Current Diabetes Reports (2020) 20:40
https://doi.org/10.1007/s11892-020-01319-7

OBESITY (KM GADDE AND P SINGH, SECTION EDITORS)

Endocrine Mechanisms Connecting Exercise to Brown Adipose Tissue Metabolism: a Human Perspective

Andrea Mendez-Gutierrez[1,2,3] · Francisco J. Osuna-Prieto[4,5] · Concepcion M Aguilera[1,2,3] · Jonatan R Ruiz[5,6] · Guillermo Sanchez-Delgado[5,6,7]

Abstract

Purpose of Review To summarize the state-of-the-art regarding the exercise-regulated endocrine signals that might modulate brown adipose tissue (BAT) activity and/or white adipose tissue (WAT) browning, or through which BAT communicates with other tissues, in humans.

Recent Findings Exercise induces WAT browning in rodents by means of a variety of physiological mechanism. However, whether exercise induces WAT browning in humans is still unknown. Nonetheless, a number of protein hormones and metabolites, whose signaling can influence thermogenic adipocyte's metabolism, are secreted during and/or after exercise in humans from a variety of tissues and organs, such as the skeletal muscle, the adipose tissue, the liver, the adrenal glands, or the cardiac muscle.

Summary Overall, it seems plausible to hypothesize that, in humans, exercise secretes an endocrine cocktail that is likely to induce WAT browning, as it does in rodents. However, even if exercise elicits a pro-browning endocrine response, this might result in a negligible effect if blood flow is restricted in thermogenic adipocyte–rich areas during exercise, which is still to be determined. Future studies are needed to fully characterize the exercise-induced secretion (i.e., to determine the effect of the different exercise frequency, intensity, type, time, and volume) of endocrine signaling molecules that might modulate BAT activity and/or WAT browning or through which BAT communicates with other tissues, during exercise. The exercise effect on BAT metabolism and/or WAT browning could be one of the still unknown mechanisms by which exercise exerts beneficial health effects, and it might be pharmacologically mimicked.

Keywords Brown fat · Physical activity · Thermogenesis · Exercise physiology

Jonatan R Ruiz and Guillermo Sanchez-Delgado share seniorship.

This article is part of the Topical Collection on *Obesity*

✉ Jonatan R Ruiz
ruizj@ugr.es

✉ Guillermo Sanchez-Delgado
gsanchezdelgado@ugr.es

[1] Department of Biochemistry and Molecular Biology II, "José Mataix Verdú" Institute of Nutrition and Food Technology (INYTA), Biomedical Research Centre (CIBM), University of Granada, Granada, Spain

[2] Biohealth Research Institute in Granada (ibs.GRANADA), Granada, Spain

[3] CIBER Fisiopatología de la Obesidad y la Nutrición (CIBEROBN), Madrid, Spain

[4] Department of Analytical Chemistry, Technology Centre for Functional Food Research and Development (CIDAF), University of Granada, Granada, Spain

[5] PROFITH "PROmoting FITness and Health through Physical Activity" Research Group, Sport and Health University Research Institute (iMUDS), Faculty of Sport Sciences, University of Granada, Granada, Spain

[6] Department of Physical Education and Sports, University of Granada, Granada, Spain

[7] Pennington Biomedical Research Center, Baton Rouge, LA, USA

Published online: 28 July 2020

Introduction

In mammals, adipose tissue is mainly found in two forms: white adipose tissue (WAT) and brown adipose tissue (BAT). Whereas WAT's main function is to store and release energy, BAT's main function is to produce heat to maintain core body temperature [1]. In BAT, heat production takes place through the uncoupling of ATP synthesis, mediated by the uncoupling protein 1 (UCP1), yet other UCP1-independent mechanisms have been described [2]. A third type of adipocytes, neither white nor brown, can be found within WAT, the so-called beige adipocytes [3]. These beige adipocytes are enriched in mitochondria and express UCP1 [3], like classic brown adipocytes. Chronic cold exposure, among other BAT-enhancing stimuli, upregulates the formation of these thermogenically competent beige cells in a process called WAT "browning" [3].

A potential clinical implication of activating BAT and/or inducing WAT browning relates to its high metabolic activity and its ability to oxidize glucose and lipids, which make it an attractive target for therapies against obesity and type 2 diabetes mellitus [4]. Moreover, both brown and beige adipocytes secrete adipokines (so-called *batokines*) exerting endocrine, paracrine, and autocrine actions that might provide favorable metabolic effects (e.g., increasing insulin sensitivity) [5].

Exercise increases both energy expenditure and heat production, and it would therefore be expected to downregulate BAT activity and WAT browning. However, although the effect of exercise on classic BAT remains controversial [6], an exercise-induced WAT browning clearly exists, at least in rodents [6]. Exercise elicits a myriad of endocrine signals that are known to regulate BAT activity and/or WAT browning (Fig. 1). This review aims to provide a summary of the state-of-the-art regarding the exercise-regulated endocrine signals (so-called *exerkines*) that might modulate human BAT activity and/or WAT browning, or through which BAT communicates with other tissues.

Protein Hormones

Norepinephrine

The sympathetic nervous system (SNS) is the classical BAT regulator. Upon cold exposure, released norepinephrine in BAT binds to the brown adipocyte β-adrenergic receptors and activates thermogenesis [1]. Although murine BAT is clearly activated by norepinephrine binding to β-3 adrenergic receptors, other β adrenergic receptors are involved in human BAT activation [7]. Exercise is able to increase norepinephrine circulating levels up to 20-fold [8] (Table 1). Therefore, although the SNS-dependent activation of BAT is mainly driven by local nerve release of norepinephrine [1], it is still possible that the exercise-induced norepinephrine plasma levels contribute to BAT activation.

Natriuretic Peptides

The main function of the heart-secreted natriuretic peptides (NPs) is to regulate blood pressure by modulating diuresis, natriuresis, and vasodilatation [9]. NPs are also involved in lipolysis induction in WAT [10] and fat oxidation in human skeletal muscle [11]. Moreover, NPs, both atrial NP (ANP) and B-type NP (BNP), promote energy dissipation in BAT and WAT browning [12, 13].

Exercise stimulates the cardiac muscle, which in turn activates the secretion of NPs. Several studies have reported an increase in ANP circulating levels after both acute moderate and high-intensity endurance exercise in different populations [14–16]. Similarly, plasma BNP concentration is also increased in response to both acute [17] and chronic endurance exercise in healthy men [18–20] (Table 1).

Irisin

The peroxisome proliferator-activated receptor-γ coactivator 1-α (PGC-1α) is one of the master transcription factors upregulated by exercise in skeletal muscle. PGC-1α activity increases the expression of the fibronectin type III domain–containing 5 (FNDC5) protein. FNDC5, after cleavage, is secreted into the bloodstream as irisin, which, at least in mice, binds to the surface of adipocytes inducing the expression of UCP1 and promoting WAT browning [21].

Several human studies have shown an increase in FDNC5 gene expression in skeletal muscle and circulating serum irisin after acute exercise (Table 1). For instance, a 50-min cycling bout at 80% of maximum oxygen consumption (VO_2max) was able to increase circulating irisin 10 min after exercise in both trained and untrained healthy adults [22]. The intensity of exercise may play an important role in the stimulation of irisin secretion [23]. Nonetheless, it should be considered that there are important between-studies inconsistencies related to commercial methods used to detect irisin [24]. Moreover, the capacity and specificity of commercially available methods for human irisin detection has been questioned, and thus, important doubts remain regarding the role of irisin in humans and its regulation by exercise [25].

Fibroblast Growth Factor 21

Fibroblast growth factor 21 (FGF21) is one of the endocrine members of the fibroblast growth factor family. It is mainly expressed by the liver, but also secreted by other tissues such as the thymus, WAT, skeletal muscle [26, 27], and BAT [28]. Indeed, the release of FGF21 is increased in murine brown

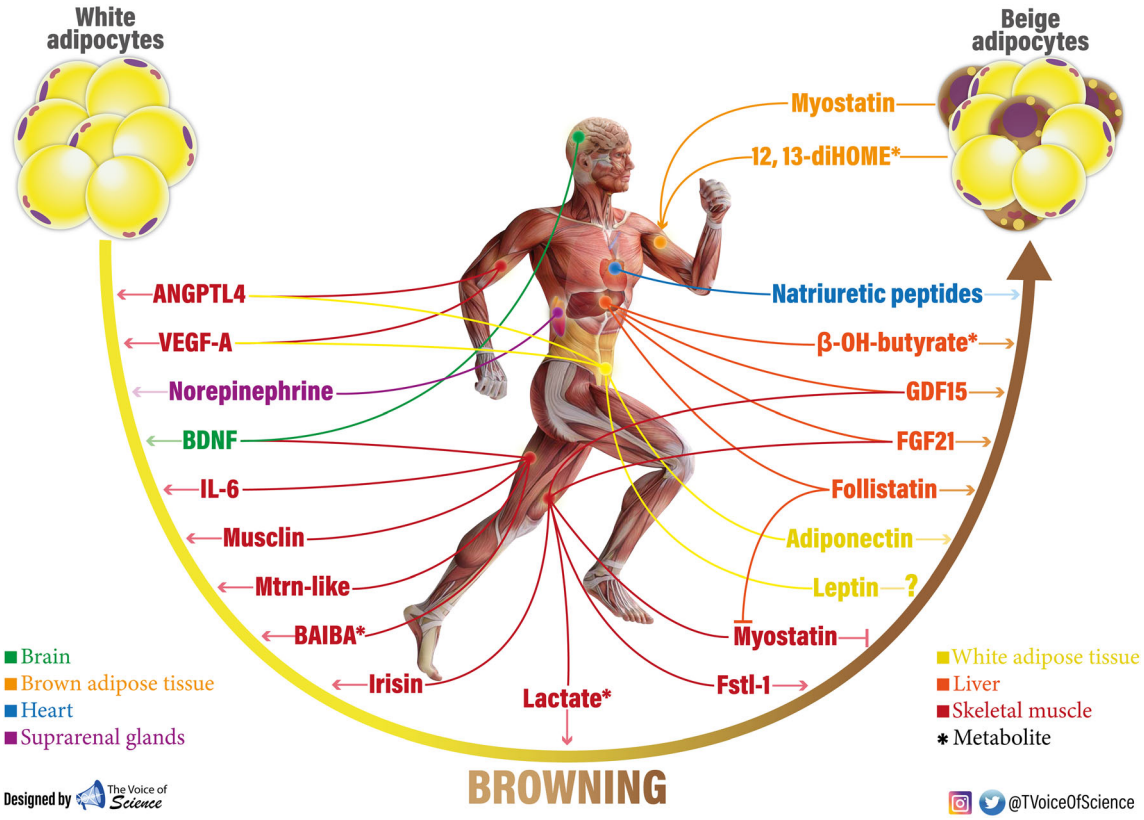

Fig. 1 Endocrine mechanisms connecting exercise to brown adipose tissue (BAT) metabolism and white adipose tissue (WAT) browning in humans. Several molecules with capacity to regulate BAT metabolism and/or WAT browning, including protein hormones and metabolites, are secreted during exercise. The brown and beige adipocytes also secrete signaling factors that can influence skeletal muscle metabolism during exercise. The represented secreting tissue is speculative for most of the molecules. The evidence supporting the information depicted in the figure mainly comes from animal studies, and still need to be confirmed in humans. ANGPTL4: angiopoietin-like 4; Baiba: beta aminobutyric acid; BDNF: brain-derived neurotrophic factor; β-OH-butyrate; GDF15: growth differentiation factor 15; FGF21: fibroblast growth factor 21; Fstl-1: follistatin protein-like 1; Mtrn-like: meteorin-like; VEGF: vascular endothelial growth factor A; 12,13-diHOME: 12,13-dihydroxy-9Z-octadecenoic acid (12,13-diHOME)

adipocytes by thermogenic activation [29]. FGF21 induces WAT browning through activation of PGC-1α [29]. In BAT, FGF21 can act in an autocrine, paracrine, and endocrine manner inducing UCP1 expression and BAT thermogenesis [29]. Interestingly, a positive association between circulating FGF21 and BAT volume has been reported in healthy men [30].

