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Review Article

Exercise-induced myokines in health and metabolic diseases

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ABSTRACT

Skeletal muscle has been emerging as a research field since the past 2 decades. Contraction of a muscle, which acts as a secretory organ, stimulates production, secretion, and expression of cytokines or other muscle fiber-derived peptides, i.e., myokines. Exercise-induced myokines influence crosstalk between different organs in an autocrine, endocrine, or paracrine fashion. Myokines are recently recognized as potential candidates for treating metabolic diseases through their ability to stimulate AMP-activated protein kinase signaling, increase glucose uptake, and improve lipolysis. Myokines may have positive effects on metabolic disorders, type 2 diabetes, or obesity. Numerous studies on myokines suggested that myokines offer a potential treatment option for preventing metabolic diseases. This review summarizes the current understanding of the positive effects of exercise-induced myokines, such as interleukin-15, brain-derived neurotrophic factor, leukemia inhibitory factor, irisin, fibroblast growth factor 21, and secreted protein acidic and rich in cysteine, on metabolic diseases.

1. Introduction

Many studies have demonstrated the benefits of exercise in preventing all-cause mortality, including cardiovascular disease, metabolic disease, and cancer.[1–3] Exercise reduces the risk of death by preventing metabolic diseases and protects against chronic diseases. Organ-to-organ crosstalk involving muscle contraction at the molecular level is emerging as a field related to exercise.[4] Additionally, adipokines are identified as hormones that mediate crosstalk between adipose tissue and brain, as well as metabolic functions during the activation of tissues.[5] The proinflammatory role of various adipocyte-produced adipokines has also been identified. Tumor necrosis factor, chemokine C–C motif ligand 2, and plasminogen activator inhibitor-1 are proinflammatory adipokines that are overly secreted in obesity, leading to metabolic and cardiovascular diseases.[6] Proinflammatory effects of these adipokines have now been clearly recognized to be counterbalanced by the protective effects of skeletal muscle-secreted peptides.[4]

Exercise-induced benefits are well known to prevent harmful effects of proinflammatory adipokines through skeletal muscle-secreted proteins.[4] A recent study by Pedersen et al.[7] demonstrated the endocrine effects of muscle fiber-derived

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cytokines or peptides produced and secreted during skeletal muscle contraction. The classified these cytokine and peptides as myokines. Furthermore, numerous studies demonstrated that myokines are exercise induced.[8–10] The most well-known exercise-induced myokine interleukin (IL)-6 was the first myokine to be identified in the bloodstream in response to muscle contractions.[11] IL-6 is a peptide that plays an anti-inflammatory role by inhibiting tumor necrosis factor-α; it also improves glucose uptake by stimulating AMP-activated protein kinase (AMPK) signaling.[12–14] Surprisingly, circulating IL-6 levels are increased during exercise without any sign of muscle damage.[15]

Myokines likely provide beneficial metabolic effects during crosstalk between skeletal muscle and liver, and skeletal muscle and adipose tissue.[16–18] Additionally, several studies demonstrated that exercise-induced myokines have positive effects on glucose uptake,[19,20] glucose tolerance,[21] regulation of fat oxidation,[11,21] and satellite cell proliferation.[22,23] Myokines, as one of multiple health factors, constitute an important area of research in metabolic diseases.[24,25] This review summarizes the potential positive effects of exercise-induced myokines, such as IL-15, brain-derived neurotrophic factor (BDNF), leukemia inhibitory factor (LIF), irisin, fibroblast growth factor 21 (FGF-21), and secreted protein acidic and rich in cysteine (SPARC), on metabolic diseases (Fig. 1 and Table 1).

2. Interleukin-15

IL-15 may play a role not only in muscle–fat interaction, but also in skeletal muscle fiber growth.[26] IL-15, a member of the IL-2 superfamily, activates its functions through the β and γ chains of the IL-2 receptor.[27,28] Quinn et al[29] showed that IL-15 can stimulate differentiated myocytes and muscle fibers to accumulate increased amounts of contractile proteins in skeletal muscle. Additionally, IL-15 stimulates muscle-specific myosin heavy-chain accumulation in differentiated myocytes and muscle fibers in culture.[29,30] Among its various roles, IL-15 has been demonstrated to regulate metabolic diseases, such as obesity and diabetes.[21] IL-15 modulates glucose uptake in incubated skeletal muscle and muscle cell cultures.[31] These results suggested that IL-15 may prevent the development of diabetes.[26] Busquets et al[19] showed that *in vivo* administration of IL-15 increased glucose uptake in skeletal muscle and *in vitro* IL-15 treatment increased glucose transporter type 4 mRNA content in C2C12 cells. These findings indicate that IL-15 may be an important mediator (regulator) of skeletal muscle fiber growth, hypertrophy, and glucose uptake.

