such as metabolomics and proteomics may be useful in future research to ascertain batokine circulating levels and establish further associations between their release with adipose tissue remodeling and improvements in metabolic health.

CONCLUSIONS

The data gathered by this review suggest that physical exercise and its released myokines have great potential to stimulate the functionality of brown and beige adipose tissue, either the thermogenic function or the secretory function that involves the release of batokines.

Given the evidence presented in this review, it is feasible to suggest that the effects of autocrine and paracrine batokines are comparable to those of physical exercise on white adipose tissue. These batokines have the potential to remodel the tissue, leading to a phenotype inversely associated with metabolic diseases and promoting a favorable microenvironment for the formation of beige adipocytes, a promising approach to restore thermogenic tissue in populations with low or negligible amounts, which would benefit from its reactivation, such as individuals with obesity.

However, our full knowledge about secreted batokines and their effects relies on preclinical evidence and remains far from comprehensive. Nonetheless, the insights addressed by currently available data indicate that further research and investigation in this area hold great promise for potential therapeutic applications in the future.

GRANTS

The present work received financial support from the grants #2019/11820-5; #2022/00221-6; #2022/15078-4, São Paulo Research Foundation (FAPESP) and National Council for Scientific and Technological Development (CNPq n° 303766/2022-0).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

G.U.O. prepared figures; G.U.O. drafted manuscript; E.C.d.F. edited and revised manuscript; G.U.O. and E.C.d.F. approved final version of manuscript.

REFERENCES

1. **Cheng L**, **Wang J**, **Dai H**, **Duan Y**, **An Y**, **Shi L**, **Lv Y**, **Li H**, **Wang C**, **Ma Q**, **Li Y**, **Li P**, **Du H**, **Zhao B.** Brown and beige adipose tissue: a novel therapeutic strategy for obesity and type 2 diabetes mellitus. *Adipocyte* 10: 48–65, 2021. doi:10.1080/21623945.2020.1870060.
2. **Cohen P**, **Kajimura S.** The cellular and functional complexity of thermogenic fat. *Nat Rev Mol Cell Biol* 22: 393–409, 2021. doi:10.1038/s41580-021-00350-0.
3. **Ikeda K**, **Yamada T.** UCP1 Dependent and independent thermogenesis in brown and beige adipocytes. *Front Endocrinol* 11: 498, 2020. doi:10.3389/fendo.2020.00498.
4. **Peres Valgas da Silva C**, **Hernández-Saavedra D**, **White J**, **Stanford K.** Cold and exercise: therapeutic tools to activate brown adipose tissue and combat obesity. *Biology* 8: 9, 2019. doi:10.3390/biology8010009.
5. **Wu J**, **Boström P**, **Sparks LM**, **Ye L**, **Choi JH**, **Giang A-H**, **Khandekar M**, **Virtanen KA**, **Nuutila P**, **Schaart G**, **Huang K**, **Tu H**, **van Marken Lichtenbelt WD**, **Hoeks J**, **Enerbäck S**, **Schrauwen P**, **Spiegelman BM.** Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. *Cell* 150: 366–376, 2012. doi:10.1016/j.cell.2012.05.016.
6. **Bartelt A**, **Heeren J.** Adipose tissue browning and metabolic health. *Nat Rev Endocrinol* 10: 24–36, 2014. doi:10.1038/nrendo.2013.204.
7. **Kajimura S**, **Spiegelman BM**, **Seale P.** Brown and beige fat: physiological roles beyond heat generation. *Cell Metab* 22: 546–559, 2015. doi:10.1016/j.cmet.2015.09.007.
8. **Whitehead A**, **Krause FN**, **Moran A**, **MacCannell ADV**, **Scragg JL**, **McNally BD**, **Boateng E**, **Murfitt SA**, **Virtue S**, **Wright J**, **Garnham J**, **Davies GR**, **Dodgson J**, **Schneider JE**, **Murray AJ**, **Church C**, **Vidal-Puig A**, **Witte KK**, **Griffin JL**, **Roberts LD.** Brown and beige adipose tissue regulate systemic metabolism through a metabolite interorgan signaling axis. *Nat Commun* 12: 1905, 2021. doi:10.1038/s41467-021-22272-3.
9. **Severinsen MC**, **Schéele C**, **Pedersen BK.** Exercise and browning of white adipose tissue—a translational perspective. *Curr Opin Pharmacol* 52: 18–24, 2020. doi:10.1016/j.coph.2020.04.004.
10. **Scheele C**, **Wolfrum C.** Brown adipose crosstalk in tissue plasticity and human metabolism. *Endocr Rev* 41: 53–65, 2020. doi:10.1210/endrev/bnz007.
