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REVIEW

Aerobic exercise and lipolysis: A review of the β-adrenergic signaling pathways in adipose tissue

Exercice aérobie et lipolyse : une revue des voies de signalisation β-adrénergiques dans les tissus adipeux

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KEYWORDS
Exercise training;
Obesity;
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Summary
Objectives. — The objective of this study was to review the beta-adrenergic (β-AR) signaling pathways in adipose tissue, highlight key proteins involved in lypolisis and examine the effects of aerobic exercise on adipose tissue metabolism.
News. — Obesity is related to increased body fat and chronic subclinical inflammation. In this framework, lipolytic signaling pathways play a key role in the adipose tissue metabolism. The sympathetic activity through beta-adrenergic receptors is responsible for the lipolysis in white adipose tissue (WAT) and thermogenesis in brown adipose tissue (BAT), as well as for the browning of WAT. Aerobic exercise training protects against obesity by reducing body fat and chronic inflammation. Along with lipid oxidation, eating behavior and epigenetic reprogramming, the benefits of exercise are related to increases in lipolysis and browning in WAT, and thermogenesis in BAT by activation of the beta-adrenergic signaling pathways.
Prospects and projects. — The β-adrenergic signaling pathways in adipose tissue in a condition of obesity reflect more complex scenarios requiring further investigations. Concerning aerobic exercise effects, researches should address other possible lipid metabolism pathways, new cytokines involved in lypolisis and inflammation, eating behavior and epigenetic. Thus, new therapeutic strategies to face obesity and associated comorbidities should come up.

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Conclusion. — Aerobic exercise training protects against obesity. It induces adipose tissue metabolism by increasing lipolysis and browning of WAT, thermogenesis in BAT, and expression of cytokines related to lipid oxidation and inflammation, not to mention eating behavior and epigenetic reprogramming. Such benefits are helpful in the prevention and treatment of obesity.

MOTS CLÉS
Entraînement physique ;
Obésité ;
Graisse du corps ;
Browning ;
Thermogenèse ;
Inflammation

Résumé
Objectifs. — Cette étude visait à examiner les voies de signalisation bêta-adrénergiques (β-AR) dans le tissu adipeux, met en évidence les protéines clés impliquées dans la lipose et examiner les effets de l'exercice aérobie sur le métabolisme du tissu adipeux.
Actualités. — L'obésité est liée à une augmentation de la masse grasse corporelle et à une inflammation infraclinique chronique. Dans ce cadre, les voies de signalisation lipolytiques jouent un rôle clé dans le métabolisme du tissu adipeux. L'activité sympathique via les récepteurs bêta-adrénergiques est responsable de la lipolyse dans le tissu adipeux blanc (WAT) et de la thermogenèse dans le tissu adipeux brun (BAT), ainsi que pour le brunissement de WAT. L'entraînement aérobique protège contre l'obésité par la réduction de la graisse corporelle et de l'inflammation chronique. Avec l'oxydation des lipides, le comportement alimentaire et la reprogrammation épigénétique, ces effets bénéfiques de l'exercice sont liés à des augmentations de la lipolyse et du brunissement de WAT, et à la thermogenèse de BAT, par activation des voies de signalisation bêta-adrénergiques.
Perspectives et projects. — Les voies de signalisation β-adrénergiques dans le tissu adipeux en état d'obésité reflètent des scénarios plus complexes et nécessitent des études plus approfondies. En ce qui concerne les effets de l'exercice aérobie, les recherches devraient porter sur d'autres voies possibles du métabolisme lipidique, les nouvelles cytokines impliquées dans la lypolyse et l'inflammation, le comportement alimentaire et l'épigénétique. Information importante pour le développement de nouvelles stratégies thérapeutiques contre l'obésité et les comorbidités associées devraient apparaître.
Conclusion. — L'entraînement aérobique protège contre l'obésité. Il induit le métabolisme du tissu adipeux en augmentant la lipolyse et le brunissement de WAT, la thermogenèse en BAT et l'expression de cytokines liées à l'oxydation des lipides et à l'inflammation, sans oublier le comportement alimentaire et la reprogrammation épigénétique. Ces avantages sont utiles dans la prévention et le traitement de l'obésité.

1. Introduction

Obesity is one of the major public health problems because of its association with a wide range of health complications such as diabetes, hypertension, atherosclerosis and cancers. Over 1.9 billion adults are overweight and 650 million are obese in the world [1]. Its complex physiopathology emerges from the interaction of genetic and environmental factors [2]. Among environmental factors are poor diet and physical inactivity.

Lipid metabolism is complex, involves different pathways and is directly related to obesity. The signaling pathways of lipolysis in white adipose tissue (WAT) plays a key role in the metabolic alterations present in obesity, and thus, the identification of the critical stages of lipolysis is strategic for the treatment of obesity and its comorbidities. There are currently researches to better understand the role of adipose tissue in the epidemiological control of obesity, mainly the molecular mechanisms associated with its complications [3]. The sympathetic nervous system (SNS) is the main responsible for WAT lipolysis and brown adipose tissue (BAT) thermogenesis. Catecholamines, mainly adrenaline, activate signaling pathways responsible for the phosphorylation of key proteins in the process of lipolysis and thermogenesis [4]. Three isoforms of beta-adrenergic receptor (β-AR) are found in adipose tissue. Although β_3-AR is predominant in adipose tissue of rodents, studies have shown that the β_1-AR plays a key role in adipose tissue metabolism and obesity control [4—6].