Numerous studies demonstrated that exercise alters IL-15 concentration in serum or at the mRNA level. The most noticeable change in serum IL-15 was observed after moderate-intensity resistance training.[32,33] Other studies showed that aerobic training increased IL-15 in human and rodent serum and at the mRNA level.[34,35] Given that IL-15 controls glucose and lipid metabolism, it may have an important role in controlling metabolic diseases, including obesity and type 2 diabetes. However, studies on IL-15 expression in the skeletal muscle and plasma after exercise showed inconsistent results. It is evident that after resistance exercise, IL-15 protein level increases in the plasma[32,33]; however, mRNA levels of IL-15 decrease after 2 hours of intensive strength training.[36] In addition, circulating levels of IL-15 were increased in healthy young men, but remained unchanged after a single bout of treadmill running.[37] Treadmill exercise increased IL-15 expression in the skeletal muscle of high-fat-induced obese rats.[35] Similar treadmill exercise conducted in our laboratory showed an increase of IL-15 expression in the soleus muscle of a transgenic diabetic Zucker rat. Our data also demonstrated that treadmill exercise improved glucose tolerance in the Zucker rat.[38] In addition, 1 hour of acute exercise increased IL-15 expression in Sprague–Dawley rats.[39] These data collectively suggest that exercise-induced IL-15 may be important for the modulation of glucose uptake and improved glucose tolerance. While the role of IL-15 in treating metabolic diseases, such as obesity and type 2 diabetes, has now been revealed, further investigation on changes in IL-15 and its potential role is required.

3. Brain-derived neurotrophic factor

Neurotrophins are well-known regulators of various neuronal processes and act primarily through tropomyosin-related kinase receptor tyrosine kinases. The mammalian family of neurotrophins consists of nerve growth factor, neurotrophin-3, neurotrophin-4/5, and BDNF. Among these neurotrophins, BDNF and its receptor tropomyosin-related kinase B are most widely and abundantly expressed in the brain.[40] To date, numerous studies suggested that BDNF may play a role not only in central metabolic pathways, but also as a metabolic regulator of skeletal muscle. Wisse and Schwartz[41] reported that BDNF is a key modulator of the hypothalamic pathway that controls body composition and energy homeostasis. BDNF is a regulator of metabolism in skeletal muscle[42] and an enhancer of glucose utilization in diabetic skeletal muscle.[43] Current studies demonstrated that BDNF reduces food intake and lowers blood glucose level in genetically modified (db/db) obese mice, suggesting that BDNF plays a role in energy balance and insulin signaling.[44–46] In addition, a recent study suggested that gene transfer of BDNF has therapeutic efficacy in mouse models of obesity and diabetes.[47] It is now known that BDNF is expressed in non-neurogenic tissues, including skeletal muscle. Animal studies demonstrated that BDNF mRNA increases in skeletal muscle in response to contraction.[48,49] Numerous studies showed that BDNF mRNA and protein expression were increased in human skeletal muscle after exercise; however, skeletal muscle-derived BDNF was not released into circulation.[42] Additionally, BDNF increased phosphorylation of AMPK and acetyl-CoA carboxylase-beta, and enhanced fat oxidation. Based on recent research evidence, BDNF appears to be a myokine that acts in an autocrine or paracrine fashion with strong effects on peripheral metabolism, including fat oxidation, and a subsequent effect on the size of adipose tissue.[50]

Skeletal muscle BDNF was reported as a key modulator in metabolic diseases, including type 2 diabetes mellitus. In previous studies about diabetes and BDNF, increased BDNF mRNA in the soleus muscle of diabetic rats compared to age-matched controls indicated that elevated BDNF may protect the distal nerve from the denervated muscle of diabetic rat.[51,52] Our