Several studies have reported exercise-induced increases in human FGF21 circulating levels (Table 1). Slusher et al. [31] reported an increase in FGF21 plasma levels after exercise in obese and normal-weight subjects, being greater in normal-weight participants. FGF21 circulating levels stay increased up to 6 h after exercise cessation in normal-weight and overweight/obese men [32]. Moreover, a recent study suggested an exercise intensity-dependent FGF21 secretion [33].

Interleukin-6

Interleukin-6 (IL-6) is mainly produced in adipose tissue and skeletal muscle by immune and non-immune cells [34]. In WAT, IL-6 can activate eosinophils to produce interleukin-4 (IL-4), which induces macrophages to acquire a M2 phenotype and in turn promotes WAT browning by local norepinephrine release [35]. Interestingly, it has been shown that the beneficial metabolic effect of BAT transplantation in mice is not present when the donor was a IL-6 knockout mouse [36].

Exercise increases circulating IL-6 up to 100-fold [37] (Table 1). Exercise intensity and duration, the form of muscular contraction (eccentric or concentric), and muscle damage are the main mechanisms that mediate the IL-6 response to acute exercise [38].

Meteorin-Like

The expression of PGC-1α4, a splice form of the gene encoding PGC-1α, in skeletal muscle stimulates the synthesis and secretion of a protein called meteorin-like. Upon binding to its receptor in adipose tissue, meteorin-like promotes an eosinophil-dependent activation of M2 macrophages, secreting IL-4 and IL-13, which in turn induces WAT browning and

Table 1 Exercise effect on circulating levels of endocrine molecules that are able to regulate brown adipose tissue metabolism and/or white adipose tissue browning, or communicate BAT with other tissues during exercise, in humans

	Moderate-intensity aerobic exercise		High-intensity aerobic exercise		Resistance exercise		Participants
	Exercise	Recovery	Exercise	Recovery	Exercise	Recovery	
Protein hormones							
Norepinephrine	↑ [15, 147–150]	↷ [15, 147–150]	↑ [16, 151–155]	↷ [16, 151–155]	↑ [155–159]	↷ [155–159]	Lean and obese children [158] Lean young men [15, 149, 151, 152, 154, 155] and women [149] Lean [16, 158], overweight [148, 153], and obese [147, 148] middle-aged men T1DM lean and overweight middle-aged adults [156, 159] Healthy lean elderly adults [157]
ANP	↑ [15, 16, 148, 160, 161]	↷ [15, 16, 148, 160, 161]	↑ [14, 16, 162, 163]	↷ [14, 16, 162, 163]	~ [161]	~ [161]	Healthy lean elderly and young adults [162] Athletes and lean sedentary young adults [163] Lean [196–198] and obese young men [160] Overweight healthy middle-aged men [14, 16, 148] and women [148] Obese healthy middle-aged adults [14]
BNP	↑ [20]	↷ [20]	↑ [17]	↷ [17]	?	?	Healthy men [17] Adults with pulmonary arterial hypertension [20]
Irisin	~ [164] ↑ [141, 165, 166]	↷ [141, 166] ~ [164]	↑ [22, 166–168] ↓ [56] ~ [164]	↷ [22, 166] ~ [164]	~ [169, 170] ↑ [171]	↓ [169] ↷ [171]	Lean young males [22, 56, 164–166, 168–171] and women [168] Pregnant women [167] Lean and overweight sedentary middle-aged men [141]
FGF21	~ [31–33, 64, 172–175] ↓ 164]	↑ [31–33, 64, 172–175] ↓ 164]	~ [33, 175, 164]	↑ [33, 175, 164]	~ [172, 176]	~ [172, 176]	Lean [31, 33, 64, 164, 172–176] and obese [31] young men Lean and overweight middle-aged men [32] Lean elderly men [174]
IL-6	↑ [177–183]	↑ [179–181]	↑ [168, 180, 182, 183]	↑ [180]	↑ [176, 182, 184]	↑ [176, 184–187]	Lean young men [168, 176, 177, 180, 185, 186] Lean young adolescents [178] Overweight middle-aged adults [179, 183] T1DM lean and overweight middle-aged adults [187] Lean and obese T2DM middle-aged men [181, 182] Obese elderly women [184]
METRNL	↑ [41]	?	?	?	?	?	Healthy active overweight young women [41]
Musclin	?	?	?	?	?	?	
GDF15	↑ [48]	↑ [48]	?	?	?	?	Healthy active young men [48]
Myostatin	~ [164]	? [164]	↑ [56, 164]	↷ [56] ? [164]	~ [188]	↓ [57] ~ [188]	Lean young men [56, 57, 164] Lean middle-aged men [188]
Follistatin	~ [32, 33, 64, 164]	↑ [32, 33, 64, 164]	~ [33, 164]	↑ [33, 164]	~ [169, 188]	↑ [169, 188]	Lean young men [33, 64, 164, 169] Lean middle-aged men [32, 188] Overweight middle-aged men [32]
Fstl-1	↑ [66]	↷ [66]	↑ [68]	↷ [68]	?	?	Healthy lean trained adult men [66] Healthy lean young men [68]
BDNF	↑ [73, 167, 189–200] ~ [201, 202]	↷ [189, 192, 193, 195–197] ~ [201]	↑ [189, 194, 198, 201, 202]	↷ [189, 201]	~ [77, 78]	?	Metabolic syndrome and healthy adults [193] Healthy young male athletes [73, 190, 194, 198, 201, 202] Healthy young adults [78, 192, 196, 197]Pregnant and post-partum women [167]

Table 1 (continued)

	Moderate-intensity aerobic exercise		High-intensity aerobic exercise		Resistance exercise		Participants
	Exercise	Recovery	Exercise	Recovery	Exercise	Recovery	
Adiponectin	~ [82–86]	~ [82, 84, 85] ↑ [86]	~ [82, 87, 88]	↑ [87, 88] ~ [82]	?	?	Elderly sedentary lean/overweight women [199] Panic-disorder adults [200]Healthy trained/untrained adults [77]Major depressed young adults [189] Young healthy sedentary men [191] Healthy lean young men [110, 114] Healthy moderate active adults [83] Healthy young lean active men [84, 86–88] Overweight young men [85]
Leptin	~ [82, 83, 95, 96, 203, 204] ↓ [97, 98, 205]	↓ [95, 203, 205] ↷ [98]	↓ [97] ~ [87, 88, 96]	↓ [88, 96] ~ [87]	~ [206]	↓ [206]	Healthy moderately active adults [83] Healthy young trained lean men [86–88, 95, 97, 205] Healthy young lean men [96, 206] Healthy trained men [203] Premenopausal obese adult women [204] Healthy sedentary adults [98]
VEGFA	↑ [103] ~ [106, 107, 207]	~ [106–108] ↑ [103, 207]	↑ [104, 208]	↷ [104]	↑ [209] ~ [105, 210]	↑ [209, 210] ~ [105, 108]	Healthy young men [103, 106, 108] Healthy young trained men [107, 207] Healthy young trained women [104] Healthy lean middle-aged adults [208] Healthy young women [209] Healthy young sedentary men [210]
ANGPTL4	~ [211] ↑ [111, 112, 114]	↑ [112, 211]	?	?	?	?	Healthy lean and obese sedentary men [211] Healthy lean and overweight adult men [111] Healthy young men [112] Ultramarathon male runners [114]
Metabolites							
BAIBA	↑ [117] ~ [118]	↑ [117] ~ [118]	?	?	?	?	Healthy young active adults [117] Healthy young untrained men [118, 212]
β-hydroxybutyrate	~ [125, 213, 214] ↑ [212, 213, 215] ↓ [212]	↑ [213, 215, 216]~ [213]	~ [217]	↑ [217]	?	?	Healthy lean young trained/untrained men [213] Healthy young trained/untrained men [125, 215, 217] Obese middle-aged men [214]
Lactate	↑ [124, 218]	↷ [124, 218]	↑ [124, 218]	↷ [124, 218]	↑ [124]	↷ [124]	Consistent response among different populations
12–13-diHOME	↑ [131, 132]	↷ [131, 132]	?	?	?	?	Young/elderly sedentary/active adults [131] Young healthy male cyclists [132]

Symbols: (↑) Increase, (↓) decreased, (~) unchanged, (?) unknown, (↷) return to basal levels. Different symbols are used within the same cell when controversial results have been published

Abbreviations: *ANGPTL4*: angiopoietin-like 4; *Baiba*: beta aminobutyric acid; *BDNF*: brain-derived neurotrophic factor; *β-OH*-butyrate; *GDF15*: growth differentiation factor 15; *FGF21*: fibroblast growth factor 21; *Fstl-1*: follistatin protein-like 1; *Mtrn-like*: meteorin-like; *T1DM*: type 1 diabetes mellitus; *T2DM*: type 2 diabetes mellitus; *VEGF*: vascular endothelial growth factor A; *12,13-diHOME*: 12,13-dihydroxy-9Z-octadecenoic acid

the expression of genes encoding the thermogenic and mitochondrial program, by means of norepinephrine release [39]. Indeed, the administration of an anti-meteorin-like antibody partially prevented cold-induced WAT browning [39]. Meteorin-like is not only produced by skeletal muscle but also by brown and beige adipocytes in response to cold [40].

In a seminal study, Rao et al. [39] showed that meteorin-like mRNA expression is induced in murine skeletal muscle after a resistance exercise session. This overexpression concurred with increased levels of circulating meteorin-like, which remained elevated 24 h after the exercise session. Importantly, Saghebjoo et al. [41] observed an increase in meteorin-like levels after a session of moderate endurance exercise in young women (Table 1).

Musclin

Firstly reported by Nishizawa et al. [42], musclin is a peptide produced by skeletal muscle that can be found in the bloodstream [42]. Musclin shares some structural similarities with natriuretic peptides and, consequently, can bind to some common receptors [43]. Musclin promotes mitochondrial biogenesis in skeletal muscle [43]. Moreover, since musclin works as a peroxisome proliferator–activated receptor γ (PPARγ) agonist, it has been suggested to play a role in the browning process [44]. It seems that musclin is secreted in response to exercise in murine models [43], yet whether it is also the case in humans remains to be elucidated.

Growth Differentiation Factor-15

Growth differentiation factor-15 (GDF15) is a protein belonging to the transforming growth factor-β (TGF-β) superfamily, whose receptor is mainly expressed in the brain and in WAT [45]. Although the major source of circulating GDF15 is the liver, it is also expressed, among others, in the skeletal muscle, WAT, and BAT [46, 47]. GDF15 is released by brown and beige adipocytes in response to thermogenic activity, targeting BAT macrophages and downregulating local inflammation [47].

It has been reported that exercise increases GDF15 circulating levels after a moderate [48] and a high-intensity [49] session. Kleinert et al. [48] showed an increase in plasma GDF15 immediately after 60 min of aerobic exercise (67% of VO2max) and during recovery in young normal-weight males (Table 1).