11. **Yang FT**, **Stanford KI.** Batokines: mediators of inter-tissue communication (a mini-review). *Curr Obes Rep* 11: 1–9, 2022. doi:10.1007/s13679-021-00465-7.
12. **Kong X**, **Yao T**, **Zhou P**, **Kazak L**, **Tenen D**, **Lyubetskaya A**, **Dawes BA**, **Tsai L**, **Kahn BB**, **Spiegelman BM**, **Liu T**, **Rosen ED.** Brown adipose tissue controls skeletal muscle function via the secretion of myostatin. *Cell Metab* 28: 631–643.e3, 2018. doi:10.1016/j.cmet.2018.07.004.
13. **Stanford KI**, **Lynes MD**, **Takahashi H**, **Baer LA**, **Arts PJ**, **May FJ**, **Lehnig AC**, **Middelbeek RJW**, **Richard JJ**, **So K**, **Chen EY**, **Gao F**, **Narain NR**, **Distefano G**, **Shettigar VK**, **Hirshman MF**, **Ziolo MT**, **Kiebish MA**, **Tseng Y-H**, **Coen PM**, **Goodyear LJ.** 12,13-diHOME: an exercise-induced lipokine that increases skeletal muscle fatty acid uptake. *Cell Metab* 27: 1111–1120.e3, 2018. doi:10.1016/j.cmet.2018.03.020.
14. **Mu WJ**, **Zhu JY**, **Chen M**, **Guo L.** Exercise-mediated browning of white adipose tissue: its significance, mechanism and effectiveness. *Int J Mol Sci* 22: 11512, 2021. doi:10.3390/ijms222111512.
15. **Bonfante ILP**, **Monfort-Pires M**, **Duft RG**, **da Silva Mateus KC**, **de Lima Júnior JC**, **Dos Santos Trombeta JC**, **Finardi EAR**, **Brunelli DT**, **Morari J**, **de Lima JAB**, **Bellotto ML**, **de Araújo TMF**, **Ramos CD**, **Chacon-Mikahil MPT**, **Velloso LA**, **Cavaglieri CR.** Combined training increases thermogenic fat activity in patients with overweight and type 2 diabetes. *Int J Obes (Lond)* 46: 1145–1154, 2022. doi:10.1038/s41366-022-01086-3.
16. **Otero-Díaz B**, **Rodríguez-Flores M**, **Sánchez-Muñoz V**, **Monraz-Preciado F**, **Ordoñez-Ortega S**, **Becerril-Elias V**, **Baay-Guzmán G**, **Obando-Monge R**, **García-García E**, **Palacios-González B**, **Villarreal-Molina MT**, **Sierra-Salazar M**, **Antuna-Puente B.** Exercise induces white adipose tissue browning across the weight spectrum in humans. *Front Physiol* 9: 1781, 2018. doi:10.3389/fphys.2018.01781.
17. **De Carvalho FG**, **Brandao CFC**, **Batitucci G**, **Souza A. D O**, **Ferrari GD**, **Alberici LC**, **Muñoz VR**, **Pauli JR**, **De Moura LP**, **Ropelle ER**, **da Silva ASR**, **Junqueira-Franco MVM**, **Marchini JS**, **de Freitas EC.** Taurine supplementation associated with exercise increases mitochondrial activity and fatty acid oxidation gene expression in the subcutaneous white adipose tissue of obese women. *Clin Nutr* 40: 2180–2187, 2021. doi:10.1016/j.clnu.2020.09.044.
18. **Cypess AM**, **Lehman S**, **Williams G**, **Tal I**, **Rodman D**, **Goldfine AB**, **Kuo FC**, **Palmer EL**, **Tseng YH**, **Doria A**, **Kolodny GM**, **Kahn CR.** Identification and importance of brown adipose tissue in adult humans. *N Engl J Med* 360: 1509–1517, 2009. doi:10.1056/NEJMoa0810780.

19. **Claessens-van Ooijen AM**, **Westerterp KR**, **Wouters L**, **Schoffelen PF**, **van Steenhoven AA**, **van Marken Lichtenbelt WD.** Heat production and body temperature during cooling and rewarming in overweight and lean men. *Obesity (Silver Spring)* 14: 1914–1920, 2006. doi:10.1038/oby.2006.223.
20. **Wolfrum C**, **Gerhart-Hines Z.** Fueling the fire of adipose thermogenesis. *Science* 375: 1229–1231, 2022. doi:10.1126/science.abl7108.