Concerning non-pharmacological therapeutic strategies for the treatment and prevention of obesity, exercise training has played an important role since it enhances energy expenditure and hence lipid metabolism [7]. Apart from other exercise mode, aerobic exercise is beneficial to the metabolic diseases management and its effects do not limit to weight loss. For instance, subclinical inflammation may be reduced by aerobic exercise as it increases the expression of anti-inflammatory cytokines such as interleukin 10 (IL-10) and 15 (IL-15) and/or diminishes the expression of proinflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and monocyte chemoattractant protein-1 [8]. In addition, aerobic exercise increases the expression of uncoupling

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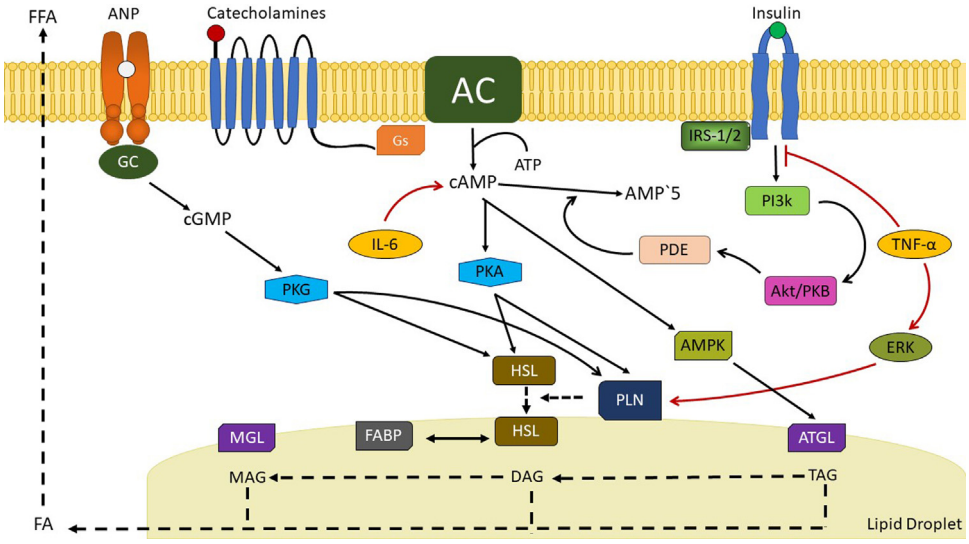

Figure 1 Signaling pathways of lipolysis in adipose tissue. AC: adenylate cyclase; Akt/PKB: protein kinase B; AMP'5: adenosine monophosphate'5; cAMP: cyclic adenosine monophosphate; AMPK: adenosine monophosphate-activated protein kinase; ANP: atrial natriuretic peptide; ATGL: adipose triglyceride lipase; DAG: diacylglycerol; ERK: extracellular signal-regulated kinase; FA: fatty acid; FABP: fatty acid binding proteins; FFA: free fatty acid; GC: guanylate cyclase; cGMP: cyclic guanosine monophosphate; Gs: stimulatory G protein; HSL: hormone-sensitive lipase; IL-6: interleukin 6; IR: insulin receptor; IRS-1/2: substrates of insulin receptor 1 and 2; MAG: monoacylglycerol; MGL: monoacylglycerol lipase; NPR-A: natriuretic peptide receptor; PDE-3B: phosphodiesterase 3B; PI3K: 3-kinase phosphatidylinositol; PKA: protein kinase A; PKG: protein kinase G; PLN: perilipin A; TAG: triacylglycerol; TNF-α: tumor necrosis factor α; βARs: beta adrenergic receptors. Continuous black arrow: lipolytic signaling pathways; continuous gray arrow: action of inflammatory cytokines; dashed black arrow: lipolysis of fatty acids; black arrow with bar: blocking the signaling pathway.

protein-1 (UCP-1) in adipocytes [9,10], which is related to adipose tissue oxidative phosphorylation, thermogenesis, BAT adipogenesis and WAT browning. Moreover, aerobic exercise increases plasma atrial natriuretic peptide (ANP) that is also involved with adipose tissue lipolysis [11] and oxidation [12]. Furthermore, aerobic exercise training is also related to eating behavior [13] and epigenetic reprogramming [14].

Considering the complex physiopathology of obesity because of the genetic and environmental elements' implications, in this study we thought to focus on the review of β-AR signaling pathways in adipose tissue, highlight key proteins involved in lypolisis and examine the effects of aerobic exercise on adipose tissue metabolism. The understanding of the relationship between exercise training and β-adrenergic signaling pathways of adipose tissue has substantial implications in the development of new therapeutic strategies for the treatment of obesity and associated comorbidities.

2. White adipose tissue

It is well known that the excess of energy obtained from diet is stored in WAT as triacylglycerol (TAG), from which the fatty acids (FA) are mobilized to attend the systemic energy demand. The WAT is composed of unilocular white adipocytes with few mitochondria and has adipoblast negative for the expression of myogenic factor 5 (*Myf5*$^{-}$) as precursor [15]. This tissue is located throughout the body, being divided into visceral (mesenteric, perigonadal and omental) and subcutaneous (inguinal) deposits. Adipocytes in visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) are different in size and metabolic activity, which influences the ability to respond to the insulin antilipolytic and catecholamines lipolytic effects [16].

In VAT there is low and high lipogenic and lipolytic effect, respectively. Since it is more lipolytic, this tissue releases more free FA (FFA) that can be stored in the liver and muscle. This ectopic storage is associated with insulin resistance, which makes this tissue more pathogenic. In addition, the proximity of visceral fat deposit with the organs, as well the drainage of FFA and inflammatory cytokines through the portal vein can contribute to the development of pathologies such as type 2 diabetes mellitus (DM2), cardiovascular diseases and others [17].