Myostatin

Growth differentiation factor-8, also known as myostatin, is another member of the TGF-β superfamily, described to be a myokine early in the 1990s [50]. Myostatin's main function is the inhibition of muscle growth, and consequently, its suppression dramatically stimulates muscle growth [51]. Myostatin loss of function not only results in muscle hypertrophy, but also in a decreased fat accumulation [52] and WAT browning [53]. The induction of WAT browning by myostatin inhibition is triggered by the activation of the AMPK enzyme and the subsequent induction of PGC-1α and FNDC5 [54]. Therefore, myostatin seems to play an important role as WAT browning inhibitor. Moreover, BAT-muscle connection through myostatin could be bidirectional, with BAT influencing muscle function by secreting myostatin [55].

Acute and chronic exercise modifies myostatin expression and circulating levels, although this effect seems to be dependent on the type and intensity of exercise [56–59] (Table 1). Chronic training decreases myostatin circulating levels in humans [60]. In contrast, high-intensity exercise acutely increases myostatin circulating levels immediately after exercise [56]. Importantly, the myostatin effect on BAT represents a proof of concept that exercise induces the secretion of not only pro-browning agents, but also browning inhibitors.

Follistatin

Follistatin can be secreted by the skeletal muscle, the liver, and other tissues including WAT and BAT [61]. Follistatin binds several members of the TGF-β superfamily including activins and myostatin to neutralize their biological activities [61]. Therefore, the follistatin-mediated suppression of the myostatin signaling has been identified as an important pathway involved in muscle metabolism, differentiation, and growth [62]. Besides the inhibition of myostatin action, follistatin likely promotes muscle growth and BAT development by direct activation of Myf5 expression and precursor cells [63]. Moreover, follistatin treatment in the skeletal muscle leads to increase FNDC5 expression and irisin secretion in mice [7]. Indeed, several studies have reported a WAT browning effect of follistatin in murine models [61].

Exercise increases follistatin levels in humans, although the effect may be dependent on the type and intensity of exercise [32, 33, 62, 65] (Table 1). For instance, Perakakis et al. [62] found that two different exercise intensities (i.e., 70% and 90% of VO_2max) acutely increase follistatin levels, independently of the presence of the metabolic syndrome. Moreover, Sargeant et al. [32] showed that circulating follistatin levels increased after a moderate-intensity bout of exercise (i.e., 60 min at 60% VO_2max) and remained elevated for at least 6 h.

Follistatin-Like Protein 1

Follistatin-like protein 1 (Fstl-1) is a glycoprotein of the follistatin family proteins group. Fstl-1 is secreted by the skeletal muscle to promote endothelial cell function through

activation of Akt-eNOS signaling in mice [65] and humans [66]. Moreover, recent studies suggest that Fstl-1 stimulates BAT thermogenesis through β3-adrenergic activation in mice [67], and that was positively correlated with levels of UCP1 and β3-adrenergic receptor expression [67].

Exercise seems to increase Fstl-1 circulating levels (Table 1). Gorgens et al. [66] observed a 22% increase in Fstl-1 serum levels immediately and 30 min after a 60-min cycling bout in trained healthy men. Levels of Fstl-1 also increased after an acute sprint interval exercise in healthy young men [68]. It seems that Fslt-1 response to a single bout of exercise displays an acute response, as Fstl-1 levels returned to baseline levels after exercise.

Brain-Derived Neurotrophic Factor

Brain-derived neurotrophic factor (BDNF) is a neurotrophin mainly expressed in the hippocampus that stimulates synaptic plasticity and memory in humans [69] and plays a role in energy homeostasis [70]. In mice, BDNF is secreted in response to an enriched environment (i.e., the presence of mazes and toys) and exercise, resulting in WAT browning in both cases [70]. Importantly, the artificial inhibition of BDNF during exercise inhibited the exercise-induced WAT browning [71]. The BDNF effects seem to be partially mediated by the expression of PGC-1α and FNDC5 [72]. Several studies have shown an increase in BDNF circulating levels after both moderate and high-intensity aerobic exercise across different populations [73–76], whereas the acute effect of resistance training remains unclear [77, 78] (Table 1).

Adiponectin

Adiponectin is a hormone secreted by WAT with anti-inflammatory and cardioprotective roles [79] and is likely to stimulate WAT browning through the recruitment of M2 macrophages [80]. In humans, adiponectin circulating levels seem to be positively associated with cold-induced BAT glucose uptake [81].

The effect of exercise on adiponectin circulating levels is controversial. Some studies report that adiponectin plasma levels remain unchanged after exercise [82–85], whereas others suggest an increase only in trained subjects [86–88]. However, chronic endurance exercise could improve adiponectin levels in obese young females [89] (Table 1).

Leptin

Leptin is mainly produced and secreted by WAT. Indeed, leptin serum concentrations are tightly correlated with fat mass [90]. Leptin regulates energy homeostasis, both by suppressing appetite and by stimulating energy expenditure, binding to its receptor in the hypothalamus [91]. Leptin seems to activate BAT through increasing sympathetic tone [92], whereas leptin deficiency results in impaired BAT function [93]. Leptin administration increases FNDC5 expression in skeletal muscle but, paradoxically, decreases FNDC5 expression in WAT and WAT browning [94].

The leptin response to exercise seems to be consistent across the data reported in the literature, but there is still some discussion (Table 1). Both moderate [95, 96] and high-intensity [87, 95] exercise seems to evoke no change or a little decrease [81, 88, 96–100] in leptin levels.

Vascular Endothelial Growth Factor A

Vascular endothelial growth factor (VEGF) is a growth factor family that stimulates angiogenesis and vasculogenesis, inducing vascular endothelial cell activation, proliferation, and migration [101]. Importantly, one of the members of this protein family, VEGF-A, is secreted by BAT and may act in a paracrine way to regulate vascularization and activate thermogenesis [102]. Several studies have reported an increase in circulating VEGF-A after a bout of aerobic and resistance exercise in both men and women [103–105], but some of them did not see any effect [106–108] (Table 1). Whereas the available evidence is still preliminary, it might be that the exercise-induced secretion of VEGF-A is also a factor contributing to BAT activation and/or WAT browning.

Angiopoietin-Like 4

Angiopoietin-like protein 4 (ANGPTL4) belongs to a family of multifunctional glycoproteins that inhibit lipoprotein lipase [109]. This protein is mainly secreted by WAT to facilitate the uptake of triglyceride-derived fatty acids by tissues with higher energy demand, such as skeletal muscle and BAT [110]. In addition to the nutritional status, the production of ANGPTL4 is regulated by exercise in humans [111–113] (Table 1). A recent study showed that acute endurance exercise increased circulating ANGPTL4 levels in healthy males, the liver being the main secreting site [112]. In another study, an increase in circulating ANGPTL-4 was observed after a 100-km ultra-marathon running in healthy men [114].

Metabolites

β-Aminoisobutyric Acid

β-Aminoisobutyric acid (BAIBA) is a non-protein amino acid derived from valine catabolism, a very active process in skeletal muscle [115]. BAIBA is secreted by the skeletal muscle cells in response to PGC-1α activity [116]. Roberts et al. [116] showed that BAIBA increases the expression of thermogenic genes in WAT, facilitating the browning

process. These effects were similar in human-induced pluripotent stem cells and in white adipocytes derived from human pluripotent cell lines.

The effects of exercise on BAIBA are controversial. An increase in BAIBA levels after 20 weeks of highly controlled endurance exercise training has been reported [116]. Similarly, another study showed that 1 h of low-intensity aerobic exercise increases plasma levels of BAIBA in recreationally active humans [117]. In contrast, a bout of endurance exercise of moderate intensity failed to induce a significant effect on serum BAIBA in untrained adults [118], and BAIBA levels were not changed after 6 weeks of aerobic exercise training in American Indian children [119].

Lactate

Lactate is a product of anaerobic glycolysis and is secreted by muscle during high-intensity exercise [120] (Table 1). Lactate seems to be involved in BAT metabolism since murine brown adipocytes overexpress the monocarboxylate transporter 1 in response to exercise, promoting the lactate internalization into brown adipocytes [121]. As a consequence, lactate-induced browning of WAT is thought to be mediated by a change in intracellular redox state (NADH-to-NAD+ ratio) [122]. However, lactate might induce WAT browning through the FGF21 expression in brown adipocytes, which likely acts in an autocrine manner to induce browning [123]. The lactate response to exercise is well recognized in sport physiology, being aerobic and resistance exercise able to elicit a significant and rapid increase in an intensity-dependent manner [124].

β-Hydroxybutyrate

β-Hydroxybutyrate is a ketone body [125], which seems to promote WAT browning through a change in intracellular redox state [122]. Interestingly, dietary β-hydroxybutyrate promotes WAT browning in animal models [126]. It has also been pointed that ketogenic diets upregulate BAT UCP1 expression [127]. In contrast, a recent study showed that β-hydroxybutyrate does not promote adipocyte browning in isolated visceral and subcutaneous fat cells [128]. β-Hydroxybutyrate is used as fuel source when glucose availability is reduced [125]. During exercise, β-hydroxybutyrate circulating concentrations are commonly decreased, as a consequence of a higher muscle uptake than hepatic production [125]. Nonetheless, it is quite common to observe increased circulating levels of β-hydroxybutyrate during prolonged exercise or after intense exercise [125] (Table 1). It is of note that the ketone bodies' response to exercise seems to be dependent on the level of training and diet [129].

12,13-Dihydroxy-9Z-octadecenoic Acid

The lipokine 12,13-dihydroxy-9Z-octadecenoic acid (12,13-diHOME) promotes an increase in fatty acid uptake, lipolysis, and thermogenesis in BAT [130]. 12-13-diHOME, as well as the enzymes involved in its synthesis, seems to be released from BAT after 1 h of cold exposure in rodents and humans [130]. Stanford et al. [131] reported an increase in 12,13-diHOME levels immediately after exercise which returned to baseline 1 h after exercise in young men and women (Table 1). They also observed higher 12-13-diHOME expression in active subjects than in sedentary ones, independently of BMI [131]. Moreover, they elegantly proved that BAT was the 12-13-diHOME secreting site during exercise by observing the absence of the exercise-induced increased in mice whose BAT had been surgically removed. These findings suggest that 12-13-diHOME is secreted by BAT during exercise impacting skeletal muscle metabolism. Another study in trained cyclist who performed a 75-km moderate-intensity test showed that 12,13-diHOME levels increase just after the exercise, persisting elevated at least during 90 min [132].

The Effect of Exercise on Human BAT and WAT Browning

To our knowledge, there are no published well-designed randomized controlled trials analyzing the effect of exercise on human BAT volume and activity or WAT browning. Findings from observational studies are contradictory. We observed no association of objectively measured physical activity [133] or fitness [134] with BAT volume or activity after an individualized cold exposure in young healthy adults. In contrast, others reported a positive association of subjectively measured physical activity with thermoneutral BAT activity in cancer patients [135] and with a higher expression of browning markers in abdominal subcutaneous WAT [136]. Findings from case-controlled studies show that endurance-trained athletes present lower BAT glucose uptake than their untrained counterparts [137–139], whereas no between-group differences in abdominal subcutaneous WAT browning markers expression were observed [137].