21. **Hamann A**, **Flier JS**, **Lowell BB.** Decreased brown fat markedly enhances susceptibility to diet-induced obesity, diabetes, and hyperlipidemia. *Endocrinology* 137: 21–29, 1996. doi:10.1210/endo.137.1.8536614.
22. **Mihalopoulos NL**, **Yap JT**, **Beardmore B**, **Holubkov R**, **Nanjee MN**, **Hoffman JM.** Cold-activated brown adipose tissue is associated with less cardiometabolic dysfunction in young adults with obesity. *Obesity (Silver Spring)* 28: 916–923, 2020. doi:10.1002/oby.22767.
23. **Becher T**, **Palanisamy S**, **Kramer DJ**, **Eljalby M**, **Marx SJ**, **Wibmer AG**, **Butler SD**, **Jiang CS**, **Vaughan R**, **Schöder H**, **Mark A**, **Cohen P.** Brown adipose tissue is associated with cardiometabolic health. *Nat Med* 27: 58–65, 2021. doi:10.1038/s41591-020-1126-7.
24. **Hanssen MJ**, **Hoeks J**, **Brans B**, **van der Lans AA**, **Schaart G**, **van den Driessche JJ**, **Jörgensen JA**, **Boekschoten MV**, **Hesselink MK**, **Havekes B**, **Kersten S**, **Mottaghy FM**, **van Marken Lichtenbelt WD**, **Schrauwen P.** Short-term cold acclimation improves insulin sensitivity in patients with type 2 diabetes mellitus. *Nat Med* 21: 863–865, 2015. doi:10.1038/nm.3891.
25. **Finlin BS**, **Memetimin H**, **Zhu B**, **Confides AL**, **Vekaria HJ**, **El Khouli RH**, **Johnson ZR**, **Westgate PM**, **Chen J**, **Morris AJ**, **Sullivan PG**, **Dupont-Versteegden EE**, **Kern PA.** The β3-adrenergic receptor agonist mirabegron improves glucose homeostasis in obese humans. *J Clin Invest* 130: 2319–2331, 2020. doi:10.1172/JCI134892.
26. **Celi FS.** Brown adipose tissue–when it pays to be inefficient. *N Engl J Med* 360: 1553–1556, 2009. doi:10.1056/NEJMe0900466.
27. **Cypess AM**, **Weiner LS**, **Roberts-Toler C**, **Franquet Elía E**, **Kessler SH**, **Kahn PA**, **English J**, **Chatman K**, **Trauger SA**, **Doria A**, **Kolodny GM.** Activation of human brown adipose tissue by a β3-adrenergic receptor agonist. *Cell Metab* 21: 33–38, 2015. doi:10.1016/j.cmet.2014.12.009.
28. **Leitner BP**, **Weiner LS**, **Desir M**, **Kahn PA**, **Selen DJ**, **Tsang C**, **Kolodny GM**, **Cypess AM.** Kinetics of human brown adipose tissue activation and deactivation. *Int J Obes (Lond)* 43: 633–637, 2019. doi:10.1038/s41366-018-0104-3.
29. **Schnyder S**, **Handschin C.** Skeletal muscle as an endocrine organ: PGC-1α, myokines and exercise. *Bone* 80: 115–125, 2015. doi:10.1016/j.bone.2015.02.008.
30. **Boström P**, **Wu J**, **Jedrychowski MP**, **Korde A**, **Ye L**, **Lo JC**, **Rasbach KA**, **Boström EA**, **Choi JH**, **Long JZ**, **Kajimura S**, **Zingaretti MC**, **Vind BF**, **Tu H**, **Cinti S**, **Højlund K**, **Gygi SP**, **Spiegelman BM.** A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature* 481: 463–468, 2012. doi:10.1038/nature10777.
31. **Rao RR**, **Long JZ**, **White JP**, **Svensson KJ**, **Lou J**, **Lokurkar I**, **Jedrychowski MP**, **Ruas JL**, **Wrann CD**, **Lo JC**, **Camera DM**, **Lachey J**, **Gygi S**, **Seehra J**, **Hawley JA**, **Spiegelman BM.** Meteorin-like is a hormone that regulates immune-adipose interactions to increase beige fat thermogenesis. *Cell* 157: 1279–1291, 2014. doi:10.1016/j.cell.2014.03.065.
32. **Knudsen JG**, **Murholm M**, **Carey AL**, **Biensø RS**, **Basse AL**, **Allen TL**, **Hidalgo J**, **Kingwell BA**, **Febbraio MA**, **Hansen JB**, **Pilegaard H.** Role of IL-6 in exercise training- and cold-induced UCP1 expression in subcutaneous white adipose tissue. *PLoS One* 9: e84910, 2014. doi:10.1371/journal.pone.0084910.
