Physical exercise and myokines.

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ABSTRACT

Among the types of muscles present in the body is skeletal muscle, which is the one that allows the development of physical activity thanks to the contractile activity of its muscle cells. It is known that physical exercise involves the release of plasma, by the skeletal muscle, of molecules called myokines as a result of muscle contraction. These myokines seem to be at the base of the beneficial effect of physical exercise on health. For this reason, this article reviews the characteristics and properties of the most important myokines and how they can contribute to a healthier aging.

Key words: physical exercise, skeletal muscle, myokines, endocrine organ, irisin

INTRODUCTION

Any bodily movement produced by skeletal muscles that requires energy expenditure is considered physical activity. According to the World Health Organization, physical exercise is a variety of planned, structured and repetitive physical activity (OMS, 2019). An adequate level of regular physical activity in adults is known to reduce the risk of suffering from certain pathologies.

Skeletal muscles make up most of the body's muscle mass and are composed of striated contractile cells and connective tissue. It is now known that the contractile activity of muscle fibers produces a series of molecules, called myokines. This term refers to a protein synthesized and secreted by a skeletal muscle cell that can exert auto, para and/or endocrine effects. Therefore, skeletal muscle can be classified as an endocrine organ. Contractile activity is the essential regulatory element for the expression and secretion of most of the myokines currently described (Pedersen et al., 2007, Schnyder and Handschin, 2015). This secretion may influence the metabolism of other organs and tissues (Duzova, 2012).

The list of myokines released as a result of muscle contraction has grown steadily (Schnyder and Handschin, 2015). Within this list are: interleukin 6 (IL-6), musclin, myostatin, folistatin, folistatin-like protein 1 (Fstl 1), apelin and irisin (Tencio et al., 2017). Other molecules that are also considered myokines are expressed by skeletal muscle, such as tumor necrosis factor-α (TNF-α), Brain-derived neurotrophic factor (BDNF), IL-8 and IL-15 (Duzova, 2012), leukemia

inhibitory factor (LIF), and more recently Fibroblast growth factor 21 (FGF-21), visfatin (León et al., 2014) and decorin (Manole et al., 2018). Of these, irisin is of special importance, as it is believed that understanding the activity of this protein may be key due to its therapeutic potential in the development of many diseases (Gouveia et al., 2016).

Therefore, the aim of this article has been to review the molecules secreted by skeletal muscle, known as myokines, studying the characteristics, functions, mechanism of action, regulation of secretion with the type of exercise, relationship with pathologies and health benefits of each myokine.

MYOKINES

In recent years, the importance of skeletal muscle as an endocrine organ has been highlighted, as it is known to secrete various molecules that intervene in the regulation and homeostasis of the organism, and that this depends on the exercise performed by skeletal muscles. In this sense, it is known that myokines stimulated by exercise play an important role in protecting against diseases derived from physical inactivity (Pedersen, 2011).

Below is an overview of the main myokines mentioned that are secreted by skeletal muscle:

INTERLEUKIN 6 (IL-6)

It was the first myokine described in muscle secretion. The muscle isoform of the IL-6 secreted by the muscle is considered an antiinflammatory and regulating substance of the acute inflammatory response (León et al., 2014).

The production of IL-6 is closely related to physical exercise, since this implies an increase in the plasma concentration of IL-6 of up to 100 times (León et al., 2014). This increase in plasma IL-6 is not linear in time, as the maximum level of IL-6 is reached at the end of the exercise or shortly thereafter. In addition, fatigue involving muscle damage is not necessary to observe an increase in secretion of this myokine. In fact, it can be seen that there is more secretion in aerobic exercise (running) than in eccentric exercise (power). It has been observed that the duration of exercise is the factor that determines the release of IL-6 into the plasma. Actually, a minimum of 6 minutes of physical activity is required to observe a two-fold increase in plasma IL-6 concentration and a minimum of 6 hours to appreciate a 100-fold increase in plasma IL-6 concentration (Pedersen and Febbraio, 2008).