The WAT has two primary metabolic activities: lipogenesis, synthesis and storage of FA in the form of TAG; and lipolysis, hydrolysis of TAG in glycerol and FA [18], being thus a therapeutic target for the obesity treatment. These primary metabolic activities are regulated by endocrine and neural mechanisms, aiming to maintain body fat homeostasis [3]. Catecholamines, mainly adrenaline, are lipolytic agents in WAT in humans and rodents [19]. Lipolysis occurs in response to the β-adrenergic stimulation by catecholamines via β-adrenergic receptors that are members of the large family of G protein-coupled receptors. In rodent WAT, β_3-AR is the predominant receptor subtype and represents the primary signaling pathway for lipolysis [20].

The signaling pathways of lipolysis in adipose tissue are illustrated in Fig. 1. The catecholamines activate β-ARs coupled to stimulatory G protein, which activate adenylate cyclase (AC). When activated, AC catalyzes the conversion

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of adenosine triphosphate to cyclic adenosine monophosphate (cAMP). This second messenger binds to and activates protein kinase A (PKA), which phosphorylates the hydroxyl groups on the serine residue of the hormone-sensitive lipase (HSL). When activated, HSL translocate from the cytosol to the interface of the lipid droplet where it binds to the FA binding proteins, FABP4 and aP2, and initiates the hydrolysis of TAG, diacylglycerol and monoacylglycerol. Then, the FA of this hydrolysis will be released and transported in plasma to supply the energy demands of other tissues and organs. The perilipin A protein, which suppresses lipolysis by blocking the access of HSL to the lipid droplet, when phosphorylated by PKA moves from the surface of the lipid droplet to the cytosol, which allows the binding between the HSL and substrate at the droplet interface lipid.

The natriuretic peptides (e.g. ANP) are also lipolytic agents that activate the natriuretic peptide A receptor. Consequently, it increases guanylate cyclase activity and the production of cyclic guanosine monophosphate that activates the protein kinase G, responsible for phosphorylating HSL in adipose tissue [21]. The lipolysis induced by natriuretic peptides does not undergo insulin action, which is associated with the inhibition of lipolysis [19]. Other lipolytic agents are adipose triglyceride lipase (ATGL), responsible for hydrolyzing TAG; lipase monoacylglycerol, growth hormone; adrenocorticotropin; glucocorticoids and TNF-α.

Regarding TNF-α, it can promote lipolysis in the adipocyte by reducing the expression and/or activity of perilipin via the mitogen-activated protein kinase family (MAPK) and inhibition of insulin receptor (IR) signaling [22]. For instance, it was observed that in the presence of TNF-α the perilipin expression was reduced and lipolysis was increased in cells derived from 3T3-L1 fibroblasts [23]. A possible mechanism for lipolytic action of TNF-α is its ability to activate the MAPK cascade, mainly the extracellular signal-regulated kinase. Concerning the IR inhibition pathway, insulin binding to IR is known to trigger tyrosine phosphorylation of this receptor and IR receptor substrates 1 (IRS-1) and 2, which leads to activation of the phosphatidylinositol 3-kinase-protein kinase B signaling cascade and, subsequently, phosphodiesterase 3B (PDE-3B) in the cytosol [3,22]. Next, the activation of PDE-3B triggers cAMP hydrolysis in adenosine monophosphate'5 [21]. In turn, TNF-α has the role of inactivating and reducing IRS-1 in adipocytes, due to its ability to neutralize tyrosine phosphorylation through IRS-1 serine phosphorylation [22].

Interleukin 6 (IL-6) is another cytokine that can act on lipid metabolism. This finding is supported by the fact that IL-6$^{-/-}$ mice developed obesity when compared to wild animals [24]. Although the regulation of lipid metabolism in adipose tissue via IL-6 has not yet been elucidated, human, rat and in vitro studies suggest that IL-6 can trigger lipolysis by increasing cAMP concentrations and, consequently, adenosine monophosphate-activated protein kinase activation (AMPK) [25]. In turn, AMPK would increase lipolysis via phosphorylation of ATGL. To illustrate, it has been observed that AMPK gene deletion reduces ATGL phosphorylation in adipose tissue of mice, thus suggesting that AMPK activates lipolysis through the phosphorylation of ATGL and maintains an adequate level of lipolysis in adipose tissue [26].

In addition to TAG storage, WAT also plays an endocrine function by producing adipokines, such as leptin, adiponectin, resistin, visfatin, TNF-α, monocyte chemotactic protein (MCP-1), plasminogen activator inhibitor, and interleukins (IL-6, IL-8, IL-10, IL-1) [27]. In obese individuals, the increase in adipose tissue, mainly visceral, results in a higher production of proinflammatory adipokines, such as TNF-α, IL-6, MCP-1 [28].

Moreover, the WAT expansion also leads to necrosis/apoptosis of adipocytes and, consequently, to the release of lipid droplets that are toxic to adipocytes and activate macrophage recruitment [2]. Activation of macrophages can be divided into two states of polarization, M1 and M2. M1 macrophages are induced by inflammatory mediators, such as interferon gamma, and produce proinflammatory cytokines such as TNF-α and IL-6, whereas M2 macrophages produce high concentrations of anti-inflammatory cytokines, such as IL-10 and IL-1 receptor antagonist [29].

