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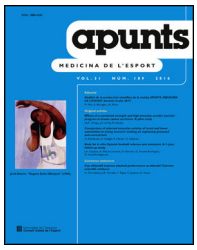

REVIEW

A systematic review of ''myokines and metabolic regulation''

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KEYWORDS
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Abstract Bad habits such as sedentary lifestyle, obesity or overfeeding, are related to the production of chronic pro-inflammatory states, the main risk factor for the development of chronic noncommunicable diseases (CNCD). However, modifying only the body weight does not reduce the risk, it is necessary to increase muscle mass, this implies there is a beneficial relationship associated with the muscle tissue that is not fully elucidated. During the last years, the most interesting cellular explanations have focused on the production of muscle cytokines called myokines, among which stand out interleukin 6, the inhibitory factor of leukemia, with others recently studied such as mionectine and muscline. Due to the multiple advances, this intends to present the most recent and representative findings about myokines, correct concepts and demonstrate their applicability in the prescription of physical exercise for health.

PALABRAS CLAVE
Miocinas;
Regulación metabólica;
Ejercicio

Revisión sistemática de ''miocinas y regulación metabólica''

Resumen Malos hábitos como el sedentarismo, obesidad o sobrealimentación, se relacionan a la evolución de estados pro-inflamatorios crónicos, principal factor de riesgo para el desarrollo de enfermedades crónicas no transmisibles (ECNT). Sin embargo, modificar únicamente el peso corporal no reduce el riesgo, es necesario también aumentar la masa muscular, dando a entender que existe una relación benéfica asociada a este tejido que no está totalmente dilucidada. Durante los últimos años, las explicaciones celulares más interesantes se han enfocado en la producción de citokinas musculares denominadas miokinas, dentro de las que se destacan la interleucina 6, el factor inhibidor de la leucemia, entre otras recientemente estudiadas como

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lo son la mionectina y la musclina. Debido a los múltiples avances, se realiza una revisión que pretende: presentar los hallazgos más recientes y representativos acerca de las miokinas, corregir conceptos y demostrar su aplicabilidad en la prescripción del ejercicio físico para la salud.

Introduction

Lifestyle changes in recent times widely involve a sedentary lifestyle, overeating, obesity and continuous exposure to toxic substances. These changes are associated with the development of chronic pro-inflammatory conditions which constitute the main risk factor for the development of chronic non-communicable diseases (CNCD).[1] This pro-inflammatory condition involves cytokines mainly produced by the immune system, fatty tissue or immune system cells associated with fatty tissues (and in particular macrophages). These cytokines are currently termed adipokines and their receptors are expressed in multiple organs, contributing to the development of CNCD.[2]

In addition to the extensive evidence connecting the presence of adipokines with CNCD, it has now become clear that a reduction in the quality and quantity of skeletal muscle mass is also a risk factor in the development of CNCD.[3] Good health maintenance thus requires not just being a suitable weight but also improving muscle mass.[4]

During the last few decades, many research projects have studied the existing relationship between beneficial systemic response and muscle contraction generated by exercise. It is known that the skeletal muscle (SM) generates glucose-lowering and antioxidant responses,[5] but the most interesting cellular explanations have focused on the production of muscle cytokines with both endocrine and auto/paracrine action called myokines.[6]

Since 2000 when Interleukin 6 (IL-6) was found to be produced by SM as a response to muscle contraction,[7] several studies have been conducted which have led to the discovery of new myokines and to an understanding of their role in the process of physiological regulation of physical exercise, both in people who are apparently healthy and in chronically ill patients.

In 2012 our work group published the review ''The role of the production of myokines through exercise'',[8] where the most relevant findings on the concept of myokines and their relationship with exercise at that time were addressed. Due to the many advances in this respect, the purpose of our present review is to present the most recent and representative findings on myokines, correct several concepts and demonstrate their applicability in the prescription of physical exercise for health.

Methodology

We performed a systematic exploratory review (Scoping review) due to the complexity of locating controlled clinical trials, following the PRISMA[9] review standardisation recommendations. Original articles and systematic reviews which included the search terms: myokines, physical exercise and metabolic regulation, as the study aim, were selected in English and Spanish between January 2007 and November 2017.