Physical inactivity, on the other hand, implies the emergence of IL-6 resistance by skeletal muscle and this may be linked to the development of insulin resistance (Tencio et al., 2017). Acute *in vitro* treatment of muscle cells with IL-6 has been shown to lead to increased uptake and translocation of GLUT4 transporter glucose. It also increases insulin-induced glucose uptake, an effect that is regulated by the activation of AMP-activated protein kinase (AMPK) (Pedersen, 2011).

On the other hand, IL-6 has characteristics that make it possible to fight obesity, which is why it is being considered as a pharmacological target in the treatment of obesity. This fact is due to its role in improving the oxidation of fatty acids, an effect that is also controlled by AMPK (Pedersen, 2011).

Likewise, it has been proven that IL-6 intervenes in the control of intake, which evidences its intervention in energetic homeostasis. High levels of IL-6 in the cerebrospinal fluid are negatively associated with body weight, which highlights that a deficiency at the central level of IL-6 is linked to obesity (Santos M. et al., 2013).

Another notable effect of this myokine is anti-inflammatory. IL-6 intervenes in the regulation of TNF-α and originates the production of two anti-inflammatory cytokines, the IL-1R antagonist and IL10 (Pedersen and Febbraio, 2008).

In summary, an increase in the circulating levels of IL-6 causes the effects detailed in the following figure 1.

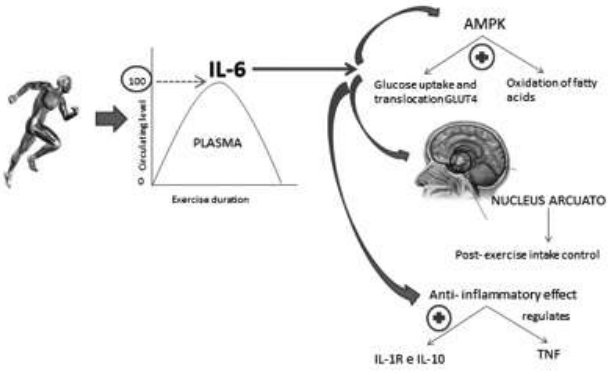

Figure 1. IL-6 in the control of glucose, obesity, intake and inflammation.

However, high concentrations of IL-6 are also observed under pathological conditions (León et al., 2014). In fact, although this myokine has beneficial effects as mentioned above, IL-6 itself is pro-inflammatory and may appear in a number of pathologies such as cancer of breast, lung, colon, prostate or melanoma (Fu et al., 2016). This seems to be related to the fact that high chronic levels of IL-6 are maintained over a prolonged period of time (Pedersen and Febbraio, 2008) as opposed to what occurs in physical exercise in which the increase in IL-6 is of an acute nature. For this reason, it is important to know which is the pattern of IL-6 beneficial secretion and from which level it is considered as inflammatory. Probably, the beneficial or harmful effect of IL-6 will depend on the pattern of acute or chronic secretion, respectively, and the levels reached in plasma, but more studies are needed.

IRISIN

It is a polypeptide hormone released into the blood as a result of exercise (Panati et al., 2016). The increase in physical activity stimulates the production of the peroxisome proliferation activated receptor (PPAR-γ) and its transcriptional coactivator (PGC-1α), which results in an increase in circulating irisin, wich is a product of type III fibronectin that contains a domain 5 (FNDC5). Apparently, after insertion of FNDC5 into the membrane, the cleavage at the level of the binding peptide occurs by means of an unknown proteolytic enzyme, the soluble irisin being released to the extracellular medium(Panati et al., 2016). It acts as a mediator of the effect of physical exercise on the metabolism of adipose tissue (Aydin et al., 2014). Specifically, it has the ability to convert white adipose tissue (WAT) into brown adipose tissue (BAT), which is more thermogenically active, thus giving rise to a phenomenon known as browning (Boström et al., 2012) (Figure 2).