In macrophages and adipocytes, receptors like Toll (TLR) 2 and 4, which participate in pathogenic and immunological recognition, can be activated by saturated FA [2] and stimulate nuclear factor kappa B, also leading to production of TNF-α and IL-6 [30]. Proinflammatory cytokines associated with the activation of N-terminal kinase Jun-c and, subsequently, phosphorylation at the serine residue of IRS1, may impair insulin receptor signaling [2]. Thus, in obesity, these macrophage infiltrates in WAT assume a pro-inflammatory phenotype, because they secrete cytokines that aggravate insulin resistance [31]. Such environment is appropriate to the development of a chronic subclinical inflammation state and hence metabolic disorders like DM2.

Thus, considering that lipolysis in WAT plays a key role in lipid metabolic alterations present in obesity; and that exercise training has both prophylactic and therapeutic effects on obesity, in this review we explored whether aerobic exercise is able to influence the β-adrenergic signaling pathways in WAT (see section 5).

3. Brown adipose tissue

The adipocytes of the brown adipose tissue (BAT) are derived from the skeletal muscle-type progenitor expressing *Myf5*, are multilocular and presents a large number of mitochondria and significant expression of UCP-1 [17]. The BAT locations in rodents are the interscapular, subscapular, axillary, perirenal and periaortic regions [16]. In humans, BAT is found in the cervical, supraclavicular, paravertebral, mediastinal and perirenal regions [16]. The BAT is important to dissipate energy through thermogenesis and maintain body temperature. Thermogenesis without tremor has multiple components, such as diet-induced thermogenesis, exercise-associated thermogenesis and non-exercise activity thermogenesis [15].

Regarding UCP-1, it belongs to a family of mitochondrial anion-carrying prote ins located in the inner membrane of the mitochondria. In BAT, UCP-1 uncouples oxidative phosphorylation, dissipating the electrochemical proton gradient across the inner membrane of the mitochondria, which produces heat and maintains body temperature [32]. Thus, UCP-1 is a crucial molecule in metabolic thermogenesis because it produces heat induced by cold and diet, being a fundamental component in energy expenditure. In

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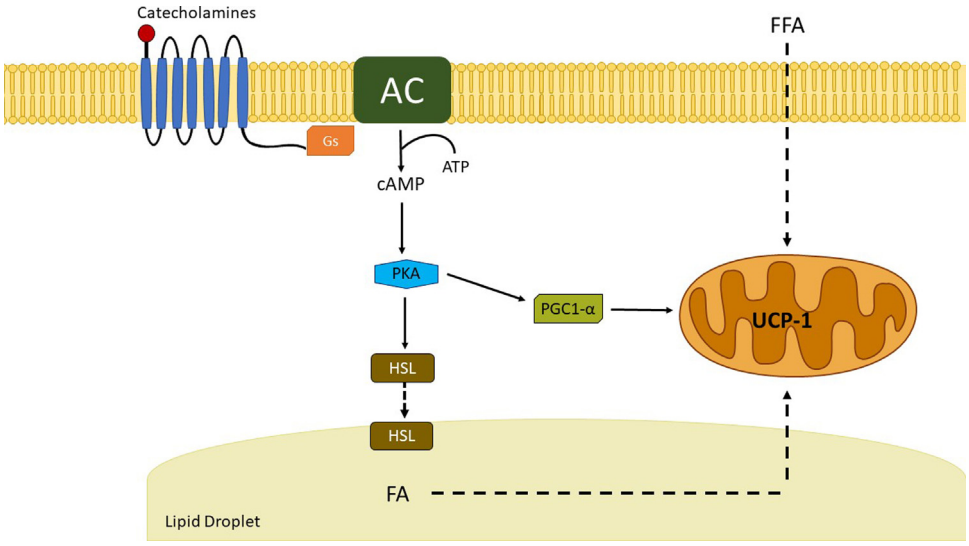

Figure 2 β-adrenergic signaling pathways in brown adipose tissue. AC: adenylate cyclase; cAMP: cyclic adenosine monophosphate; FA: fatty acid; FFA: free fatty acid; Gs: stimulatory G protein; HSL: hormone-sensitive lipase; PGC1α: peroxisome proliferator-activated receptor-γ coactivator 1-α; PKA: protein kinase A; UCP-1: decoupling protein 1; βARs: beta-adrenergic receptors. Continuous black arrow: β-adrenergic signaling pathway; Black seta dashed: lipolysis fatty acids and free fatty acids.

addition, due to its energy expenditure in thermogenesis, the UCP-1 present in BAT is considered a therapeutic target in the fight against obesity and metabolic syndrome [15].

The SNS regulates the BAT thermogenesis, mainly under cold conditions. The β-adrenergic signaling pathways in BAT are shown in Fig. 2. The noradrenaline released by the SNS binds to the β-ARs that activate the AC-cAMP-PKA signaling pathway. Then, PKA phosphorylates intracellular lipases, such as HSL, which hydrolyzes TAGs in FA [33]. Next, FA activate UCP-1 decoupling by displacing the guanidine nucleoside diphosphate (GDP) from UCP-1, and are oxidized by mitochondria as an energy source for heat production. In addition to intracellular lipids, adipocytes can also use as energy source glucose and FFA [34]. The WAT reserves appear to provide the main energy source to sustain thermogenesis by lipolysis, but the lipid stores in the BAT are fundamental for thermogenesis [35].

The three isoforms of β-AR are present in the BAT, and the β_3 isoform is the more prevalent [32]. Studies on genetically modified animal models have shown that mice knockout for the three-receptor subtypes ($\beta1^{-/-}$, $\beta2^{-/-}$, $\beta3^{-/-}$) present hypothermia in response to cold [36]. However, even β_3-AR being predominant in BAT, β_3-$AR^{-/-}$ mice exhibit cold-induced adaptations, such as increased UCP-1 content in BAT [6]. Contrary to these findings, β_1-$AR^{-/-}$ mice present hypothermia in response to cold [4]. In addition, deletion of β_1-AR was also associated with the inhibition of cold-induced BAT hyperplasia [37]. These findings highlight, thus, the importance of β_1-ARs in BAT thermogenesis.