33. **Carrière A**, **Jeanson Y**, **Berger-Müller S**, **André M**, **Chenouard V**, **Arnaud E**, **Barreau C**, **Walther R**, **Galinier A**, **Wdziekonski B**, **Villageois P**, **Louche K**, **Collas P**, **Moro C**, **Dani C**, **Villarroya F**, **Casteilla L.** Browning of white adipose cells by intermediate metabolites: an adaptive mechanism to alleviate redox pressure. *Diabetes* 63: 3253–3265, 2014. doi:10.2337/db13-1885.
34. **Stanford KI**, **Goodyear LJ.** Exercise regulation of adipose tissue. *Adipocyte* 5: 153–162, 2016. doi:10.1080/21623945.2016.1191307.
35. **Machado SA**, **Pasquarelli-do-Nascimento G**, **da Silva DS**, **Farias GR**, **de Oliveira Santos I**, **Baptista LB**, **Magalhães KG.** Browning of the white adipose tissue regulation: new insights into nutritional and metabolic relevance in health and diseases. *Nutr Metab (Lond)* 19: 61, 2022. doi:10.1186/s12986-022-00694-0.
36. **Barberá MJ**, **Schlüter A**, **Pedraza N**, **Iglesias R**, **Villarroya F**, **Giralt M.** Peroxisome proliferator-activated receptor α activates transcription of the brown fat uncoupling protein-1 gene. *J Biol Chem* 276: 1486–1493, 2001. doi:10.1074/jbc.m006246200.
37. **Villarroya F**, **Peyrou M**, **Giralt M.** Transcriptional regulation of the uncoupling protein-1 gene. *Biochimie* 134: 86–92, 2017. doi:10.1016/j.biochi.2016.09.017.
38. **Qu Y**, **Chen S**, **Zhou L**, **Chen M**, **Li L**, **Ni Y**, **Sun J.** The different effects of intramuscularly-injected lactate on white and brown adipose tissue in vivo. *Mol Biol Rep* 49: 8507–8516, 2022. doi:10.1007/s11033-022-07672-y.
39. **Lowell BB**, **Flier JS.** Brown adipose tissue, β3-adrenergic receptors, and obesity. *Annu Rev Med* 48: 307–316, 1997. doi:10.1146/annurev.med.48.1.307.
40. **Motiani P**, **Virtanen KA**, **Motiani KK**, **Eskelinen JJ**, **Middelbeek RJ**, **Goodyear LJ**, **Savolainen AM**, **Kemppainen J**, **Jensen J**, **Din MU**, **Saunavaara V**, **Parkkola R**, **Löyttyniemi E**, **Knuuti J**, **Nuutila P**, **Kalliokoski KK**, **Hannukainen JC.** Decreased insulin-stimulated brown adipose tissue glucose uptake after short-term exercise training in healthy middle-aged men. *Diabetes Obes Metab* 19: 1379–1388, 2017. doi:10.1111/dom.12947.
41. **Martinez-Tellez B**, **Sanchez-Delgado G**, **Acosta FM**, **Alcantara JMA**, **Amaro-Gahete FJ**, **Martinez-Avila WD**, **Merchan-Ramirez E**, **Muñoz-Hernandez V**, **Osuna-Prieto FJ**, **Jurado-Fasoli L**, **Xu H**, **Ortiz-Alvarez L**, **Arias-Tellez MJ**, **Mendez-Gutierrez A**, **Labayen I**, **Ortega FB**, **Schönke M**, **Rensen PCN**, **Aguilera CM**, **Llamas-Elvira JM**, **Gil Á**, **Ruiz JR.** No evidence of brown adipose tissue activation after 24 weeks of supervised exercise training in young sedentary adults in the ACTIBATE randomized controlled trial. *Nat Commun* 13: 5259, 2022. doi:10.1038/s41467-022-32502-x.
42. **Nakhuda A**, **Josse AR**, **Gburcik V**, **Crossland H**, **Raymond F**, **Metairon S**, **Good L**, **Atherton PJ**, **Phillips SM**, **Timmons JA.** Biomarkers of browning of white adipose tissue and their regulation during exercise- and diet-induced weight loss. *Am J Clin Nutr* 104: 557–565, 2016. doi:10.3945/ajcn.116.132563.
43. **Stinkens R**, **Brouwers B**, **Jocken JW**, **Blaak EE**, **Teunissen-Beekman KF**, **Hesselink MK**, **van Baak MA**, **Schrauwen P**, **Goossens GH.** Exercise training-induced effects on the abdominal subcutaneous adipose tissue phenotype in humans with obesity. *J Appl Physiol (1985)* 125: 1585–1593, 2018. doi:10.1152/japplphysiol.00496.2018.