The data bases used were: Pubmed, Web of Science, Ovid, Science Direct, the search chain used the terms: (Myokines AND exercise), (Interleukin 6 AND exercise), (LIF AND exercise), (Interleukin 15 AND exercise), (BDNF AND exercise), (FGF21 AND exercise). In total, 3671 articles were found, 75 articles of which were selected, including 4 articles which were considered in the review, due to their relevance. The flow diagram of the search and selection of articles is contained in Fig. 1.

Results

The skeletal muscle (SM) as an organ with endocrine properties

For a long time the SM was considered to be an organ solely restricted to locomotion, protein storage and heat generation. However, it is now known that the SM has a high capacity for gene expression and repression through intracellular signals which become particularly present during exercise. The second messengers identified include: the increase in intracellular calcium, the depletion of adenosine triphosphate (ATP), Nicotinamide adenine dinucleotide (NAD) and the increase in reactive oxygen species (ROS) in addition to extracellular signals such as extracellular oxygen pressure, endocrine signalling and mechanical stimuli.[10]

The main regulator of gene activity with regard to exercise is made up of the peroxisome proliferation-activated receptor-gamma coactivator 1α (PCG-1α),[11] a protein which is necessary for gene transcription and which induces, among other functions, adaptive SM processes. Some responses associated with PCG-1α are: the increase in the expression of insulin receptors, the uptake of fatty acids and glucose, glycogen storage and mitochondrial biogenesis.[11]

PCG-1α also promotes the synthesis of myokines with an endocrine effect on the SM itself and on fatty tissue organs,[12] bone,[13] brain,[14] pancreas,[15] intestine,[16] and brown fat,[17] among others. The term myokine was coined in 2003 by Dr. Bente Klarlund Pedersen in the muscle research centre in Copenhagen - Denmark[18] and through the muscle secretoma study hundreds of substances have been found to be expressive in response to exercise.[19] A graphic summary of the production of myokines through exercise is contained in Fig. 2.

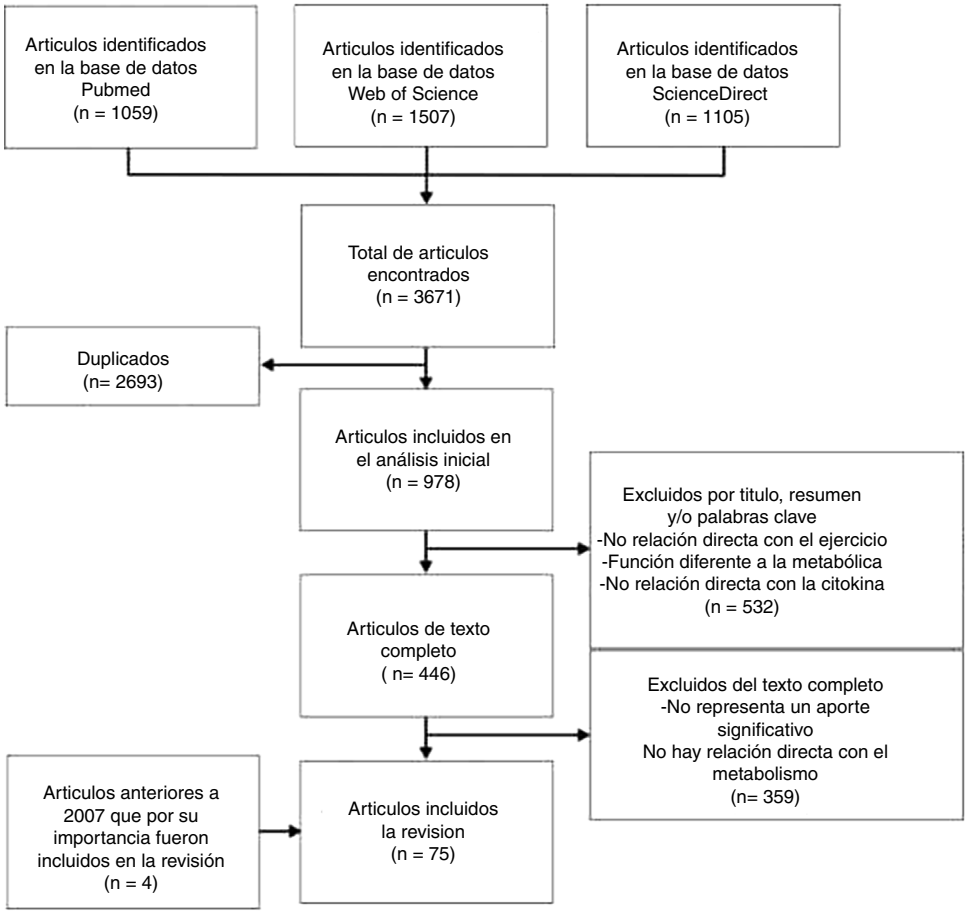

Figure 1 Flow diagram of the search and selection of articles.