Even direct sympathetic stimulation modulates BAT activity, therefore, other factors such as hormones, cytokines, adipokines, myokines and growth factors may interact with the sympathetic pathway or even modulate this signaling pathway in the regulation of BAT activity [15]. For example, elevated TNF-α concentration suppressed UCP-1 expression in the BAT of a genetic model for obese mice (ob/ob) [38]. It is also known that the peroxisome proliferator-activated receptor-γ coactivator 1-α (PGC-1α) is responsible for co-activating multiple signals for biogenesis and mitochondrial activity in the BAT [39].

Similar to WAT, BAT plays an important endocrine function, inasmuch as it secrets factors such as IL-6, IL-1, fibroblast growth factor 21 (FGF-21), and insulin-like growth factor 1 (IGF-1). These factors will act in organs and tissues such as liver, pancreas, brain and WAT by modulating sympathetic tone, FA oxidation, insulin secretion and glucose uptake [15,32].

Then, because BAT is important to dissipate energy through thermogenesis and maintain body temperature; and that exercise training also induces thermogenesis and is beneficial to reduce body fat, we reviewed here whether aerobic exercise is capable of affecting β-adrenergic signaling pathways in BAT (see section 5).

4. Beige adipose tissue

In addition to the BAT, that is found in specific body deposits, adipocytes with characteristics of brown adipocytes can be found in the WAT, mainly due to cold environmental conditions and β-adrenergic stimulation [40]. Such phenomenon is known as tissue browning and these adipocytes are named ''beige'' or ''brite'' (brown in white) [41]. It is originated from the smooth muscle cell-like with progenitors marked by myosin 11 (*Myh11*) and *Myf5*$^{-}$ [15]. Under stimulation, beige adipocytes also are multilocular and have multiple mitochondria and expression of UCP-1. These adipocytes can also originate from mature white adipocytes in response to cold or β-adrenergic stimulation [16].

The predominant activation of β_3-ARs in WAT by catecholamines induces lipolysis and UCP-1 synthesis, which is not normally expressed in this tissue [42]. Subcutaneous adipose tissue is more likely to browning compared to VAT, since subcutaneous adipocytes are predominantly smaller

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and have a greater potential for cell differentiation [43]. In mice, inguinal adipose tissue has been considered to be the deposition of beige adipocytes, due to its greater sympathetic innervation and higher noradrenaline concentration [33].

Although only partially elucidated, the browning process seems to be controlled by factors such as nutritional and metabolic status, physical activity level and environmental condition [32]. Factors like the gene expression of PGC-1α and PR domain containing 16 (Prdm16) have also been associated with the browning process. Overexpression of the Prdm16 gene is associated with increased energy expenditure, lower body weight gain and improved glucose tolerance in obese mice [44]. The interest in this tissue is due to its capacity to increase energy expenditure, being a potential therapeutic target in the treatment of obesity and associated diseases.

Therefore, since WAT browning stimulates thermogenesis and increases energy expenditure; and that exercise training triggers thermogenesis and is beneficial to reduce body fat, here we examined whether aerobic exercise is efficient to alter WAT browning (see section 5).

5. Exercise and adipose tissue

While physical inactivity is considered one of the most important public health problems of the 21st century, regular physical activity promotes important health benefits because it can reduce risks for chronic diseases, such as obesity, hypertension, DM2 and cancers [45]. In addition, exercise training has not only prophylactic value, but also therapeutic effects. In this way, our focus in this review was to examine the effects of aerobic exercise on adipose tissue metabolism, although studies on exercise training and obesity is not limited to lipolysis and BAT, as lipid oxidation, eating behavior and epigenetic reprogramming are also under investigation.

Aerobic exercise training is able to reduce adipocyte size and lipid content by repeated activation of lipolysis, since an exercise session can reduce FA synthesis and increase lipolysis in adipose tissue. Moreover, it leads to skeletal muscle adaptations, like increased mitochondrial density and proliferation of capillaries and proteins, that improves the transport and oxidation of FFA [46].

The increased use of FA during exercise requires the interaction of neural, hormonal, circulatory and muscular factors, which increases energy demand and facilitate the oxidation of intramuscular FFA and TAG in skeletal muscles [46]. The effects of exercise on β-adrenergic signaling pathway in WAT and BAT are illustrated in Fig. 3. Elevated catecholamines during exercise are responsible for activating the β-adrenergic signaling pathway in adipocytes, increasing lipolytic activity through HSL phosphorylation (Fig. 3A). Lipolysis may also be activated by ANP, which are involved in lipid mobilization during exercise. For example, Moro et al. [11] demonstrated that, under β-adrenergic inhibition, exercise was capable of increasing the concentrations of circulating ANP in humans. In addition, exercise may also increase lipolysis in adipose tissue via the paracrine actions of IL-6 secreted by skeletal muscle into the systemic blood stream [47].

The immune cells of adipose tissue are also affected by obesity and exercise. It is suggested that, by limiting the expansion of adipose tissue, exercise training may attenuate the changes resulting from obesity in the immune cells of this tissue [48]. For example, obese mice submitted to moderate-intensity exercise training had a reduction in infiltrated M1 macrophages and in proinflammatory cytokines (i.e. TNF-α and IL-6) in their VAT, compared to that of control mice [49]. In addition, moderate-intensity exercise training also induced phenotypic alteration of M1 macrophage into M2 macrophage in the adipose tissue of obese mice [50].