44. **Norheim F**, **Langleite TM**, **Hjorth M**, **Holen T**, **Kielland A**, **Stadheim HK**, **Gulseth HL**, **Birkeland KI**, **Jensen J**, **Drevon CA.** The effects of acute and chronic exercise on PGC-1α, irisin and browning of subcutaneous adipose tissue in humans. *FEBS J* 281: 739–749, 2014. doi:10.1111/febs.12619.
45. **Dewal RS**, **Stanford KI.** Effects of exercise on brown and beige adipocytes. *Biochim Biophys Acta Mol Cell Biol Lipids* 1864: 71–78, 2019. doi:10.1016/j.bbalip.2018.04.013.
46. **Vosselman MJ**, **Hoeks J**, **Brans B**, **Pallubinsky H**, **Nascimento EBM**, **van der Lans AAJJ**, **Broeders EPM**, **Mottaghy FM**, **Schrauwen P**, **van Marken Lichtenbelt WD.** Low brown adipose tissue activity in endurance-trained compared with lean sedentary men. *Int J Obes (Lond)* 39: 1696–1702, 2015. doi:10.1038/ijo.2015.130.
47. **Villarroya J**, **Cereijo R**, **Gavaldà-Navarro A**, **Peyrou M**, **Giralt M**, **Villarroya F.** New insights into the secretory functions of brown adipose tissue. *J Endocrinol* 243: R19–R27, 2019. doi:10.1530/joe-19-0295.
48. **Leow MK**, **Rengaraj A**, **Narasimhan K**, **Verma SK**, **Yaligar J**, **Thu GLT**, **Sun L**, **Goh HJ**, **Govindharajulu P**, **Sadananthan SA**, **Michael N**, **Meng W**, **Gallart-Palau X**, **Sun L**, **Karnani N**, **Sze NSK**, **Velan SS.** Activated brown adipose tissue releases exosomes containing mitochondrial methylene tetrahydrofolate dehydrogenase (NADP dependent) 1-like protein (MTHFD1L). *Biosci Rep* 42: BSR20212543, 2022. doi:10.1042/BSR20212543.
49. **Martins FF**, **Souza-Mello V**, **Aguila MB**, **Mandarim-de-Lacerda CA.** Brown adipose tissue as an endocrine organ: updates on the emerging role of batokines. *Horm Mol Biol Clin Investig* 44: 219–227, 2023. doi:10.1515/hmbci-2022-0044.
50. **Shaw A**, **Tóth BB**, **Király R**, **Arianti R**, **Csomós I**, **Póliska S**, **Vámos A**, **Korponay-Szabó IR**, **Bacso Z**, **Győry F**, **Fésüs L**, **Kristóf E.** Irisin stimulates the release of CXCL1 from differentiating human subcutaneous and deep-neck derived adipocytes via upregulation of NFκB

pathway. *Front Cell Dev Biol* 9: 737872, 2021. doi:10.3389/fcell.2021.737872.
51. **Jeanson Y**, **Ribas F**, **Galinier A**, **Arnaud E**, **Ducos M**, **André M**, **Chenouard V**, **Villarroya F**, **Casteilla L**, **Carrière A.** Lactate induces FGF21 expression in adipocytes through a p38-MAPK pathway. *Biochem J* 473: 685–692, 2016. doi:10.1042/bj20150808.
52. **Sharp LZ**, **Shinoda K**, **Ohno H**, **Scheel DW**, **Tomoda E**, **Ruiz L**, **Hu H**, **Wang L**, **Pavlova Z**, **Gilsanz V**, **Kajimura S.** Human BAT possesses molecular signatures that resemble beige/brite cells. *PLoS One* 7: e49452, 2012. doi:10.1371/journal.pone.0049452.
53. **Mendez-Gutierrez A**, **Osuna-Prieto FJ**, **Aguilera CM**, **Ruiz JR**, **Sanchez-Delgado G.** Endocrine mechanisms connecting exercise to brown adipose tissue metabolism: a human perspective. *Curr Diab Rep* 20: 40, 2020. doi:10.1007/s11892-020-01319-7.
54. **Szczepańska E**, **Gietka-Czernel M.** FGF21: a novel regulator of glucose and lipid metabolism and whole-body energy balance. *Horm Metab Res* 54: 203–211, 2022. doi:10.1055/a-1778-4159.
55. **Garritson JD**, **Boudina S.** The effects of exercise on white and brown adipose tissue cellularity, metabolic activity and remodeling. *Front Physiol* 12: 772894, 2021. doi:10.3389/fphys.2021.772894.