The results from exercise intervention studies in humans are controversial and inconclusive. Motiani et al. [140] observed a decreased insulin-stimulated BAT activity after 2 weeks of cycling at high or moderate intensity in seven and in eleven participants, respectively. A 12-week strength and endurance exercise intervention increased (1.82-fold) mRNA expression of UCP1 in subcutaneous WAT in normal-weight participants and in pre-diabetes mellitus patients, yet no effect of exercise on expression of UCP1 or PRDM16, TBX1, TMEM26, and CD137 was reported when

healthy and pre-diabetes were analyzed separately [141]. Similarly, a 6-week endurance exercise training had no effect on browning marker expression in abdominal subcutaneous WAT in six obese men [141, 142]. Unfortunately, these studies [141, 142] did not provide data on BAT volume or activity before and after the exercise intervention. Moreover, the lack of a control group likely biased their results, since human BAT activity is highly fluctuating across seasons and is highly dependent upon environmental temperature [143].

Well-designed randomized controlled trials analyzing the effect of exercise on human BAT volume and activity and/or WAT browning are highly desirable. Current technological limitations to study human thermogenic fat may however preclude those studies to draw firm conclusions. Indeed, the best radiological technique available for the study of human BAT in vivo, the positron emission tomography/computerized tomography (PET/CT), is not able to detect small beige adipocytes droplets within WAT, but only metabolically active areas bigger than some millimeters [144]. Importantly, most human thermogenic adipocytes are likely to be widespread within WAT depots, and, therefore, would not constitute big enough areas to be detected by current PET/CT scans. Moreover, the available radiotracers for PET/CT present important limitations for assessing BAT metabolism [144]. For instance, a reduction in BAT ^{18}F-fluorodeoxuglucose (a glucose analogue and the most commonly used radiotracer for BAT assessment) uptake after an exercise program might not represent lower BAT activity, but an exercise-induced shift to a more lipolytic metabolism in BAT [145]. On the other hand, the histological or molecular analyses of beige markers might not be adequate in superficial adipose tissue depots, since human WAT browning seems to occur in deeper anatomical locations [146]. Thus, obtaining adequate adipose tissue biopsies for assessing the effect of exercise on human WAT browning might be very invasive and, therefore, unfeasible.

Concluding Remarks

In this review, we have summarized the available scientific evidence regarding the exercise-induced secretion of a variety of endocrine signaling molecules that are able to stimulate BAT metabolism and WAT browning in humans. Despite that the effect of exercise on human BAT metabolism and WAT browning cannot be fully determined, it seems plausible to hypothesize that, as in rodents, this circulating cocktail results in BAT activation and/or WAT browning in humans. Nevertheless, it should be noted that exercise also stimulates the secretion of some BAT inhibitors and that the overall effect of the exercise-induced circulating molecules would be highly dependent on the tissue (i.e., BAT, WAT) blood flow. Therefore, even if exercise elicits a pro-browning endocrine cocktail, this might result in a negligible effect if blood flow is restricted in thermogenic adipocytes during exercise, something that is likely to occur. Consequently, there is an urgent need to determine the blood flow regulation in human beige–rich areas (e.g., supraclavicular fossae) during and after exercise. In addition, it might be plausible that performing exercise (secreting pro-browning molecules) during or followed by cold exposure (likely increasing blood flow to thermogenic adipose tissue areas) might result in a much more pronounced BAT activation and/or WAT browning, as it seems to be suggested by rodent studies.

In conclusion, there is growing evidence showing that many of the rodent's endocrine mechanisms impacting BAT metabolism and/or WAT browning during and after exercise are also present in humans. Unfortunately, current technological limitations prevent reaching definitive conclusions regarding the effect of exercise on human BAT and/or WAT metabolism. If confirmed in humans, WAT browning would be one of the still unknown molecular mechanisms by which exercise exerts beneficial health effects in humans, which might be pharmacologically mimicked. Future studies are needed to fully characterize the exercise-induced secretion of these endocrine signaling molecules, determining the effect of the different exercise criteria including frequency, intensity, type, time, and volume.

Acknowledgments This study was performed as part of a PhD thesis conducted within the Official Doctoral Programme in Biomedicine of the University of Granada, Spain.

Funding Information This study was supported by the Spanish Ministry of Economy and Competitiveness via *Retos de la Sociedad* (DEP2016-79512-R) and *European Regional Development Funds* (ERDF), the Spanish Ministry of Education (FPU13/04365, FPU16/02828 FPU16/03653), the *Redes Temáticas de Investigación Cooperativa* RETIC (Red SAMID RD16/0022), the University of Granada *Plan Propio de Investigación 2016*–Excellence actions: Unit of Excellence on Exercise and Health (UCEES), the University of Granada *Plan Propio de Investigación 2018* (*Programa Contratos Puente* and *Perfeccionamiento de Doctores*), the *Junta de Andalucía*, *Consejería de Conocimiento, Investigación y Universidades* (ERDF; ref. SOMM17/6107/UGR), and the *Fundación Alfonso Martín Escudero*.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Cannon B, Nedergaard J. Brown adipose tissue: function and physiological significance. Physiol Rev. 2004;84(1):277–359.

2. Chang SH, Song NJ, Choi JH, Yun UJ, Park KW. Mechanisms underlying UCP1 dependent and independent adipocyte thermogenesis. Obes Rev. 2019;20(2):241–51.
3. Petrovic N, Walden TB, Shabalina IG, Timmons JA, Cannon B, Nedergaard J. Chronic peroxisome proliferator-activated receptor gamma (PPARgamma) activation of epididymally derived white adipocyte cultures reveals a population of thermogenically competent, UCP1-containing adipocytes molecularly distinct from classic brown adipocyt. J Biol Chem. 2010;285(10):7153–64.
4. Betz MJ, Enerbäck S. Targeting thermogenesis in brown fat and muscle to treat obesity and metabolic disease. Nat Rev Endocrinol. 2018;14(2):77–87.
5. Villarroya F, Cereijo R, Villarroya J, Giralt M. Brown adipose tissue as a secretory organ. Nat Rev Endocrinol. 2017;13(1):26–35.
6. Lehnig AC, Stanford KI. Exercise-induced adaptations to white and brown adipose tissue. J Exp Biol. 2018;221(Pt Suppl 1).
7. Riis-Vestergaard MJ, Richelsen B, Bruun JM, Li W, Hansen JB, Pedersen SB. Beta-1 and not beta-3-adrenergic receptors may be the primary regulator of human brown adipocyte metabolism. J Clin Endocrinol Metab. 2019;0954162(478):1–4.
8. Zouhal H, Jacob C, Delamarche P, Gratas-Delamarche A. Catecholamines and the effects of exercise, training and gender. Sports Med. 2008;38(5):401–23.
9. Volpe M. Natriuretic peptides and cardio-renal disease. Int J Cardiol. 2014;176(3):630–9.
10. Lafontan M, Moro C, Berlan M, Crampes F, Sengenes C, Galitzky J. Control of lipolysis by natriuretic peptides and cyclic GMP. Trends Endocrinol Metab. 2008;19(4):130–7.
11. Engeli S, Birkenfeld AL, Badin PM, Bourlier V, Louche K, Viguerie N, et al. Natriuretic peptides enhance the oxidative capacity of human skeletal muscle. J Clin Invest. 2012;122(12):4675–9.
12. Bordicchia M, Liu D, Amri EZ, Ailhaud G, Dessì-Fulgheri P, Zhang C, et al. Cardiac natriuretic peptides act via p38 MAPK to induce the brown fat thermogenic program in mouse and human adipocytes. J Clin Invest. 2012;122(3):1022–36.
13. Liu D, Ceddia RP, Collins S. Cardiac natriuretic peptides promote adipose "browning" through mTOR complex-1. Mol Metab. 2018;9:192–8.
14. Haufe S, Kaminski J, Utz W, Haas V, Mähler A, Daniels MA, et al. Differential response of the natriuretic peptide system toweight loss and exercise in overweight or obese patients. J Hypertens. 2015;33(7):1458–64.
15. Moro C, Polak J, Hejnova J, Klimcakova E, Crampes F, Stich V, et al. Atrial natriuretic peptide stimulates lipid mobilization during repeated bouts of endurance exercise. Am J Physiol Endocrinol Metab. 2006;290(5):E864–9.
16. Peres D, Mourot L, Ménétrier A, Bouhaddi M, Degano B, Regnard J, et al. Intermittent versus constant aerobic exercise in middle-aged males: acute effects on arterial stiffness and factors influencing the changes. Eur J Appl Physiol. 2018;118(8):1625–33.
17. Huang W-S, Lee M-S, Perng H-W, Yang S-P, Kuo S-W, Chang H-D. Circulating brain natriuretic peptide values in healthy men before and after exercise. Metabolism. 2002;51(11):1423–6.
18. Ohba H, Takada H, Musha H, Nagashima J, Mori N, Awaya T, et al. Effects of prolonged strenuous exercise on plasma levels of atrial natriuretic peptide and brain natriuretic peptide in healthy men. Am Heart J. 2001;141(5):751–8.
19. Aengevaeren VL, Hopman MTE, Thijssen DHJ, van Kimmenade RR, de Boer M-J, Eijsvogels TMH. Endurance exercise-induced changes in BNP concentrations in cardiovascular patients versus healthy controls. Int J Cardiol. 2017;227:430–5.
20. Pathak V, Aris R, Jensen BC, Huang W, Ford HJ. Effect of 6-min walk test on pro-BNP levels in patients with pulmonary arterial hypertension. Lung. 2018;196(3):315–9.
21. de Oliveira M, Mathias LS, Rodrigues BM, Mariani BG, Graceli JB, De Sibio MT, et al. The roles of triiodothyronine and irisin in improving the lipid profile and directing the browning of human adipose subcutaneous cells. Mol Cell Endocrinol. 2020;506:110744.
22. Qiu S, Bosnyák E, Treff G, Steinacker JM, Nieß AM, Krüger K, et al. Acute exercise-induced irisin release in healthy adults: associations with training status and exercise mode. Eur J Sport Sci. 2018;18(9):1226–33.
23. Dünnwald T, Melmer A, Gatterer H, Salzmann K, Ebenbichler C, Burtscher M, et al. Supervised short-term high-intensity training on plasma irisin concentrations in type 2 diabetic patients. Int J Sports Med. 2019;40(3):158–64.
24. Albrecht E, Norheim F, Thiede B, Holen T, Ohashi T, Schering L, et al. Irisin - a myth rather than an exercise-inducible myokine. Sci Rep. 2015;5:8889.
25. Hofmann T, Elbelt U, Stengel A. Irisin as a muscle-derived hormone stimulating thermogenesis - a critical update. Peptides. 2014;54:89–100.
26. Izumiya Y, Bina HA, Ouchi N, Akasaki Y, Kharitonenkov A, Walsh K. FGF21 is an Akt-regulated myokine. FEBS Lett. 2008;582(27):3805–10.
27. Muise ES, Azzolina B, Kuo DW, El-Sherbeini M, Tan Y, Yuan X, et al. Adipose fibroblast growth factor 21 is up-regulated by peroxisome proliferator-activated receptor and altered metabolic states. Mol Pharmacol. 2008;74(2):403–12.
28. Hondares E, Gallego-Escuredo JM, Flachs P, Frontini A, Cereijo R, Goday A, et al. Fibroblast growth factor-21 is expressed in neonatal and pheochromocytoma-induced adult human brown adipose tissue. Metabolism. 2014;63(3):312–7.
29. Fisher FM, Kleiner S, Douris N, Fox EC, Mepani RJ, Verdeguer F, et al. FGF21 regulates PGC-1α and browning of white adipose tissues in adaptive thermogenesis. Genes Dev. 2012;26(3):271–81.
30. Soundarrajan M, Deng J, Kwasny M, Rubert NC, Nelson PC, El-Seoud DA, et al. Activated brown adipose tissue and its relationship to adiposity and metabolic markers: an exploratory study. Adipocyte. 2020;9(1):87–95.
31. Slusher AL, Whitehurst M, Zoeller RF, Mock JT, Maharaj M, Huang CJ. Attenuated fibroblast growth factor 21 response to acute aerobic exercise in obese individuals. Nutr Metab Cardiovasc Dis. 2015;25(9):839–45.
32. Sargeant JA, Aithal GP, Takamura T, Misu H, Takayama H, Douglas JA, et al. The influence of adiposity and acute exercise on circulating hepatokines in normal-weight and overweight/obese men. Appl Physiol Nutr Metab. 2018;43(5):482–90.
33. Willis SA, Sargeant JA, Thackray AE, Yates T, Stensel DJ, Aithal GP, et al. Effect of exercise intensity on circulating hepatokine concentrations in healthy men. Appl Physiol Nutr Metab. 2019;44(10):1065–72.
34. Ma Y, Gao M, Sun H, Liu D. Interleukin-6 gene transfer reverses body weight gain and fatty liver in obese mice. Biochim Biophys Acta - Mol Basis Dis. 2015;1852(5):1001–11.
35. Mauer J, Chaurasia B, Goldau J, Vogt MC, Ruud J, Nguyen KD, et al. Signaling by IL-6 promotes alternative activation of macrophages to limit endotoxemia and obesity-associated resistance to insulin. Nat Immunol. 2014;15(5):423–30.
36. Stanford KI, Middelbeek RJW, Townsend KL, An D, Nygaard EB, Hitchcox KM, et al. Brown adipose tissue regulates glucose homeostasis and insulin sensitivity. J Clin Invest. 2013;123(1):215–23.