The VAT seems to be more sensitive to exercise training than SAT. The greater reduction in VAT in response to exercise training as compared to SAT appears to be related to the higher lipolytic response and triglyceride depletion in VAT [17]. This tissue exhibits higher and lower density and sensitivity of β-ARs and α-ARs, respectively [51]. Moderate-intensity aerobic exercise training has been shown to reduce VAT in obese mice [52]. The visceral fat reduction induced by exercise training may mediate the anti-inflammatory effect, with subsequent reduction in the concentrations of pro-inflammatory adipokines [28]. The anti-inflammatory effect of exercise training is also associated with reduced recruitment of M1 macrophages [49] and, consequently, reduction of pro-inflammatory cytokines (i.e. TNF-α and IL-6) in adipose tissue of mice [5].

Different mechanisms may contribute to this anti-inflammatory effect of exercise training:

- increased release of cortisol and adrenaline from the adrenal glands [53];
- increased myokines production and release;
- reduction in TLR-4 expression in monocytes and macrophages, which inhibits the pro-inflammatory cytokines cascade [54];
- inhibition of monocytes and macrophages infiltration into adipose tissue;
- change in macrophages phenotype present in adipose tissue;
- reduction in pro-inflammatory monocytes circulation and;
- increase in regulatory T cells circulation [28].

Regarding myokines, their discovery highlights the association between exercise and inflammation. After an exercise session, the release of myokines (i.e. IL-6, TNF-α, IL-10) into blood stream may influence metabolism and modify the production of cytokines in other tissues and organs [55]. Interleukin 6 has pro- and anti-inflammatory effects, and its chronic high level is associated with the development of obesity and DM2. However, the increase in IL-6 due to muscle contractions during exercise and its return to baseline post-exercise concentrations is an important regulator of the cellular metabolism of other tissues [56], as it increases glucose uptake and intramuscular lipid oxidation [8]. The anti-inflammatory effect of IL-6 may be in part due to its ability to increase IL-10 and IL-1ra production by monocytes and macrophages [57].

Despite that, Berthold et al. [58] showed that a single exercise bout high-intensity exercise increased plasma IL-6 in control mice but not in IL-6 knockout (IL-6 iMKO) mice. Furthermore, HSLSer563 and HSLSer660 phosphorylation increased in VAT and phosphoenolpyruvate carboxykinase

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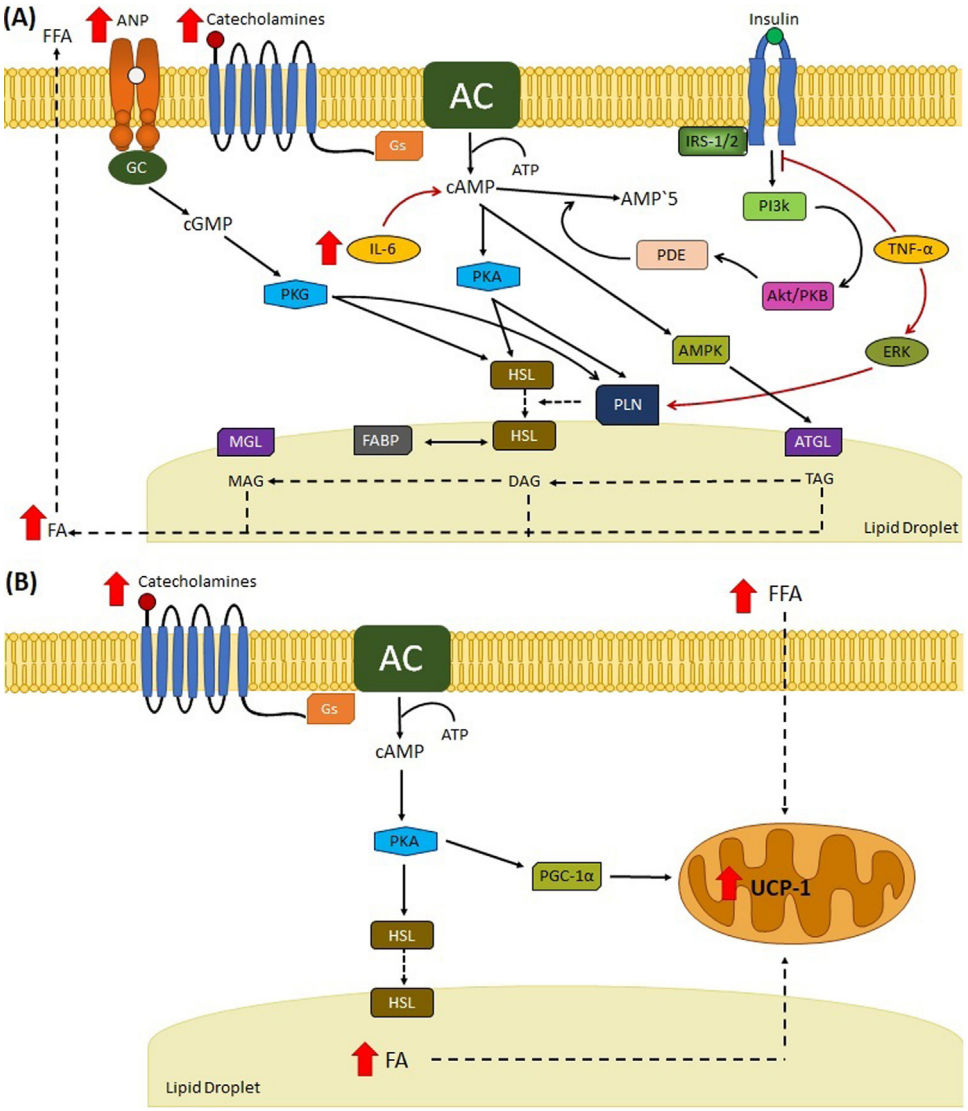