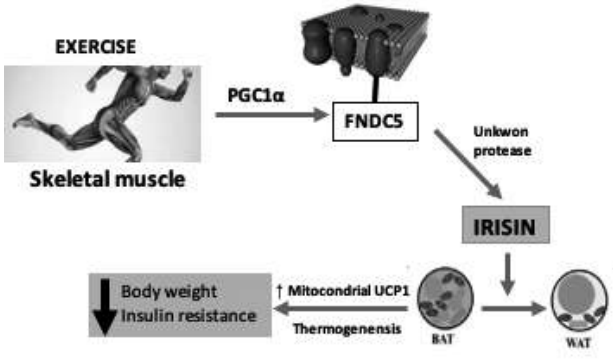

Figure 2. Schematic representation of the mechanism of action of the irisin and its function.

Both aerobic exercise and resistance exercise increase the levels of irisin secreted into the blood plasma. However, the modality of exercise that implies a

greater secretion of this is aerobic exercise (Daskalopoulou et al., 2014).

It should be noted that irisin is not a protein secreted exclusively by muscle tissue, but is also considered an adipokine as it is secreted by adipose tissue (Roca-Rivada et al., 2013).

Several studies have shown a positive relationship between irisin, insulin sensitivity and weight loss (Trujillo et al., 2016). There is controversy about the effects of irisin in relation to obesity and its release during exercise, as it may be conditioned by the type of training carried out, whether acute or chronic. When training chronically, the body composition is modified, decreasing the fat percentage and that makes it possible for the irisin level to decrease (Pimenta et al., 2013). This is why some studies have linked body mass index (BMI) and plasma irisin levels positively (Park et al., 2013), while others have shown an inverse relationship (Moreno-Navarrete et al., 2013). However, during physical exercise a decrease in plasma irisin concentration has been observed as the BMI value increases (Fox et al., 2017). There is insufficient evidence to clarify the contribution of adiposity to basal irisin levels during physical activity. Even so, it must be taken into account that the level of adiposity may alter the level of irisin and this could decrease the response to exercise and its concentration during exercise (Roca-Rivada et al., 2013).

In addition, irisin is attributed with a therapeutic role in insulin resistance thanks to the activation of glucose transporters. It has even been observed that it may accelerate the generation of beta cells from the pancreas due to the stimulation of betatrophin p38 MAPK pathway, which may be a new pathway for the treatment of diabetes (Gizaw et al., 2017).

In relation to aging there are studies on the benefits of irisin in this process. Thus, it is believed that irisin is capable of protecting the brain against the neurodegeneration inherent in aging because it favours neurogenesis. This is because it stimulates the production of BDNF, which plays a critical role in synaptic function and neuronal survival (Kim and Song, 2018). Another noteworthy effect is the fact that, in *in vitro* studies, irisin overexpression reduces the basal transcription of the endogenous mRNA of the enzyme β-secretase (BACE1), an enzyme that originates the proteolytic excision of the amyloid precursor protein (APP) giving rise to the amyloid peptides characteristic of Alzheimer's disease (Wang et al., 2013) (Figure 3).

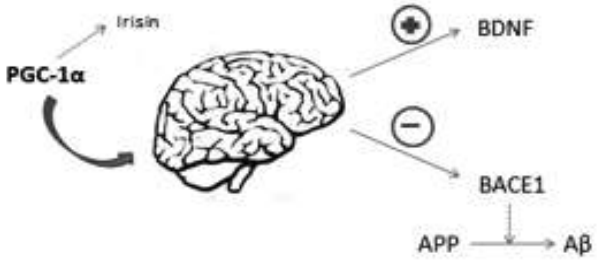

Figure 3. Regulatory effect of irisin on the brain.

On the other hand, it has also been described that irisin slows down the aging process by lengthening telomeres (Trujillo et al., 2016). In this case, the p38 MAPK pathway is also involved, which positively regulates the expression of human reverse telomerase transcriptase (hTERT) (Matsuo et al., 2012).

Irisin is currently considered a molecule with therapeutic potential against cancer. Several findings demonstrate its suppressive effect on malignant breast cancer cells, as well as the ability to induce apoptosis on these cells (Gannon et al., 2014).

APELIN

It is released into the plasma in the form of a protein called preproapelin. It can be found in different isoforms of high molecular weight, all of them coming from the proteolytic excision of the initial

propeptide. The most abundant isoform present is apelin pyroglutamate (Moreno-Aliaga et al., 2008). The latter constitutes the endogenous ligand of apelin receptors (APJ) coupled to Gi and Gq proteins (Tencio et al., 2017).