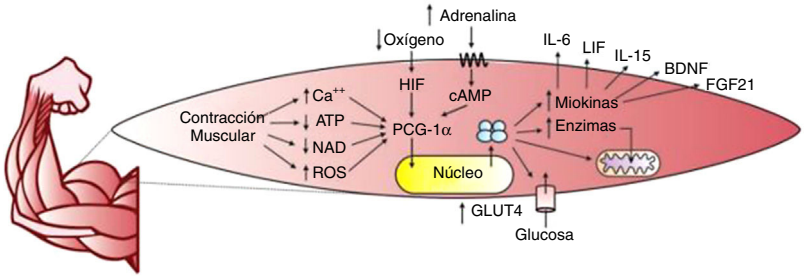

Figure 2 ATP = adenosine triphosphate, NAD = Nicotinamide Adenine Dinucleotide, ROS = Reactive Oxygen Species, HIF = hypoxia inducible factor, cAMP = cyclic cAMP, PCG-1α = peroxisome proliferation-activated receptor-gamma coactivator 1α, GLUT4 = glucose transporter 4. IL-6 = Interleukin 6, LIF = leukaemia inhibitor factor, IL-15 = Interleukin 15, BDNF = brain-derived neurotrophic factor, FGF21 = fibroblast growth factor 21.

The most recent findings regarding the main myokines and their potential application are described below, both for the advocacy of physical exercise for health and for sports training.

Interleukin 6 (IL-6)

Interleukin (IL-6), is a protein of 212 amino acids and a weight of de ∼26 kDa, produced by fatty tissue, the SM and different immune system cells.[20] It is associated with physical exercise and its plasmatic concentration increases several times after it[21] as a result of muscle contraction and changes in intracellular energy behaviour.[22]

The IL-6 (IL-6R) membrane receptor requires a pair of glycoproteins to act as co-receptors (gp130), to form the complex IL-6-IL6R-gp130 and to activate their intracellular action. Given that few cells express IL-6R, unlike the gp130 present in practically all cellular populations,[23] lIL-6 requires a soluble receptor (sIL-6R)[24] to attach itself to them all.

When soluble receptors are used the signalling pathway is called ''trans'', and when membrane receptors are used the signalling pathway is called ''classic'',[25] with