37. Pedersen BK, Fischer CP. Physiological roles of muscle-derived interleukin-6 in response to exercise. Curr Opin Clin Nutr Metab Care. 2007;10(3):265–71.
38. Reihmane D, Dela F. Interleukin-6: possible biological roles during exercise. Eur J Sport Sci. 2014;14(3):242–50.
39. Rao RRR, Long JZZ, White JPP, Svensson KJJ, Lou J, Lokurkar I, et al. Meteorin-like is a hormone that regulates immune-adipose interactions to increase beige fat thermogenesis. Cell. 2014;157(6):1279–91.
40. Li Z-Y, Zheng S-L, Wang P, Xu T-Y, Guan Y-F, Zhang Y-J, et al. Subfatin is a novel adipokine and unlike Meteorin in adipose and brain expression. CNS Neurosci Ther. 2014;20(4):344–54.
41. Saghebjoo M, Einaloo A, Mogharnasi M, Ahmadabadi F. The response of meteorin-like hormone and interleukin-4 in overweight women during exercise in temperate, warm and cold water. Horm Mol Biol Clin Investig. 2018;36(3):20180027.
42. Nishizawa H, Matsuda M, Yamada Y, Kawai K, Suzuki E, Makishima M, et al. Musclin, a novel skeletal muscle-derived secretory factor. J Biol Chem. 2004;279(19):19391–5.
43. Subbotina E, Sierra A, Zhu Z, Gao Z, Koganti SRK, Reyes S, et al. Musclin is an activity-stimulated myokine that enhances physical endurance. Proc Natl Acad Sci U S A. 2015;112(52):16042–7.
44. Jeremic N, Chaturvedi P, Tyagi SC. Browning of White fat: novel insight into factors, mechanisms, and therapeutics. J Cell Physiol. 2017;232(1):61–8.
45. Morris A. Advances in GDF15 research. Nat Rev Endocrinol. 2020;16(3):129.
46. Laurens C, Parmar A, Murphy E, Carper D, Lair B, Maes P, et al. Growth and differentiation factor 15 is secreted by skeletal muscle during exercise and promotes lipolysis in humans. JCI insight. 2020;5(6):e131870.
47. Campderrós L, Moure R, Cairó M, Gavaldà-Navarro A, Quesada-López T, Cereijo R, et al. Brown adipocytes secrete GDF15 in response to thermogenic activation. Obesity (Silver Spring). 2019;27(10):1606–16.
48. Kleinert M, Clemmensen C, Sjøberg KA, Carl CS, Jeppesen JF, Wojtaszewski JFP, et al. Exercise increases circulating GDF15 in humans. Mol Metab. 2018;9:187–91.
49. Galliera E, Lombardi G, Marazzi MG, Grasso D, Vianello E, Pozzoni R, et al. Acute exercise in elite rugby players increases the circulating level of the cardiovascular biomarker GDF-15. Scand J Clin Lab Invest. 2014;74(6):492–9.
50. McPherron AC, Lawler AM, Lee S-J. Regulation of skeletal muscle mass in mice by a new TGF-p superfamily member. Nature. 1997;387(6628):83–90.
51. Schuelke M, Wagner KR, Stolz LE, Hübner C, Riebel T, Kömen W, et al. Myostatin mutation associated with gross muscle hypertrophy in a child. N Engl J Med. 2004;350(26):2682–8.
52. McPherron AC, Lee S-J. Suppression of body fat accumulation in myostatin-deficient mice. J Clin Invest. 2002;109(5):595–601.
53. Zhang C, McFarlane C, Lokireddy S, Masuda S, Ge X, Gluckman PD, et al. Inhibition of myostatin protects against diet-induced obesity by enhancing fatty acid oxidation and promoting a brown adipose phenotype in mice. Diabetologia. 2012;55(1):183–93.
54. Shan T, Liang X, Bi P, Kuang S. Myostatin knockout drives browning of white adipose tissue through activating the AMPK-PGC1α-Fndc5 pathway in muscle. FASEB J. 2013;27(5):1981–9.
55. Kong X, Yao T, Zhou P, Kazak L, Tenen D, Lyubetskaya A, et al. Brown adipose tissue controls skeletal muscle function via the secretion of myostatin. Cell Metab. 2018;28(4):631–43.
56. Kabak B, Belviranli M, Okudan N. Irisin and myostatin responses to acute high-intensity interval exercise in humans. Horm Mol Biol Clin Investig. 2018;35(3):20180008.
57. Kazemi F. The correlation of resistance exercise-induced myostatin with insulin resistance and plasma cytokines in healthy young men. J Endocrinol Investig. 2016;39(4):383–8.
58. Saremi A, Gharakhanloo R, Sharghi S, Gharaati MR, Larijani B, Omidfar K. Effects of oral creatine and resistance training on serum myostatin and GASP-1. Mol Cell Endocrinol. 2010;317(1–2):25–30.
59. Paoli A, Pacelli QF, Neri M, Toniolo L, Cancellara P, Canato M, et al. Protein supplementation increases postexercise plasma myostatin concentration after 8 weeks of resistance training in young physically active subjects. J Med Food. 2015;18(1):137–43.
60. Bagheri R, Moghadam BH, Church DD, Tinsley GM, Eskandari M, Moghadam BH, et al. The effects of concurrent training order on body composition and serum concentrations of follistatin, myostatin and GDF11 in sarcopenic elderly men. Exp Gerontol. 2020;133:110869.
61. Singh R, Braga M, Reddy STT, Lee SJS-J, Parveen M, Grijalva V, et al. Follistatin targets distinct pathways to promote brown adipocyte characteristics in brown and white adipose tissues. Endocrinology. 2017;158(5):1217–30.
62. Perakakis N, Mougios V, Fatouros I, Siopi A, Draganidis D, Peradze N, et al. Physiology of activins/follistatins: associations with metabolic and anthropometric variables and response to exercise. J Clin Endocrinol Metab. 2018;103(10):3890–9.
63. Li J-X, Cummins CL. Getting the skinny on follistatin and fat. Endocrinology. 2017;158(5):1109–12.
64. Hansen JS, Pedersen BK, Xu G, Lehmann R, Weigert C, Plomgaard P. Exercise-induced secretion of FGF21 and follistatin are blocked by pancreatic clamp and impaired in type 2 diabetes. J Clin Endocrinol Metab. 2016;101(7):2816–25.
65. Ouchi N, Oshima Y, Ohashi K, Higuchi A, Ikegami C, Izumiya Y, et al. Follistatin-like 1, a secreted muscle protein, promotes endothelial cell function and revascularization in ischemic tissue through a nitric-oxide synthase-dependent mechanism. J Biol Chem. 2008;283(47):32802–11.
66. Görgens SW, Raschke S, Holven KB, Jensen J, Eckardt K, Eckel J. Regulation of follistatin-like protein 1 expression and secretion in primary human skeletal muscle cells. Arch Physiol Biochem. 2013;119(2):75–80.
67. Fang D, Shi X, Lu T, Ruan H, Gao Y. The glycoprotein follistatin-like 1 promotes brown adipose thermogenesis. Metabolism. 2019;98:16–26.
68. Kon M, Ebi Y, Nakagaki K. Effects of acute sprint interval exercise on follistatin-like 1 and apelin secretions. Arch Physiol Biochem. 2019; :1–5.
69. Tapia-Arancibia L, Rage F, Givalois L, Arancibia S. Physiology of BDNF: focus on hypothalamic function. Front Neuroendocrinol. 2004;25(2):77–107.
70. Stanford KI, Goodyear LJ. Exercise regulation of adipose tissue. Adipocyte. 2016;5(2):153–62.
71. Cao L, Choi EY, Liu X, Martin A, Wang C, Xu X, et al. White to brown fat phenotypic switch induced by genetic and environmental activation of a hypothalamic-adipocyte axis. Cell Metab. 2011;14(3):324–38.
72. Wrann CD, White JP, Salogiannnis J, Laznik-Bogoslavski D, Wu J, Ma D, et al. Exercise induces hippocampal BDNF through a PGC-1α/FNDC5 pathway. Cell Metab. 2013;18(5):649–59.
73. Hung C-L, Tseng J-W, Chao H-H, Hung T-M, Wang H-S. Effect of acute exercise mode on serum brain-derived neurotrophic factor (BDNF) and task switching performance. J Clin Med. 2018;7(10):301.
74. Simão AP, Mendonça VA, Avelar NCP, da Fonseca SF, Santos JM, de Oliveira ACC, et al. Whole body vibration training on muscle strength and brain-derived neurotrophic factor levels in elderly woman with knee osteoarthritis: a randomized clinical trial study. Front Physiol. 2019;10:756.
75. Marinus N, Hansen D, Feys P, Meesen R, Timmermans A, Spildooren J. The impact of different types of exercise training