56. **Meister BM**, **Hong SG**, **Shin J**, **Rath M**, **Sayoc J**, **Park JY.** Healthy versus unhealthy adipose tissue expansion: the role of exercise. *J Obes Metab Syndr* 31: 37–50, 2022. doi:10.7570/jomes21096.
57. **Bartness TJ**, **Vaughan CH**, **Song CK.** Sympathetic and sensory innervation of brown adipose tissue. *Int J Obes (Lond)* 34, *Suppl* 1: S36–S42, 2010. doi:10.1038/ijo.2010.182.
58. **Liu X**, **Zhang Z**, **Song Y**, **Xie H**, **Dong M.** An update on brown adipose tissue and obesity intervention: Function, regulation and therapeutic implications. *Front Endocrinol (Lausanne)* 13: 1065263, 2023. doi:10.3389/fendo.2022.1065263.
59. **van Marken Lichtenbelt W.** Brown adipose tissue and the regulation of nonshivering thermogenesis. *Curr Opin Clin Nutr Metab Care* 15: 547–552, 2012. doi:10.1097/mco.0b013e3283599184.
60. **Sanchez-Delgado G**, **Martinez-Tellez B**, **Olza J**, **Aguilera CM**, **Gil Á**, **Ruiz JR.** Role of exercise in the activation of brown adipose tissue. *Ann Nutr Metab* 67: 21–32, 2015. doi:10.1159/000437173.
61. **Zouhal H**, **Jacob C**, **Delamarche P**, **Gratas-Delamarche A.** Catecholamines and the effects of exercise, training and gender. *Sports Med* 38: 401–423, 2008. doi:10.2165/00007256-200838050-00004.
62. **De Matteis R**, **Lucertini F**, **Guescini M**, **Polidori E**, **Zeppa S**, **Stocchi V**, **Cinti S**, **Cuppini R.** Exercise as a new physiological stimulus for brown adipose tissue activity. *Nutr Metab Cardiovasc Dis* 23: 582–590, 2013. doi:10.1016/j.numecd.2012.01.013.
63. **Townsend LK**, **Wright DC.** Looking on the "brite" side exercise-induced browning of white adipose tissue. *Pflugers Arch Eur Arch* 471: 455–465, 2019. doi:10.1007/s00424-018-2177-1.
64. **Ranallo RF**, **Rhodes EC.** Lipid metabolism during exercise. *Sports Med* 26: 29–42, 1998. doi:10.2165/00007256-199826010-00003.
65. **Almeida DL**, **Moreira VM**, **Cardoso LE**, **Junior MDF**, **Pavanelo A**, **Ribeiro TA**, **da Silva Franco CC**, **Tófolo LP**, **Peres MNC**, **Ribeiro MVG**, **Ferreira ARO**, **Gomes RM**, **Miranda RA**, **Trevenzoli IH**, **Armitage JA**, **Palma-Rigo K**, **de Freitas Mathias PC.** Lean in one way, in obesity another: effects of moderate exercise in brown adipose tissue of early overfed male Wistar rats. *Int J Obes (Lond)* 46: 137–143, 2022. doi:10.1038/s41366-021-00969-1.
66. **Kolahdouzi S**, **Talebi-Garakani E**, **Hamidian G**, **Safarzade A.** Exercise training prevents high-fat diet-induced adipose tissue remodeling by promoting capillary density and macrophage polarization. *Life Sci* 220: 32–43, 2019. doi:10.1016/j.lfs.2019.01.037.
67. **Loustau T**, **Coudiere E**, **Karkeni E**, **Landrier JF**, **Jover B**, **Riva C.** Murine double minute-2 mediates exercise-induced angiogenesis in adipose tissue of diet-induced obese mice. *Microvasc Res* 130: 104003, 2020. doi:10.1016/j.mvr.2020.104003.
68. **Min SY**, **Learnard H**, **Kant S**, **Gealikman O**, **Rojas-Rodriguez R**, **DeSouza T**, **Desai A**, **Keaney JF**, **Corvera S**, **Craige SM.** Exercise rescues gene pathways involved in vascular expansion and promotes functional angiogenesis in subcutaneous white adipose tissue. *Int J Mol Sci* 20: 2046, 2019. doi:10.3390/ijms20082046.
69. **Kawanishi N**, **Yano H**, **Yokogawa Y**, **Suzuki K.** Exercise training inhibits inflammation in adipose tissue via both suppression of macrophage infiltration and acceleration of phenotypic switching from M1 to M2 macrophages in high-fat-dietinduced obese mice. *Exerc Immunol Rev* 16: 105–118, 2010.