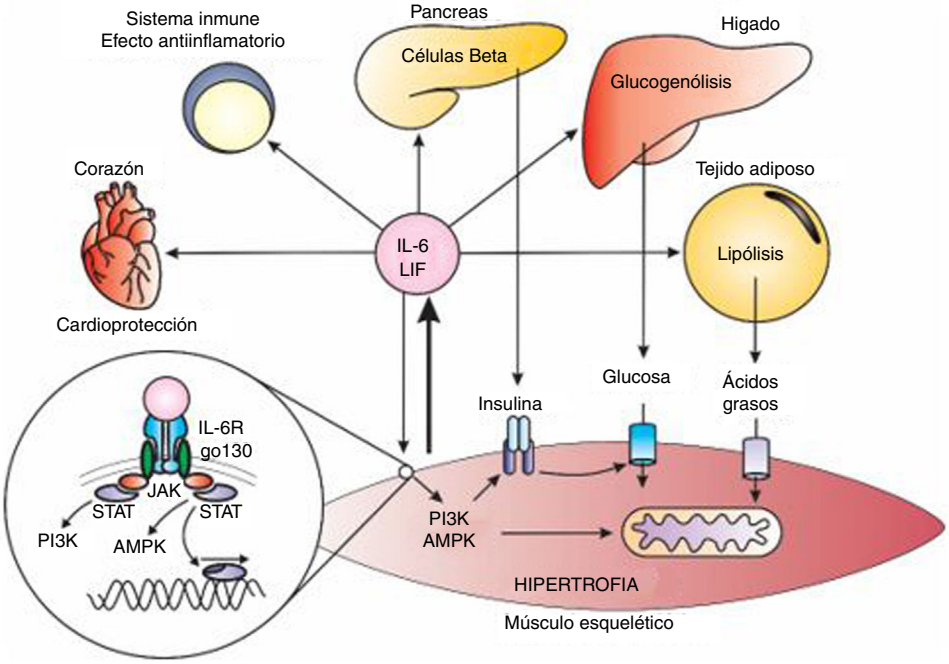

Figure 3 Endocrine and autocrine responses to Interleukin 6 (IL-6) and the leukaemia inhibitory factor (LIF), PI3K = Phosphatidyl Inositol 3 Kinase, AMPK = AMP activated protein kinase, JAK = Janus Kinase, STAT = Signal transduction and activators of transcription.

the classic being anti-inflammatory and the trans being inflammatory.[26]

During physical exercise the SM produces IL-6, but not sIL-6R, since the latter is produced by an enzymatic cleavage from other cells in the presence of inflammatory cytokines such as the tumour necrosis factor-alpha (TNF-α).[27] In this way, IL-6, like myokine, only acts in cells which express IL-6R. On uniting with its receptor, the intracellular signalling involves Janus Kinases (JAK), which phosphorylate proteins responsible for the transduction signals and activators of transcription (STAT), which promote protein transcription in the nucleus.[28] The JAK also phosphorylate kinase proteins activated by AMP (AMPK) and Phosphatidyl Inositol 3 Kinase (PI3K),[29] enhancing uptake and use of energetic substrates, the increase in sensitivity to insulin and oxidation of fatty acids.[30] In addition to this, the IL-6 plays a part in hypertrophy and myogenesis through stimuli generated on satellite cells.[31]

Furthermore, IL-6 increases lipolysis and sensitivity to insulin in fatty tissue,[32] optimises the production of insulin in the pancreas[33] and increases glycogenolysis and lipolysis in the liver.[34] It has also been discovered that the sharp rise of IL-6 in the heart, limits cardiac lesions and has a cardio protective effect, in contrast to chronic elevation where there are deleterious effects.[35]

The sharp rise of plasmatic concentration of IL-6 also has an anti-inflammatory effect and regulates the acute inflammatory response. This occurs when the liberation of anti-inflammatory cytokines enables IL-1 (IL-1ra) and IL10[40] receptor antagonists and inhibit the production of the tumour necrosis factor alpha (TNFα).[36]

Growing evidence of the beneficial effects of IL-6 are a contrast to the classical vision of its inflammatory effect. During exercise IL-6 may increase its baseline concentration up to 100 times, with the sharpest increase having a medium short life, unlike inflammation where the IL-6 increases in the company of other inflammatory cytokines such as TNF-α[37] (Fig. 3).

Leukaemia inhibitory factor (LIF)

The LIF is a 19.7 kDa protein made up of 181 amino acids associated with the differentiation of leukaemia myeloid cells and with stimulus for the formation of haematopoietic cells.[38] LIF shares the co-receptor gp130 with IL-6, and therefore has a good proportion of inflammatory and anti-inflammatory effects. With regard to exercise, LIF is associated with muscle hypertrophy[39] and with muscle hyperplasia.[40] due to paracrine action on satellite cells. It has also recently been suggested that LIF increases glucose uptake by the MS[41] in mice (Fig. 3).

Interleukin 15 (IL-15)

IL15 is a cytokine of 12.9 kDa, which was discovered in 1994 in T lymphocytes and which has usually been linked with inflammatory processes.[42] However, IL15 is also produced by the SM in response to exercise (particularly in strength training),[43] and IL-15 (IL15Rα) receptors have been found in the cells responsible for energy control: the rhabdomyocytes, adipocytes and hepatocytes.[44]

The intracellular signalling of IL15Rα is also associated with the JAK/STAT system, which explains the similarity existing in metabolic response with IL-6 and LIF.[45] A major expression of IL-15 in the SM leads to greater uptake of glucose (seemingly due to the expression of GLUT4 receptors),[46] greater uptake of fatty acids and an increase

in the gene expression which promotes oxidative processes[47] generating an additional antioxidant effect.[48] Initially IL-15 was shown to be an activator of protein synthesis but recent evidence has focused not just on its anabolic action but on its effect at rhabdomyocytes metabolism regulation level.[49]