Aerobic exercise has been shown to favorably affect the secretion of apelin. However, further examination of changes in plasma levels of apelin based on different types of physical exercise is required (Jang et al., 2019).

In conditions of obesity there is an increase in apelin levels, and there is a positive relationship between this and the BMI (Zulet et al., 2007). It appears that this positive relationship is due to the stimulation of fat cell proliferation by apelin.

Another activity related to apelin is intake control. Some authors have shown in rats that injecting apelin decreases intake, but more conclusive studies are needed. It has also been associated with insulinemia, stating that insulin exerts an evident dominance in the gene expression of apelin in adipocytes (Zulet et al., 2007). It is also involved in the secretion of cholecystokinin (CCK), the hormone responsible for the contraction of the gallbladder causing it to release bile into the small intestine (Wang G et al., 2004).

On the other hand, the cardiovascular system is an important source of apelin.There has been an increase in APJ mRNA levels in myocardial tissue as a result of exercise, improving cardiac function and lowering blood pressure (Tencio et al., 2017, Zulet et al., 2007). Treatment with apelin in rats has been shown to increase cardiac pumping and thus blood output from the heart. Finally, its hypotensive effect dependent on nitric oxide (NO) should be highlighted, as well as the vasodilator effect it exerts to counteract the vasoconstriction mediated by angiotensin II (Lee et al., 2006). This last effect can be explained by the homology of the apelin receptor with the angiotensin AT1 receptor (Zhang et al., 2017).

Due to the presence of the APJ receptor in neurons, it has also been described as a neuroprotective agent and regulator of neuroendocrine function. This fact is possible by the activation of Akt and Raf/ERK-1/2 kinases and the release of adrenocorticotropin (ACTH) (Carpéné et al., 2007) (Figure 4).

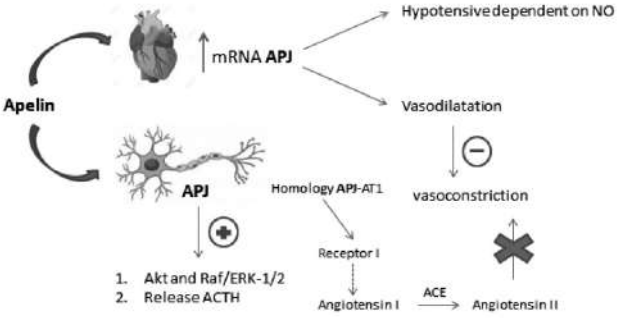

Figure 4. Effects of apelin on heart and neurons.

However, there are studies that show that apelina/APJ system is a mediator of oxidative stress in vascular tissue (Carpéné et al., 2007). Apelin stimulates NADPH oxidase, causing the progression of atherosclerosis. Therefore, APJ may be involved in the development of hypercholesterolemia associated with atherosclerosis, but more studies are needed (Hashimoto et al., 2007).

In general, further research is needed to determine the beneficial effects of apelin.

MUSCLIN

It is a myokine secreted by type II muscle fibers (FT-II). It is a peptide similar to the family of natriuretic peptides (NP) that performs its main actions in muscle and liver (Tencio et al., 2017).

The effects of diet and exercise modality, continuous or in intervals, on the regulation of musclin still need to be clarified (Tencio et al., 2017). However, it has been shown that the concentration of this can be regulated by intermittent exercise of high intensity, indicating that intense physical activity and short duration may achieve an increase in the amount of secreted musclin in people with metabolic syndrome (Castro-Valencia et al., 2018).

It is known that the level of expression of musclin is strongly related to nutritional changes and its physiological role could be linked to glucose metabolism, since it seems that in fasting situations the expression of musclin decreases markedly, while it increases when eating (Nishizawa et al., 2004).

By contrast, in pathological situations such as insulin resistance, an increase in muscline mRNA expression has been observed. An increase in plasma levels of musclin has even been seen in subjects with obesity associated with insulin resistance (Chen et al., 2017).