on peripheral blood brain-derived neurotrophic factor concentrations in older adults: a meta-analysis. Sports Med. 2019;49(10):1529–46.
76. Devenney KE, Guinan EM, Kelly ÁM, Mota BC, Walsh C, Olde Rikkert M, et al. Acute high-intensity aerobic exercise affects brain-derived neurotrophic factor in mild cognitive impairment: a randomised controlled study. BMJ Open Sport Exerc Med. 2019;5(1):e000499.
77. Goekint M, De Pauw K, Roelands B, Njemini R, Bautmans I, Mets T, et al. Strength training does not influence serum brain-derived neurotrophic factor. Eur J Appl Physiol. 2010;110(2):285–93.
78. Correia PR, Pansani A, MacHado F, Andrade M, da Silva AC, Scorza FA, et al. Acute strength exercise and the involvement of small or large muscle mass on plasma brain-derived neurotrophic factor levels. Clinics. 2010;65(11):1123–6.
79. Woodward L, Akoumianakis I, Antoniades C. Unravelling the adiponectin paradox: novel roles of adiponectin in the regulation of cardiovascular disease. Br J Pharmacol. 2017;174(22):4007–20.
80. Hui X, Gu P, Zhang J, Nie T, Pan Y, Wu D, et al. Adiponectin enhances cold-induced browning of subcutaneous adipose tissue via promoting M2 macrophage proliferation. Cell Metab. 2015;22(2):279–90.
81. Sun L, Yan J, Goh HJ, Govindharajulu P, Verma S, Michael N, et al. Fibroblast growth factor-21, leptin, and adiponectin responses to acute cold-induced brown adipose tissue activation. J Clin Endocrinol Metab. 2020;105(3).
82. Kraemer RR, Aboudehen KS, Carruth AK, Durand RJ, Acevedo EO, Hebert EP, et al. Adiponectin responses to continuous and progressively intense intermittent exercise. Med Sci Sports Exerc. 2003;35(8):1320–5.
83. Ferguson MA, White LJ, McCoy S, Kim HW, Petty T, Wilsey J. Plasma adiponectin response to acute exercise in healthy subjects. Eur J Appl Physiol. 2004;91(2–3):324–9.
84. Punyadeera C, Zorenc AHG, Koopman R, McAinch AJ, Smit E, Manders R, et al. The effects of exercise and adipose tissue lipolysis on plasma adiponectin concentration and adiponectin receptor expression in human skeletal muscle. Eur J Endocrinol. 2005;152(3):427–36.
85. Jamurtas AZ, Theocharis V, Koukoulis G, Stakias N, Fatouros IG, Kouretas D, et al. The effects of acute exercise on serum adiponectin and resistin levels and their relation to insulin sensitivity in overweight males. Eur J Appl Physiol. 2006;97(1):122–6.
86. Jürimäe J, Hofmann P, Jürimäe T, Mäestu J, Purge P, Wonisch M, et al. Plasma adiponectin response to sculling exercise at individual anaerobic threshold in college level male rowers. Int J Sports Med. 2006;27(4):272–7.
87. Jürimäe J, Purge P, Jürimäe T. Adiponectin is altered after maximal exercise in highly trained male rowers. Eur J Appl Physiol. 2005;93(4):502–5.
88. Jürimäe J, Purge P, Jürimäe T. Adiponectin and stress hormone responses to maximal sculling after volume-extended training season in elite rowers. Metabolism. 2006;55(1):13–9.
89. Racil G, Ben Ounis O, Hammouda O, Kallel A, Zouhal H, Chamari K, et al. Effects of high vs. moderate exercise intensity during interval training on lipids and adiponectin levels in obese young females. Eur J Appl Physiol. 2013;113(10):2531–40.
90. Maffei M, Halaas J, Ravussin E, Pratley RE, Lee GH, Zhang Y, et al. Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. Nat Med. 1995;1(11):1155–61.
91. Kuryszko J, Sławuta P, Sapikowski G. Secretory function of adipose tissue. Pol J Vet Sci. 2016;19(2):441–6.
92. Enriori PJ, Sinnayah P, Simonds SE, Garcia Rudaz C, Cowley MA. Leptin action in the dorsomedial hypothalamus increases sympathetic tone to brown adipose tissue in spite of systemic leptin resistance. J Neurosci. 2011;31(34):12189–97.
93. Kotzbeck P, Giordano A, Mondini E, Murano I, Severi I, Venema W, et al. Brown adipose tissue whitening leads to brown adipocyte death and adipose tissue inflammation. J Lipid Res. 2018;59(5):784–94.
94. Rodríguez A, Becerril S, Méndez-Giménez L, Ramírez B, Sáinz N, Catalán V, et al. Leptin administration activates irisin-induced myogenesis via nitric oxide-dependent mechanisms, but reduces its effect on subcutaneous fat browning in mice. Int J Obes. 2015;39(3):397–407.
95. Desgorces FD, Chennaoui M, Gomez-Merino D, Drogou C, Bonneau D, Guezennec CY. Leptin, catecholamines and free fatty acids related to reduced recovery delays after training. Eur J Appl Physiol. 2004;93(1–2):153–8.
96. Olive JL, Miller GD. Differential effects of maximal- and moderate-intensity runs on plasma leptin in healthy trained subjects. Nutrition. 2001;17(5):365–9.
97. Zaccaria M, Ermolao A, Roi GS, Englaro P, Tegon G, Varnier M. Leptin reduction after endurance races differing in duration and energy expenditure. Eur J Appl Physiol. 2002;87(2):108–11.
98. Legakis IN, Mantzouridis T, Saramantis A, Lakka-Papadodima E. Rapid decrease of leptin in middle-aged sedentary individuals after 20 minutes of vigorous exercise with early recovery after the termination of the test. J Endocrinol Investig. 2004;27(2):117–20.
99. Park KM, Park SC, Kang S. Effects of resistance exercise on adipokine factors and body composition in pre- and postmenopausal women. J Exerc Rehabil. 2019;15(5):676–82.
100. Salvadori A, Fanari P, Brunani A, Marzullo P, Codecasa F, Tovaglieri I, et al. Leptin level lowers in proportion to the amount of aerobic work after four weeks of training in obesity. Horm Metab Res. 2015;47(3):225–31.
101. Klagsbrun M, D'Amore PA. Vascular endothelial growth factor and its receptors. Cytokine Growth Factor Rev. 1996;7(3):259–70.
102. Sun K, Kusminski CM, Luby-Phelps K, Spurgin SB, An YA, Wang QA, et al. Brown adipose tissue derived VEGF-A modulates cold tolerance and energy expenditure. Mol Metab. 2014;3(4):474–83.
103. Kraus RM, Stallings HW, Yeager RC, Gavin TP. Circulating plasma VEGF response to exercise in sedentary and endurance-trained men. J Appl Physiol. 2004;96(4):1445–50.
104. Jürimäe J, Vaiksaar S, Purge P. Circulating inflammatory cytokine responses to endurance exercise in female rowers. Int J Sports Med. 2018;39(14):1041–8.
105. Ribeiro F, Ribeiro IP, Gonçalves AC, Alves AJ, Melo E, Fernandes R, et al. Effects of resistance exercise on endothelial progenitor cell mobilization in women. Sci Rep. 2017;7(1):17880.
106. Landers-Ramos RQ, Jenkins NT, Spangenburg EE, Hagberg JM, Prior SJ. Circulating angiogenic and inflammatory cytokine responses to acute aerobic exercise in trained and sedentary young men. Eur J Appl Physiol. 2014;114(7):1377–84.
107. Jürimäe J, Tillmann V, Purge P, Jürimäe T. Acute inflammatory response to prolonged sculling in competitive male rowers. J Sports Med Phys Fitness. 2016;56(11):1368–75.
108. Larkin KA, MacNeil RG, Dirain M, Sandesara B, Manini TM, Buford TW. Blood flow restriction enhances post-resistance exercise angiogenic gene expression. Med Sci Sports Exerc. 2012;44(11):2077–83.
109. Dijk W, Kersten S. Regulation of lipid metabolism by angiopoietin-like proteins. Curr Opin Lipidol. 2016;27(3):249–56.
110. Yu J, Zheng J, Liu XF, Feng ZL, Zhang XP, Cao LL, et al. Exercise improved lipid metabolism and insulin sensitivity in rats fed a high-fat diet by regulating glucose transporter 4 (GLUT4)