In fatty tissue IL-15 promotes lipolysis on producing greater mitochondrial activity[50] and inhibiting the differentiation of preadipocytes.[51] There is thus an inversely proportional relationship between the concentration of IL-15 in plasma and fatty tissue, particularly visceral.[52] In brown fat, IL-15 increases the expression of uncoupling proteins, the transport of fatty acids and the thermogenic effect,[53] which is an indication that IL-15 could generate interesting changes in body composition. However, the previously described effects are the results of experimentation in mice, and physiological responses in human beings are yet to be studied.[54]

IL-15 has recently been described as a major modulator of the immune system with an anti-inflammatory effect, on reducing the expression of TNF-α,[55] with a potentially beneficial effect in illnesses such as obesity and diabetes mellitus type 2 (DM2).[56]

Brain-derived neurotrophic factor (BDNF)

BDNF is a protein with a weight of 27 kDa, produced in particular by the central nervous system, with a major role in neuronal development and in the processes of memory and learning.[57] Low levels of BDNF have been found in neurodegenerative and metabolic diseases such as obesity, DM2 and cardiovascular disease.[58]

BDNF is attached to a kinase B receptor related to tropomyosin (TrkB), where it interacts with different second messengers including PI3K, and this to a large extent explains its metabolic and mitogenic functions.[59] At present, BDNF is considered a myokine, produced during particularly aerobic physical exercise and under energetic stress conditions.[60,61]

Due to autocrine action, BDNF plays an important role in regeneration and probably in muscle adaptation secondary to exercise.[62] Due to endocrine action, changes in plasmatic BDNF caused by physical exercise are related to effects in the brain cortex, optimising the execution of superior mental functions, particularly in older adults.[63] In addition, BDNF generates greater oxidation of fats, a reduction in the size of fatty tissue, greater sensitivity to insulin and a reduction in appetite due to direct interaction on a hypothalamic level.[64]

Fibroblast growth factor 21 (FGF-21)

FGF-21 belongs to a family of growth factors produced by several cells and with controversial physiological effects.[65] It forms part of a superfamily of growth factors and its molecular weight ranges between 17 and 26 kDa.[64] FGF-21 is attached to a membrane receptor (FGFR1) and relies on an enzymatic cofactor called β-Klotho. The complex FGFR1/β-Klotho is found in the fatty tissue and the SM, and is intracellularly linked with the phosphorylation of STAT and other protein expression regulators such as the kinase proteins activated by mitogens (MAPK).[66]

FGF-21 is produced by the SM during physical exercise,[67] and leads to enhanced muscle metabolic activity with greater oxidative capacity of glucose and fatty acids,[68] in addition to a major antioxidant effect.[69] However, its myokine effect is disputed since in conditions of non exercise and even in many pathologies it is possible to find that it has increased.

Other myokines with metabolic effect

There are currently other myokines which are the object of investigation due to their potential metabolic effect. Myonectine is linked to exercise with the metabolism of fatty acids,[70] Fibronectin type III (Irisin) has a potential effect on the formation of beige fat from white fat,[71] Beta-amino-isobutyric acid (BAIBA) is able to reduce fatty tissue,[72] the secreted protein acidic and rich in cysteine (SPARC or osteonectin) has an effect on the metabolism of carbohydrates[73] and Musclin induces mitochondrial biogenesis.[74]

Discussion

Myokines, training and health

To guarantee sufficient, continuous support of substrates with which energy reserves may be replaced and tissue repair ensured, the SM generates myokines to promote hydrolysis of triglycerides in fatty tissue and a higher uptake of fatty acids by the SM, among which are found IL-6, IL-15, BDNF, FGF21 and BAIBA. In turn, these generate a reduction in size of adipocytes (particularly visceral), which has an interesting effect in relation to the effects of physical exercise on conditions such as obesity.[75]

Since SM also uses carbohydrates during exercise, several myokines (IL-6, LIF, IL-15, FGF-21, FNDC5, SPARC) also favour the expression of GLUT4 in SM through independent mechanisms of insulin, which reduces plasmatic concentrations in glucose during exercise and up to 24 h after it. These effects reinforce the already well-known impact on the prevention and management of the different forms of Diabetes Mellitus.[75]

Since inflammation, like exercise, requires metabolic substrates, it is possible to understand how several myokines are related to the immune system and are involved in inflammatory processes.