In terms of musclin effects include increased mitochondrial biogenesis and improved aerobic capacity (Subbotina et al., 2015).

Studies carried out on neuronal cells of primates cultivated *in vitro* under depolarization conditions have shown an increase in the expression and secretion of musclin and also changes in neuronal morphology (Pollen and Kriegstein, 2016).

Moreover, it should be noted that musclin is involved in hypertension and can be considered as a pharmacological target for the treatment of the same. It knows that musclin induces vasoconstriction dependent on the intracellular concentration of calcium and an attenuation of this vasoconstriction has been observed through the treatment with an ab14355 antibody, which blocks NPR-C type receptors present in the cells of the cardiovascular tissue and prevents the effect of musclin (Li et al., 2013).

In conclusion, musclin is a protein that under physiological conditions seems to favour the use of glucose by the muscle and its resistance to exercise by stimulating mithocondrial biogenesis. On the other hand, in conditions related to insulin resistance, such as obesity and diabetes, it seems that there is an overexpression of musclin, caused by basically type II muscle fibers predominant in patients with these disorders, whose purpose is unknown. So the role of musclin *in vivo* in humans is still to be determinated and further studies are needed to clarify its functions under physiological and pathological conditions.

MYOSTATIN

It is a member of the Transforming growth factor beta family (TGF-β) and plays an essential role in the regulation of skeletal muscle mass growth (Lee and Mcpherron, 2001). It interacts with actin type IIB receptors (ActRIIB) and the TGF-β type I receptor (ALK5) and it is thanks to this interaction that it is related to the regulation of muscle mass in an inverse way (Sharma et al., 2015, Tencio et al., 2017).

Thus, with respect to exercise, a decrease in muscle and plasma levels of myostatin has been observed in aerobic exercise (Hittel et al., 2010). The decrease of this myokine promotes an increase in muscle mass, leading to increased energy expenditure (Buehring and Binkley, 2013).

Possible myostatin inhibitors have been investigated with the aim of promoting muscle growth. These include folistatin, which is capable of binding and inhibiting the activity of members of the TGF-β family (Lee and Mcpherron, 2001).

Furthermore, myostatin has been linked to obesity. The decrease of this myokine potentiates an increase

in muscle mass, which leads to higher energy expenditure, increased lipid uptake and a more active metabolism, which means a decrease in adipose tissue (Buehring and Binkley, 2013).

In general, the expression of myostatin is increased in metabolic diseases and it is of interest to decrease the level of myostatin in order to improve these pathologies. Physical activity reduces myostatin levels and is therefore a tool for the recovery of these diseases. However, more conclusive studies are needed to confirm these findings.

OTHERS MYOKINES

In addition to the myokines cited above, other molecules have recently been described that are also secreted by skeletal muscle, but still need more studies to determine their effects. Among others, **DECORIN**, which acts as antagonist of myostatin (Manole et al., 2018) and is in charge of restructuring the muscle during hypertrophy, as it increases the expression of genes involved in skeletal muscle growth pathways (Kanzleiter et al., 2018), 2014); and the **FIBROBLASTIC GROWTH FACTOR 21 (FGF 21)**, whose level is increased in certain respiratory deficiencies causing an improvement in the mitochondrial activity of the skeletal muscle cell (Ji et al., 2015).

CONCLUSIONS

Myokines are the link that makes it possible to understand the relationship between physical activity and metabolic changes and the adaptations that usually arise in organs and tissues with exercise.

More information on the relationship between fibre types and myokines is needed to clarify the link between function and muscle development. In addition, more studies are needed on the changes driven by different modalities of exercise in myokines, either continuous or at intervals, as well as on the physiological differences observable between muscle groups in different parts of the body.

In conclusion, we can see muscle as a more complex tissue thanks to its endocrine function. In addition, a better understanding of its functionality will allow us to develop future preventive and efficient measures against aging and as a powerful therapeutic tool. This fact has meant a change of focus in pathological situations such as obesity or metabolic syndrome, not only paying attention to adipose tissue but also to skeletal muscle.

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