and musclin expression. Brazilian J Med Biol Res. 2016;49(5): e5129.
111. Catoire M, Alex S, Paraskevopulos N, Mattijssen F, Evers-van Gogh I, Schaart G, et al. Fatty acid-inducible ANGPTL4 governs lipid metabolic response to exercise. Proc Natl Acad Sci U S A. 2014;111(11):E1043–52.
112. Ingerslev B, Hansen JS, Hoffmann C, Clemmesen JO, Secher NH, Scheler M, et al. Angiopoietin-like protein 4 is an exercise-induced hepatokine in humans, regulated by glucagon and cAMP. Mol Metab. 2017;6(10):1286–95.
113. Kersten S, Lichtenstein L, Steenbergen E, Mudde K, Hendriks HFJ, Hesselink MK, et al. Caloric restriction and exercise increase plasma ANGPTL4 levels in humans via elevated free fatty acids. Arterioscler Thromb Vasc Biol. 2009;29(6):969–74.
114. Górecka M, Krzemiński K, Buraczewska M, Kozacz A, Dąbrowski J, Ziemba AW. Effect of mountain ultra-marathon running on plasma angiopoietin-like protein 4 and lipid profile in healthy trained men. Eur J Appl Physiol. 2020;120(1):117–25.
115. Shimomura Y, Honda T, Shiraki M, Murakami T, Sato J, Kobayashi H, et al. Branched-chain amino acid catabolism in exercise and liver disease. J Nutr. 2018;136:250S–3S.
116. Roberts LD, Boström P, O'Sullivan JF, Schinzel RT, Lewis GD, Dejam A, et al. β-Aminoisobutyric acid induces browning of white fat and hepatic β-oxidation and is inversely correlated with cardiometabolic risk factors. Cell Metab. 2014;19(1):96–108.
117. Stautemas J, Van Kuilenburg ABP, Stroomer L, Vaz F, Blancquaert L, Lefevere FBD, et al. Acute aerobic exercise leads to increased plasma levels of R- and S-β-aminoisobutyric acid in humans. Front Physiol. 2019; 10 (SEP) :1240.
118. Morales FE, Forsse JS, Andre TL, McKinley-Barnard SK, Hwang PS, Anthony IG, et al. BAIBA does not regulate UCP-3 expression in human skeletal muscle as a response to aerobic exercise. J Am Coll Nutr. 2017;36(3):200–9.
119. Short KR, Chadwick JQ, Teague AM, Tullier MA, Wolbert L, Coleman C, et al. Effect of obesity and exercise training on plasma amino acids and amino metabolites in American Indian adolescents. J Clin Endocrinol Metab. 2019;104(8):3249–61.
120. Kristensen M, Albertsen J, Rentsch M, Juel C. Lactate and force production in skeletal muscle. J Physiol. 2005;562(2):521–6.
121. De Matteis R, Lucertini F, Guescini M, Polidori E, Zeppa S, Stocchi V, et al. Exercise as a new physiological stimulus for brown adipose tissue activity. Nutr Metab Cardiovasc Dis. 2013;23(6):582–90.
122. Carrière A, Jeanson Y, Berger-Müller S, André M, Chenouard V, Arnaud E, et al. Browning of white adipose cells by intermediate metabolites: an adaptive mechanism to alleviate redox pressure. Diabetes. 2014;63(10):3253–65.
123. Jeanson Y, Ribas F, Galinier A, Arnaud E, Ducos M, André M, et al. Lactate induces FGF21 expression in adipocytes through a p38-MAPK pathway. Biochem J. 2016;473(6):685–92.
124. Schranner D, Kastenmüller G, Schönfelder M, Römisch-Margl W, Wackerhage H. Metabolite concentration changes in humans after a bout of exercise: a systematic review of exercise metabolomics studies. Sport Med - open. 2020;6(1):11.
125. Evans M, Cogan KE, Egan B. Metabolism of ketone bodies during exercise and training: physiological basis for exogenous supplementation. J Physiol. 2017;595(9):2857–71.
126. Wang W, Ishibashi J, Trefely S, Shao M, Cowan AJ, Sakers A, et al. A PRDM16-driven metabolic signal from adipocytes regulates precursor cell fate. Cell Metab. 2019; 30 (1) :174–189.e5.
127. Srivastava S, Baxa U, Niu G, Chen X, Veech RL. A ketogenic diet increases brown adipose tissue mitochondrial proteins and UCP1 levels in mice. IUBMB Life. 2013;65(1):58–66.
128. de Oliveira CR, Andreotti S, Komino ACM, de Fatima SF, Sertié RAL, Christoffolete MA, et al. Physiological concentrations of β-hydroxybutyrate do not promote adipocyte browning. Life Sci. 2019;232:116683.
129. Margolis LM, O'Fallon KS. Utility of ketone supplementation to enhance physical performance: a systematic review. Adv Nutr. 2019;11(2):412–9.
130. Lynes MD, Leiria LO, Lundh M, Bartelt A, Shamsi F, Huang TL, et al. The cold-induced lipokine 12,13-diHOME promotes fatty acid transport into brown adipose tissue. Nat Med. 2017;23(5): 631–7.
131. Stanford KI, Lynes MD, Takahashi H, Baer LA, Arts PJ, May FJ, et al. 12,13-diHOME: an exercise-induced lipokine that increases skeletal muscle fatty acid uptake. Cell Metab. 2018;27(5):1111–1120.e3.
132. Nieman DC, Shanely RA, Luo B, Meaney MP, Dew DA, Pappan KL. Metabolomics approach to assessing plasma 13- and 9-hydroxy-octadecadienoic acid and linoleic acid metabolite responses to 75-km cycling. Am J Physiol - Regul Integr Comp Physiol. 2014;307(1):68–74.
133. Acosta FM, Martinez-Tellez B, Sanchez-Delgado G, Migueles JH, Contreras-Gomez MA, Martinez-Avila WD, et al. Association of objectively measured physical activity with brown adipose tissue volume and activity in young adults. J Clin Endocrinol Metab. 2018;104(2):223–33.
134. Martinez-Tellez B, Sanchez-Delgado G, Amaro-Gahete FJ, Acosta FM, Ruiz JR. Relationships between cardiorespiratory fitness/muscular strength and 18F-fluorodeoxyglucose uptake in brown adipose tissue after exposure to cold in young, sedentary adults. Sci Rep. 2019;9(1):11314.
135. Dinas PC, Nikaki A, Jamurtas AZ, Prassopoulos V, Efthymiadou R, Koutedakis Y, et al. Association between habitual physical activity and brown adipose tissue activity in individuals undergoing PET-CT scantle. Clin Endocrinol. 2015;82(1):147–54.
136. Dinas PC, Valente A, Granzotto M, Rossato M, Vettor R, Zacharopoulou A, et al. Browning formation markers of subcutaneous adipose tissue in relation to resting energy expenditure, physical activity and diet in humans. Horm Mol Biol Clin Investig. 2017; 31 (1).
137. Vosselman MJ, Hoeks J, Brans B, Pallubinsky H, Nascimento EBM, Van Der Lans AAJJ, et al. Low brown adipose tissue activity in endurance-trained compared with lean sedentary men. Int J Obes. 2015;39(12):1696–702.
138. Singhal V, Maffazioli GD, Ackerman KE, Lee H, Elia EF, Woolley R, et al. Effect of chronic athletic activity on brown fat in young women. PLoS One. 2016;11(5):e0156353.
139. Trexler ET, McCallister D, Smith-Ryan AE, Branca RT. Incidental finding of low brown adipose tissue activity in endurance-trained individuals: methodological considerations for positron emission tomography. J Nat Sci. 2017;3(3):e335.
140. Motiani P, Virtanen KA, Motiani KK, Eskelinen JJ, Middelbeek RJ, Goodyear LJ, et al. Decreased insulin-stimulated brown adipose tissue glucose uptake after short-term exercise training in healthy middle-aged men. Diabetes Obes Metab. 2017;19(10): 1379–88.
141. Norheim F, Langleite TM, Hjorth M, Holen T, Kielland A, Stadheim HK, et al. The effects of acute and chronic exercise on PGC-1α, irisin and browning of subcutaneous adipose tissue in humans. FEBS J. 2014;281(3):739–49.
142. Tsiloulis T, Carey AL, Bayliss J, Canny B, Meex RCR, Watt MJ. No evidence of white adipocyte browning after endurance exercise training in obese men. Int J Obes. 2018;42(4):721–7.
143. Martinez-Tellez B, Xu H, Sanchez-Delgado G, Acosta FM, Rensen PCN, Llamas-Elvira JM, et al. Association of wrist and ambient temperature with cold-induced brown adipose tissue and skeletal muscle [18F]FDG uptake in young adults. Am J Physiol Regul Integr Comp Physiol. 2018;315(6):R1281–8.

144. Carpentier AC, Blondin DP, Virtanen KA, Richard D, Haman F, Turcotte ÉE. Brown adipose tissue energy metabolism in humans. Front Endocrinol (Lausanne). 2018; 9 :447.
145. Blondin DP, Labbé SM, Noll C, Kunach M, Phoenix S, Guérin B, et al. Selective impairment of glucose but not fatty acid or oxidative metabolism in brown adipose tissue of subjects with type 2 diabetes. Diabetes. 2015;64(7):2388–97.
146. Cypess AM, White AP, Vernochet C, Schulz TJ, Xue R, Sass CA, et al. Anatomical localization, gene expression profiling and functional characterization of adult human neck brown fat. Nat Med. 2013;19(5):635–9.
147. Mittendorfer B, Fields DA, Klein S. Excess body fat in men decreases plasma fatty acid availability and oxidation during endurance exercise. Am J Physiol - Endocrinol Metab. 2004;286(3): E354–62.
148. Fenzl M, Schnizer W, Aebli N, Schlegel C, Villiger B, Disch A, et al. Release of ANP and fat oxidation in overweight persons during aerobic exercise in water. Int J Sport Med. 2013;34(9): 795–9.
149. Bloomer RJ, Canale RE, Shastri S, Suvarnapathki S. Effect of oral intake of capsaicinoid beadlets on catecholamine secretion and blood markers of lipolysis in healthy adults: a randomized, placebo controlled, double-blind, cross-over study. Lipids Health Dis. 2010;9:72.
150. Onus K, Cannon J, Liberts L, Marino FE. Acute effects of a dopamine/norepinephrine reuptake inhibitor on neuromuscular performance following self-paced exercise in cool and hot environments. J Therm Biol. 2016;60:60–9.
151. Skriver K, Roig M, Lundbye-Jensen J, Pingel J, Helge JW, Kiens B, et al. Acute exercise improves motor memory: exploring potential biomarkers. Neurobiol Learn Mem. 2014;116:46–58.
152. Goto C, Nishioka K, Umemura T, Jitsuiki D, Sakagutchi A, Kawamura M, et al. Acute moderate-intensity exercise induces vasodilation through an increase in nitric oxide bioavailiability in humans. Am J Hypertens. 2007;20(8):825–30.
153. Ceresini G, Marchini L, Fabbo A, Freddi M, Pasolini G, Reali N, et al. Evaluation of circulating galanin levels after exercise-induced pituitary hormone secretion in man. Metabolism. 1997;46(3):282–6.
154. Kliszczewicz BM, Esco MR, Quindry JC, Blessing DL, Oliver GD, Taylor KJ, et al. Autonomic responses to an acute bout of high-intensity body weight resistance exercise vs. treadmill running. J strength Cond Res. 2016;30(4):1050–8.
155. Kraemer WJ, Gordon SE, Fragala MS, Bush JA, Szivak TK, Flanagan SD, et al. The effects of exercise training programs on plasma concentrations of proenkephalin peptide F and catecholamines. Peptides. 2015;64:74–81.
156. Turner D, Gray BJ, Luzio S, Dunseath G, Bain SC, Hanley S, et al. Similar magnitude of post-exercise hyperglycemia despite manipulating resistance exercise intensity in type 1 diabetes individuals. Scand J Med Sci Sports. 2016;26(4):404–12.
157. Shimizu R, Hotta K, Yamamoto S, Matsumoto T, Kamiya K, Kato M, et al. Low-intensity resistance training with blood flow restriction improves vascular endothelial function and peripheral blood circulation in healthy elderly people. Eur J Appl Physiol. 2016;116(4):749–57.
158. Rubin DA, Castner DM, Pham H, Ng J, Adams E, Judelson DA. Hormonal and metabolic responses to a resistance exercise protocol in lean children, obese children and lean adults. Pediatr Exerc Sci. 2014;26(4):444–54.
159. Turner D, Luzio S, Gray BJ, Dunseath G, Rees ED, Kilduff LP, et al. Impact of single and multiple sets of resistance exercise in type 1 diabetes. Scand J Med Sci Sports. 2015;25(1):e99–109.
160. Koppo K, Larrouy D, Marques MA, Berlan M, Bajzova M, Polak J, et al. Lipid mobilization in subcutaneous adipose tissue during exercise in lean and obese humans. Roles of insulin and natriuretic peptides. Am J Physiol - Endocrinol Metab. 2010;299(2):E258–65.
161. MacDonald JR, MacDougall JD, Interisano SA, Smith KM, McCartney N, Moroz JS, et al. Hypotension following mild bouts of resistance exercise and submaximal dynamic exercise. Eur J Appl Physiol Occup Physiol. 1999;79(2):148–54.
162. Poveda JJ, Berrazueta JR, Ochoteco A, Montalbán C, García-Unzueta MT, Fernández C, et al. Age-related responses of vasoactive factors during acute exercise. Horm Metab Res. 1998;30(11):668–72.
163. Poveda JJ, Riestra A, Salas E, Cagigas ML, López-Somoza C, Amado JA, et al. Contribution of nitric oxide to exercise-induced changes in healthy volunteers: effects of acute exercise and long-term physical training. Eur J Clin Investig. 1997;27(11): 967–71.
164. He Z, Tian Y, Valenzuela PL, Huang C, Zhao J, Hong P, et al. Myokine/adipokine response to "aerobic" exercise: is it just a matter of exercise load? Front Physiol. 2019;10(691).
165. Ozbay S, Ulupınar S, Şebin E, Altınkaynak K. Acute and chronic effects of aerobic exercise on serum irisin, adropin, and cholesterol levels in the winter season: indoor training versus outdoor training. Chin J Physiol. 2020;63(1):21–6.
166. Daskalopoulou SS, Cooke AB, Gomez YH, Mutter AF, Filippaios A, Mesfum ET, et al. Plasma irisin levels progressively increase in response to increasing exercise workloads in young, healthy, active subjects. Eur J Endocrinol. 2014;171(3):343–52.
167. Rojas Vega S, Kleinert J, Sulprizio M, Hollmann W, Bloch W, Strüder HK. Responses of serum neurotrophic factors to exercise in pregnant and postpartum women. Psychoneuroendocrinology. 2011;36(2):220–7.
168. Wiecek M, Szymura J, Maciejczyk M, Kantorowicz M, Szygula Z. Acute anaerobic exercise affects the secretion of asprosin, irisin, and other cytokines - a comparison between sexes. Front Physiol. 2018;9:1782.
169. Philippou A, Maridaki M, Tenta R, Koutsilieris M. Hormonal responses following eccentric exercise in humans. Hormones. 2017;16(4):402–13.
170. Blizzard Leblanc DR, Rioux B V., Pelech C, Moffatt TL, Kimber DE, Duhamel TA, et al. Exercise-induced irisin release as a determinant of the metabolic response to exercise training in obese youth: the exit trial. Physiol Rep. 2017; 5 (23).
171. Tsuchiya Y, Ando D, Takamatsu K, Goto K. Resistance exercise induces a greater irisin response than endurance exercise. Metabolism. 2015;64(9):1042–50.
172. Morville T, Sahl RE, Trammell SA, Svenningsen JS, Gillum MP, Helge JW, et al. Divergent effects of resistance and endurance exercise on plasma bile acids, FGF19, and FGF21 in humans. JCI insight. 2018;3(15):122737.
173. JanssenDuijghuijsen LM, Keijer J, Mensink M, Lenaerts K, Ridder L, Nierkens S, et al. Adaptation of exercise-induced stress in well-trained healthy young men. Exp Physiol. 2017;102(1):86–99.
174. Taniguchi H, Tanisawa K, Sun X, Higuchi M. Acute endurance exercise lowers serum fibroblast growth factor 21 levels in Japanese men. Clin Endocrinol. 2016;85(6):861–7.
175. Kim KH, Kim SH, Min Y-K, Yang H-M, Lee J-B, Lee M-S. Acute exercise induces FGF21 expression in mice and in healthy humans. PLoS One. 2013;8(5):e63517.
176. Parmar B, Lewis JE, Samms RJ, Ebling FJPP, Cheng CC, Adams AC, et al. Eccentric exercise increases circulating fibroblast activation protein α but not bioactive fibroblast growth factor 21 in healthy humans. Exp Physiol. 2018;103(6):876–83.
177. Marques CG, Santos VC, Levada-Pires AC, Jacintho TM, Gorjão R, Pithon-Curi TC, et al. Effects of DHA-rich fish oil supplementation on the lipid profile, markers of muscle damage, and