Figure 3 Effect of exercise on β-adrenergic signaling pathways in white (A) and brown (B) adipose tissue. AC: adenylate cyclase; Akt/PKB: protein kinase B; AMP'5: adenosine monophosphate'5; cAMP: cyclic adenosine monophosphate; AMPK: adenosine monophosphate-activated protein kinase; ANP: atrial natriuretic peptide; ATGL: adipose triglyceride lipase; DAG: diacylglycerol; ERK: extracellular signal-regulated kinase; FA: fatty acid; FABP: fatty acid binding proteins; FFA: free fatty acid; GC: guanylate cyclase; cGMP: cyclic guanosine monophosphate; Gs: stimulatory G protein; HSL: hormone-sensitive lipase; IL-6: interleukin 6; IR: insulin receptor; IRS-1/2: substrates of insulin receptor 1 and 2; MAG: monoacylglycerol; MGL: monoacylglycerol lipase; NPR-A: natriuretic peptide receptor; PDE-3B: phosphodiesterase 3B; PGC1α: peroxisome proliferator-activated receptor-γ coactivator 1-α; PI3K: 3-kinase phosphatidylinositol; PKA: protein kinase A; PKG: protein kinase G; PLN: perilipin A; TAG: triacylglycerol; TNF-α: tumor necrosis factor α; UCP-1: decoupling protein 1; βARs: beta adrenergic receptors. Continuous black arrow: signaling lipolytic pathways; continuous gray arrow: action of inflammatory cytokines; dashed black arrow: lipolysis of fatty acids and free fatty acids; Red arrow: effect of exercise; black arrow with bar: blocking the signaling pathway.

protein decreased in SAT with moderate-intensity exercise in both control and IL-6iMKO animals. Both exercise protocols increased pyruvate dehydrogenaseSer232 phosphorylation in VAT only in IL-6 iMKO mice and decreased TNF-α messenger ribonucleic acid (mRNA) in SAT and VAT only in control mice. They suggested that skeletal muscle IL-6 regulates markers of lipolysis in VAT in the basal state and pyruvate availability for glyceroneogenesis in VAT during exercise. Moreover, skeletal muscle IL-6 may contribute to exercise-induced anti-inflammatory effects in SAT and VAT.

Other myokine thought to target human adipose tissue to promote lipolysis seems to be triggered by aerobic exercise. One of such is the growth and differentiation factor 15 (GDF15), that is related to appetite suppression and weight loss. Laurens et al., [59] demonstrated in vitro that human primary myotubes from healthy volunteers submitted to electrical pulse stimulation to mimic either acute intense or chronic moderate exercise increased GDF15 gene expression and secretion, as well as GDF15 protein. In addition, physiological concentrations of recombinant GDF15 protein

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increased lipolysis in human adipose tissue, while blocking GDF15.

Concerning thermogenesis, exercise can increase BAT thermogenesis and WAT browning through the SNS activation (Fig. 3B). The increase of catecholamines induced by exercise activates β-ARs and its signaling pathway that phosphorylates HSL, increasing lipolysis and, consequently, UCP-1 activity [10]. Recently, moderate-intensity aerobic exercise training has been shown to increase UCP-1 protein expression in epididymal WAT of rats [60]. Associated with this mechanism, the increase of natriuretic peptides and myokines by exercise activates BAT thermogenesis and WAT browning via the increase in the expression of UCP-1 [10]. The metabolic changes associated with muscle contractions lead to increases in the release of myokines (i.e. IL-6, IL-15 and irisin) capable of interacting with the adipose tissue [61]. For example, irisin is involved with subcutaneous WAT browning and activation the thermogenesis of this adipose tissue by increasing the UCP-1 expression [62]. Its release into the blood stream occurs by the proteolytic cleavage of fibronectin type III domain containing 5 from skeletal muscle, which is stimulated by the increase in the expression of PGC-1α induced by exercise [62]. In turn, the increase in PGC-1α expression is caused by the elevation of catecholamine by exercise, which is responsible for stimulating the mitochondrial proteins expression involved in FA oxidation [63]. In rats submitted to moderate-intensity aerobic exercise training, for instance, the expression of PGC-1α protein was higher than in control rats [60]. Additionally, aerobic exercise training may increase noradrenergic tone and vascularization in BAT, in addition to increasing the browning of visceral WAT in rats [9]. Furthermore, mice exercised in a voluntary wheel-running presented higher UCP-1 gene expression in SAT than their respective controls [64]. These findings suggest a therapeutic potential of exercise training against metabolic complications related to obesity with visceral fat accumulation.

Related to eating behavior, it has been established that exercise can influence appetite-regulating hormones, although exercise may influence or be influenced by other behavioral, and environmental factors that are thought to affect their post-exercise dietary intake. Indeed, Joo et al. [13] demonstrated that engaging in regular exercise may influence participants to regulate food intake as a means of controlling their body shape or improving health.

Touching epigenetic reprogramming, exercise training appears to affect adipocyte deoxyribonucleic acid (DNA) methylation to affect adipocyte metabolism, including lipolysis and lipogenesis. For example, as reviewed by Dhasarathy et al. [14], six months of exercise promoted association between differential DNA methylation and mRNA expression and a connection to genes known to be involved in the pathogenesis of obesity (i.e. increased lipogenesis in basal states). Moreover, maternal aerobic exercise has been shown to reduce offspring birth weight and protect male offspring from weight gain in adulthood by increasing daytime energy expenditure. In addition, inasmuch as maternal high-fat induces hypermethylation of the PGC-1α promoter and reduces expression of its target genes at birth with maintenance of the effect into adulthood, maternal exercise ameliorated the effect of maternal high-fat diet on PGC-1α hypermethylation and gene expression in mice.