70. **Honkala SM**, **Motiani P**, **Kivelä R**, **Hemanthakumar KA**, **Tolvanen E**, **Motiani KK**, **Eskelinen J-J**, **Virtanen KA**, **Kemppainen J**, **Heiskanen MA**, **Löyttyniemi E**, **Nuutila P**, **Kalliokoski KK**, **Hannukainen JC.** Exercise training improves adipose tissue metabolism and vasculature regardless of baseline glucose tolerance and sex. *BMJ Open Diab Res Care* 8: e000830, 2020. doi:10.1136/bmjdrc-2019-000830.
71. **Liang J**, **Zhang X**, **Xia W**, **Tong X**, **Qiu Y**, **Qiu Y**, **He J**, **Yu B**, **Huang H**, **Tao J.** Promotion of aerobic exercise induced angiogenesis is associated with decline in blood pressure in hypertension. *Hypertension* 77: 1141–1153, 2021. doi:10.1161/hypertensionaha.120.16107.
72. **Holloway TM**, **Snijders T**, **Van Kranenburg J**, **Van Loon LJ**, **Verdijk LB.** Temporal response of angiogenesis and hypertrophy to resistance training in young men. *Med Sci Sports Exerc* 50: 36–45, 2018. doi:10.1249/mss.0000000000001409.
73. **Fu P**, **Zhu R**, **Jia J**, **Hu Y**, **Wu C**, **Cieszczyk P**, **Holmberg HC**, **Gong L.** Aerobic exercise promotes the functions of brown adipose tissue in obese mice via a mechanism involving COX2 in the VEGF signaling pathway. *Nutr Metab (Lond)* 18: 56, 2021. doi:10.1186/s12986-021-00581-0.
74. **Longo M**, **Zatterale F**, **Naderi J**, **Parrillo L**, **Formisano P**, **Raciti GA**, **Beguinot F**, **Miele C.** Adipose tissue dysfunction as determinant of obesity-associated metabolic complications. *Int J Mol Sci* 20: 2358, 2019. doi:10.3390/ijms20092358.
75. **Nisoli E**, **Tonello C**, **Benarese M**, **Liberini P**, **Carruba MO.** Expression of nerve growth factor in brown adipose tissue: implications for thermogenesis and obesity. *Endocrinology* 137: 495–503, 1996. doi:10.1210/endo.137.2.8593794.
76. **Lee MW**, **Lee M**, **Oh KJ.** Adipose tissue-derived signatures for obesity and type 2 diabetes: adipokines, batokines and micrornas. *J Clin Med* 8: 854, 2019. doi:10.3390/jcm8060854.
77. **Yan P**, **Xu Y**, **Wan Q**, **Feng J**, **Li H**, **Yang J**, **Zhong H**, **Zhang Z.** Plasma neuregulin 4 levels are associated with metabolic syndrome in patients newly diagnosed with type 2 diabetes mellitus. *Dis Markers* 2018: 6974191, 2018. doi:10.1155/2018/6974191.
78. **Elias I**, **Franckhauser S**, **Bosch F.** New insights into adipose tissue VEGF-A actions in the control of obesity and insulin resistance. *Adipocyte* 2: 109–112, 2013. doi:10.4161/adip.22880.
79. **Park J**, **Kim M**, **Sun K**, **An YA**, **Gu X**, **Scherer PE.** VEGF-A–Expressing adipose tissue shows rapid beiging and enhanced survival after transplantation and confers IL-4–independent metabolic improvements. *Diabetes* 66: 1479–1490, 2017. doi:10.2337/db16-1081.
80. **Sun K**, **Kusminski CM**, **Luby-Phelps K**, **Spurgin SB**, **An YA**, **Wang QA**, **Holland WL**, **Scherer PE.** Brown adipose tissue derived VEGF-A modulates cold tolerance and energy expenditure. *Mol Metab* 3: 474–483, 2014. doi:10.1016/j.molmet.2014.03.010.
81. **Villarroya F**, **Cereijo R**, **Villarroya J**, **Giralt M.** Brown adipose tissue as a secretory organ. *Nat Rev Endocrinol* 13: 26–35, 2017. doi:10.1038/nrendo.2016.136.
82. **Pellegrinelli V**, **Peirce VJ**, **Howard L**, **Virtue S**, **Türei D**, **Senzacqua M**, **Frontini A**, **Dalley JW**, **Horton AR**, **Bidault G**, **Severi I**, **Whittle A**, **Rahmouni K**, **Saez-Rodriguez J**, **Cinti S**, **Davies AM**, **Vidal-Puig A.** Adipocyte-secreted BMP8b mediates adrenergic-induced remodeling of the neuro-vascular network in adipose tissue. *Nat Commun* 9: 4974, 2018. doi:10.1038/s41467-018-07453-x.