Final considerations

Up until now the findings linked to the understanding of myokines have led to the start of a promising field of research on the chemical communication between muscle and other organs and this will lead to the development of drugs acting as agonists for the beneficial effects of exercise. Yet more important still is the research which may take place on the optimisation and individualisation of training programmes and physical exercise for health. A general summary of known myokines and their effects on the body may be found in Fig. 4.

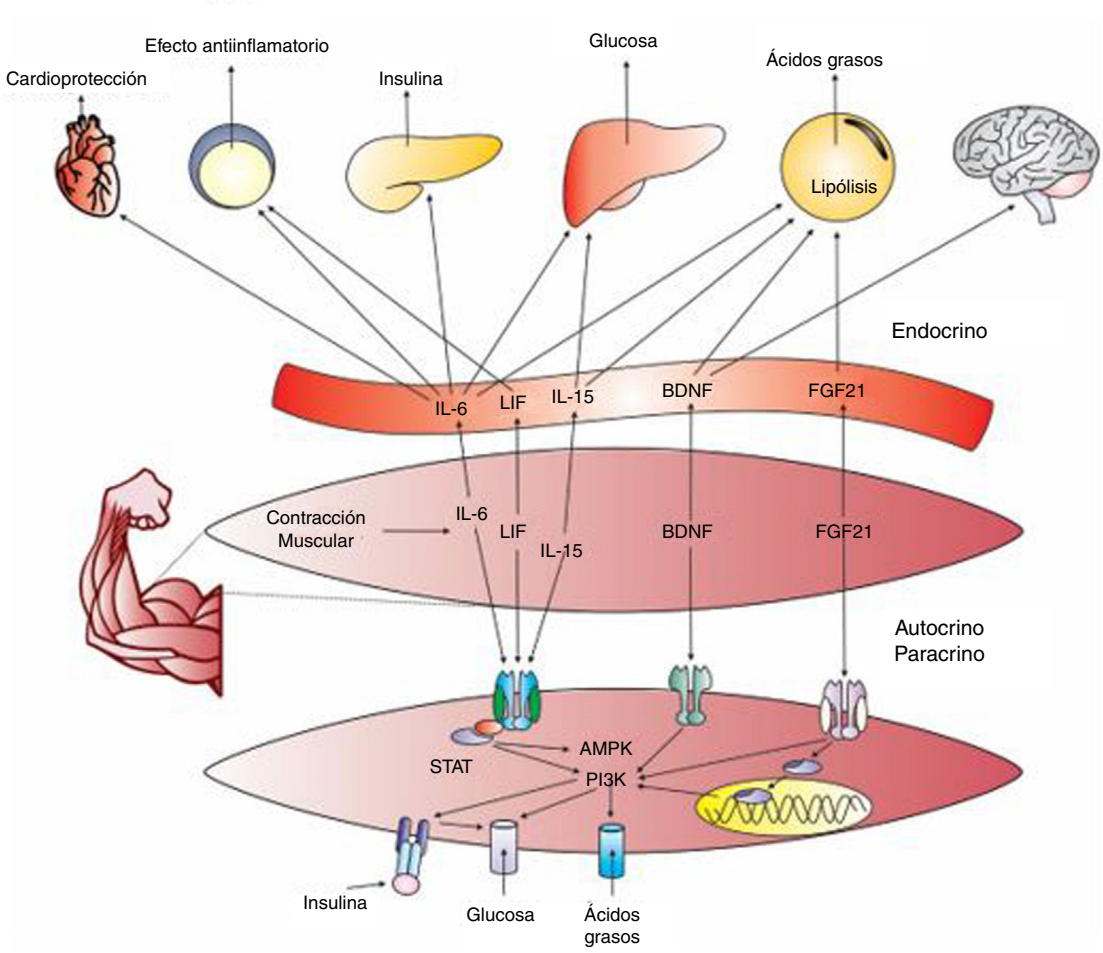

Figure 4 IL-6 = Interleukin 6, LIF = leukaemia inhibitory factor, IL-15 = Interleukin 15, PI3K = Phosphatidyl Inositol 3 Kinase, BDNF = brain-derived neurotrophic factor, FGF21 = fibroblast growth factor 21, AMPK = AMP activated protein kinase, STAT = signal transduction and activators of transcription.

Conflict of interest

Authors declare that they don't have any conflict of interests.

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