Aerobic exercise may also affect different gene expression which are related to lipid metabolism. For example, low-intensity endurance training was shown to decrease intrahepatic lipid deposits via reduction of the expression of hypoxia-inducible factor-1α and hypoxia-inducible protein 2 in a murine model of non-alcoholic fatty liver disease, thereby reducing the liver fat content [65]. Moreover, the protein kinase CδI (PKCδI), a member of the novel protein kinase C family, is a gene closely related to obesity. Zhao et al., [66] reported preliminary results on that aerobic exercise can regulate the alternative splicing of PKCδI pre-mRNA and increase the level of PKCδI full length, via a regulatory effect of splicing trans-factor SFRS10, thereby it may inhibit the formation of fat cells and hence obesity. Therefore, this issue warrants further investigations.

Regarding exercise mode, we point out that obesity management may also benefit from different exercise type, duration and intensity. For instance, Bittel et al. [67] reported recently that a single bout of resistance exercise reduced the lipaemic response to a mixed meal in obese men with prediabetes without changing chylomicron-TAG or total triacylglycerol-rich lipoprotein (TRL)-TAG fractional clearance rates. However, resistance exercise reduced endogenous and meal-derived fatty acid incorporation into chylomicron-TAG and TRL-TAG. Exercise also increased whole-body lipid oxidation, skeletal muscle mitochondrial respiration, oxidative gene expression in skeletal muscle, and the expression of key lipolysis genes in adipose tissue. Moreover, Sun et al. [68] evaluated the impact of long- term high-intensity interval training (HIIT) on body composition, inflammatory mediators, adipokines, lipolysis genes, and metabolic phenotype in adipose tissue of aged rats and compared the results with those from a volume-matched moderate-intensity continuous training (MICT). They reported that HIIT significantly decreased fat mass, serum high-sensitivity C-reactive protein, perirenal adipose tissue leptin, and increased serum interleukin-10 levels in aged rats, compared to MICT. HIIT also increased pregnenolone, cortisol, and corticosterone in both adipose tissue and serum. Both exercise protocols enhanced hormone-sensitive lipase and adipose triglyceride lipase expression, and decreased palmitic acid, stearic acid, octadecadienoic acid, urea, 1-heptadecanol, and α-tocopherol. While MICT was related to glycerolipid metabolism, HIIT was related to steroid hormone biosynthesis. Furthermore, Miklosz et al. [69] submitted male rats to a single run on a treadmill at the speed of 18 m/min for 30 min; or at the speed of 18 m/min for 120 min; or for 30 min at the speed of 28 m/min. These single aerobic exercise bouts induced changes in the mRNA and protein expression of ATGL, HSL, comparative gene identification 58 and G0/G1 switch gene 2 in skeletal muscles. The strongest pro-lipolytic response was observed in the soleus, followed by the red gastrocnemius. On the other hand, in the white gastrocnemius the expression of components of the lipolytic complex's components was reduced in response to exercise. These changes were not accompanied by alterations in muscle TAG content, with the exception of the reduction observed in the red gastrocnemius after 2-h run. Thus, it was suggested that the magnitude of these effects depend on muscle oxidative capacity, as well as the duration and intensity of exercise. In addition, Thomsen et al. [12]

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demonstrated that sub-maximal aerobic exercise increased the plasma concentrations of mid-regional proANP, a stable marker of ANP secretion, which provides an estimate of lipid oxidation.

Finally, it is noteworthy that post-exercise effects also are important concerning lipid metabolism. According to Lundsgaard et al. [70], it is well known that whole-body FA oxidation remains augmented after an aerobic exercise session. Plasma FA availability is high, during early recovery (i.e. 0—4 h) due to hormonal factors and increased adipose tissue blood flow. Such availability of adipose-derived FA, conjugated with the hydrolysis of lipoprotein lipase-derived very low-density lipoprotein-TAG in skeletal muscle capillaries as well as TAG hydrolysis within the muscle serve as substrates for the increased mitochondrial FA oxidation post-exercise. The increased reliance on FA oxidation in the skeletal muscle cell is probably due to enhanced FA uptake into the mitochondria through the carnitine palmitoyltransferase 1 reaction, and synchronous AMPK-mediated pyruvate dehydrogenase inhibition of glucose oxidation. Thus, glucose taken up by the skeletal muscles is directed towards the resynthesis of glycogen. In addition, FA seem to be critical signaling molecules for peroxisome proliferator-activated receptor signaling post-exercise, and thus for induction of the exercise-induced FA oxidative gene adaptation program in skeletal muscle following exercise.

6. Conclusion

Evidences reported in this review support the idea that exercise plays a key role in the management of obesity. Apart from other exercise mode, aerobic exercise training protects against obesity, since it induces adipose tissue metabolism by increasing lipolysis and browning of WAT, thermogenesis in BAT, and expression of cytokines related to lipid oxidation and inflammation, not to mention eating behavior and epigenetic reprogramming. Such benefits are helpful in the prevention and treatment of obesity. Nonetheless, more studies are needed to better clarify how exercise training modulates the β-adrenergic signaling pathways in adipose tissue metabolism, so that the therapeutic potential of exercise training in the treatment of obesity and its complications is further established.

Disclosure of interest

The authors declare that they have no competing interest.

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