83. **Michailidou Z**, **Gomez-Salazar M**, **Alexaki VI.** Innate immune cells in the adipose tissue in health and metabolic disease. *J Innate Immun* 14: 4–30, 2022. doi:10.1159/000515117.
84. **Cereijo R**, **Gavaldà-Navarro A**, **Cairó M**, **Quesada-López T**, **Villarroya J**, **Morón-Ros S**, **Sánchez-Infantes D**, **Peyrou M**, **Iglesias R**, **Mampel T**, **Turatsinze J-V**, **Eizirik DL**, **Giralt M**, **Villarroya F.** CXCL14, a brown adipokine that mediates brown-fat-to-macrophage communication in thermogenic adaptation. *Cell Metab* 28: 750–763. e6, 2018. doi:10.1016/j.cmet.2018.07.015.
85. **Hui X**, **Gu P**, **Zhang J**, **Nie T**, **Pan Y**, **Wu D**, **Feng T**, **Zhong C**, **Wang Y**, **Lam KSL**, **Xu A.** Adiponectin enhances cold-induced browning of subcutaneous adipose tissue via promoting M2 macrophage proliferation. *Cell Metab* 22: 279–290, 2015. doi:10.1016/j.cmet.2015.06.004.
86. **Campderrós L**, **Moure R**, **Cairó M**, **Gavaldà-Navarro A**, **Quesada-López T**, **Cereijo R**, **Giralt M**, **Villarroya J**, **Villarroya F.** Brown adipocytes secrete GDF15 in response to thermogenic activation. *Obesity (Silver Spring)* 27: 1606–1616, 2019. doi:10.1002/oby.22584.
87. **Gavaldà-Navarro A**, **Villarroya J**, **Cereijo R**, **Giralt M**, **Villarroya F.** The endocrine role of brown adipose tissue: an update on actors

and actions. *Rev Endocr Metab Disord* 23: 31–41, 2022. doi:10.1007/s11154-021-09640-6.

88. **Nedergaard J**, **Cannon B.** The browning of white adipose tissue: some burning issues. *Cell Metab* 20: 396–407, 2014. doi:10.1016/j.cmet.2014.07.005.
89. **Chen Q**, **Huang L**, **Pan D**, **Hu K**, **Li R**, **Friedline RH**, **Kim JK**, **Zhu LJ**, **Guertin DA**, **Wang Y-X.** A brown fat-enriched adipokine Adissp controls adipose thermogenesis and glucose homeostasis. *Nat Commun* 13: 7633, 2022. doi:10.1038/s41467-022-35335-w.
90. **Li Z**, **Yi CX**, **Katiraei S**, **Kooijman S**, **Zhou E**, **Chung CK**, **Gao Y**, **van den Heuvel JK**, **Meijer OC**, **Berbée JFP**, **Heijink M**, **Giera M**, **Willems van Dijk K**, **Groen AK**, **Rensen PCN**, **Wang Y.** Butyrate reduces appetite and activates brown adipose tissue via the gut-brain neural circuit. *Gut* 67: 1269–1279, 2018. doi:10.1136/gutjnl-2017-314050.
91. **Wang D**, **Liu CD**, **Li HF**, **Tian ML**, **Pan JQ**, **Shu G**, **Jiang QY**, **Yin YL**, **Zhang L.** LSD1 mediates microbial metabolite butyrate-induced thermogenesis in brown and white adipose tissue. *Metabolism* 102: 154011, 2020. doi:10.1016/j.metabol.2019.154011.
92. **Quan LH**, **Zhang C**, **Dong M**, **Jiang J**, **Xu H**, **Yan C**, **Liu X**, **Zhou H**, **Zhang H**, **Chen L**, **Zhong FL**, **Luo ZB**, **Lam SM**, **Shui G**, **Li D**, **Jin W.** Myristoleic acid produced by enterococci reduces obesity through brown adipose tissue activation. *Gut* 69: 1239–1247, 2020. doi:10.1136/gutjnl-2019-319114.
93. **Armani A**, **Feraco A**, **Camajani E**, **Gorini S**, **Lombardo M**, **Caprio M.** Nutraceuticals in brown adipose tissue activation. *Cells* 11: 3996, 2022. doi:10.3390/cells11243996.
94. **Rosenbaum M**, **Leibel RL.** Adaptive thermogenesis in humans. *Int J Obes (Lond)* 34, *Suppl* 1: S47–S55, 2010. doi:10.1038/ijo.2010.184.