neutrophil function in wheelchair basketball athletes before and after acute exercise. Appl Physiol Nutr Metab. 2015;40(6):596–604.
178. Lau KK, Obeid J, Breithaupt P, Belostotsky V, Arora S, Nguyen T, et al. Effects of acute exercise on markers of inflammation in pediatric chronic kidney disease: a pilot study. Pediatr Nephrol. 2015;30(4):615–21.
179. Viana JL, Kosmadakis GC, Watson EL, Bevington A, Feehally J, Bishop NC, et al. Evidence for anti-inflammatory effects of exercise in CKD. J Am Soc Nephrol. 2014;25(9):2121–30.
180. Islam H, Townsend LK, McKie GL, Medeiros PJ, Gurd BJ, Hazell TJ. Potential involvement of lactate and interleukin-6 in the appetite-regulatory hormonal response to an acute exercise bout. J Appl Physiol. 2017;123(3):614–23.
181. Sabaratnam R, Pedersen AJTT, Kristensen JM, Handberg A, Wojtaszewski JFPP, Højlund K. Intact regulation of muscle expression and circulating levels of myokines in response to exercise in patients with type 2 diabetes. Physiol Rep. 2018;6(12):e13723.
182. Mendham AE, Donges CE, Liberts EA, Duffield R. Effects of mode and intensity on the acute exercise-induced IL-6 and CRP responses in a sedentary, overweight population. Eur J Appl Physiol. 2011;111(6):1035–45.
183. Harris RA, Padilla J, Hanlon KP, Rink LD, Wallace JP. The flow-mediated dilation response to acute exercise in overweight active and inactive men. Obesity (Silver Spring). 2008;16(3):578–84.
184. Tajra V, Tibana RA, Vieira DCL, de Farias DL, Teixeira TG, Funghetto SS, et al. Identification of high responders for interleukin-6 and creatine kinase following acute eccentric resistance exercise in elderly obese women. J Sci Med Sport. 2014;17(6):662–6.
185. Jackman JS, Bell PG, Gill S, van Someren K, Davison GW, Cockburn E. Assessing the usefulness of acute physiological responses following resistance exercise: sensitivity, magnitude of change, and time course of measures. Appl Physiol Nutr Metab. 2019;44(3):309–19.
186. Hasenoehrl T, Wessner B, Tschan H, Vidotto C, Crevenna R, Csapo R. Eccentric resistance training intensity may affect the severity of exercise induced muscle damage. J Sports Med Phys Fitness. 2017;57(9):1195–204.
187. Turner D, Luzio S, Kilduff LP, Gray BJ, Dunseath G, Bain SC, et al. Reductions in resistance exercise-induced hyperglycaemic episodes are associated with circulating interleukin-6 in type 1 diabetes. Diabet Med. 2014;31(8):1009–13.
188. Han DS, Hsiao MY, Wang TG, Chen SY, Yang WS. Association of serum myokines and aerobic exercise training in patients with spinal cord injury: An observational study. BMC Neurol. 2016;16(1):142.
189. Gustafsson G, Lira CM, Johansson J, Wisén A, Wohlfart B, Ekman R, et al. The acute response of plasma brain-derived neurotrophic factor as a result of exercise in major depressive disorder. Psychiatry Res. 2009;169(3):244–8.
190. Bos I, Jacobs L, Nawrot TS, de Geus B, Torfs R, Int Panis L, et al. No exercise-induced increase in serum BDNF after cycling near a major traffic road. Neurosci Lett. 2011;500(2):129–32.
191. Seifert T, Brassard P, Wissenberg M, Rasmussen P, Nordby P, Stallknecht B, et al. Endurance training enhances BDNF release from the human brain. Am J Physiol Regul Integr Comp Physiol. 2010;298(2):R372–7.
192. Rasmussen P, Brassard P, Adser H, Pedersen MV, Leick L, Hart E, et al. Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. Exp Physiol. 2009;94(10):1062–9.
193. Gold SM, Schulz KH, Hartmann S, Mladek M, Lang UE, Hellweg R, et al. Basal serum levels and reactivity of nerve growth factor and brain-derived neurotrophic factor to standardized acute exercise in multiple sclerosis and controls. J Neuroimmunol. 2003;138(1–2):99–105.
194. Winter B, Breitenstein C, Mooren FC, Voelker K, Fobker M, Lechtermann A, et al. High impact running improves learning. Neurobiol Learn Mem. 2007;87(4):597–609.
195. Goekint M, Heyman E, Roelands B, Njemini R, Bautmans I, Mets T, et al. No influence of noradrenaline manipulation on acute exercise-induced increase of brain-derived neurotrophic factor. Med Sci Sports Exerc. 2008;40(11):1990–6.
196. Tang SW, Chu E, Hui T, Helmeste D, Law C. Influence of exercise on serum brain-derived neurotrophic factor concentrations in healthy human subjects. Neurosci Lett. 2008;431(1):62–5.
197. Tsai CL, Pan CY, Chen FC, Wang CH, Chou FY. Effects of acute aerobic exercise on a task-switching protocol and brain-derived neurotrophic factor concentrations in young adults with different levels of cardiorespiratory fitness. Exp Physiol. 2016;101(7):836–50.
198. Griffin ÉW, Mullally S, Foley C, Warmington SA, O'Mara SM, Kelly ÁM. Aerobic exercise improves hippocampal function and increases BDNF in the serum of young adult males. Physiol Behav. 2011;104(5):934–41.
199. Laske C, Banschbach S, Stransky E, Bosch S, Straten G, MacHann J, et al. Exercise-induced normalization of decreased BDNF serum concentration in elderly women with remitted major depression. Int J Neuropsychopharmacol. 2010;13(5):595–602.
200. Ströhle A, Stoy M, Graetz B, Scheel M, Wittmann A, Gallinat J, et al. Acute exercise ameliorates reduced brain-derived neurotrophic factor in patients with panic disorder. Psychoneuroendocrinology. 2010;35(3):364–8.
201. Rojas Vega S, Strüder HK, Vera Wahrmann B, Schmidt A, Bloch W, Hollmann W. Acute BDNF and cortisol response to low intensity exercise and following ramp incremental exercise to exhaustion in humans. Brain Res. 2006;1121(1):59–65.
202. Ferris LT, Williams JS, Shen CL. The effect of acute exercise on serum brain-derived neurotrophic factor levels and cognitive function. Med Sci Sports Exerc. 2007;39(4):728–34.
203. Duclos M, Corcuff JB, Ruffie A, Roger P, Manier G. Rapid leptin decrease in immediate post-exercise recovery. Clin Endocrinol. 1999;50(3):337–42.
204. Sari R, Balci MK, Balci N, Karayalcin U. Acute effect of exercise on plasma leptin level and insulin resistance in obese women with stable caloric intake. Endocr Res. 2006;32(1–2):9–17.
205. Jürimäe J, Jürimäe T. Leptin responses to short term exercise in college level male rowers. Br J Sports Med. 2005;39(1):6–9.
206. Zafeiridis A, Smilios I, Considine RV, Tokmakidis SP. Serum leptin responses after acute resistance exercise protocols. J Appl Physiol. 2003;94(2):591–7.
207. Sureda A, Mestre-Alfaro A, Banquells M, Riera J, Drobnic F, Camps J, et al. Exercise in a hot environment influences plasma anti-inflammatory and antioxidant status in well-trained athletes. J Therm Biol. 2015;47:91–8.
208. Baria MR, Miller MM, Borchers J, Desmond S, Onate J, Magnussen R, et al. High intensity interval exercise increases platelet and transforming growth factor- β yield in platelet-rich plasma. PM R. 2020; (August) :2–31.
209. Ribeiro F, Ribeiro IP, Gonçalves AC, Alves AJ, Melo E, Fernandes R, et al. Effects of resistance exercise on endothelial progenitor cell mobilization in women. Sci Rep. 2017;7(1):1–9.
210. Gavin TP, Drew JL, Kubik CJ, Pofahl WE, Hickner RC. Acute resistance exercise increases skeletal muscle angiogenic growth factor expression. Acta Physiol. 2007;191(2):139–46.
211. Norheim F, Hjorth M, Langleite TM, Lee S, Holen T, Bindesbøll C, et al. Regulation of angiopoietin-like protein 4 production during and after exercise. Physiol Rep. 2014;2(8):1–12.
212. Fery F, Balasse EO. Response of ketone body metabolism to exercise during transition from postabsorptive to fasted state1. Fery F, Balasse EO. Response of ketone body metabolism to exercise

during transition from postabsorptive to fasted state. Am J Physiol - Endocrinol Metab. 1986;250(5):E495–501.
213. Johnson RH, Walton JL. The effect of exercise upon acetoacetate metabolism in athletes and non-athletes. Q J Exp Physiol Cogn Med Sci. 1972;57(1):73–9.
214. Matoulek M, Svobodova S, Vetrovska R, Stranska Z, Svacina S. Post-exercise changes of beta hydroxybutyrate as a predictor of weight changes. Physiol Res. 2014;63(Suppl 2):S321–5.
215. Parker MT. Post-exercise reported. :452–5.
216. Zhang W, Bi S. Hypothalamic regulation of brown adipose tissue thermogenesis and energy homeostasis. Front Endocrinol (Lausanne). 2015;6(1):83.
217. Rennie MJ, Jennett S, Johnson RH. The metabolic effects of strenuous exercise: a comparison between untrained subjects and racing cyclists. Q J Exp Physiol Cogn Med Sci. 1974;59(3):201–12.
218. Devlin J, Paton B, Poole L, Sun W, Ferguson C, Wilson J, et al. Blood lactate clearance after maximal exercise depends on active recovery intensity. J Sports Med Phys Fitness. 2014;54(3):271–8.