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Review Article

The Role of Exercise-Induced Myokines in Muscle Homeostasis and the Defense against Chronic Diseases

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Chronic inflammation is involved in the pathogenesis of insulin resistance, atherosclerosis, neurodegeneration, and tumour growth. Regular exercise offers protection against type 2 diabetes, cardiovascular diseases, colon cancer, breast cancer, and dementia. Evidence suggests that the protective effect of exercise may to some extent be ascribed to the antiinflammatory effect of regular exercise. Here we suggest that exercise may exert its anti-inflammatory effect via a reduction in visceral fat mass and/or by induction of an anti-inflammatory environment with each bout of exercise. According to our theory, such effects may in part be mediated via muscle-derived peptides, so-called "myokines". Contracting skeletal muscles release myokines with endocrine effects, mediating direct anti-inflammatory effects, and/or specific effects on visceral fat. Other myokines work locally within the muscle and exert their effects on signalling pathways involved in fat oxidation and glucose uptake. By mediating anti-inflammatory effects in the muscle itself, myokines may also counteract TNF-driven insulin resistance. In conclusion, exercise-induced myokines appear to be involved in mediating both systemic as well as local anti-inflammatory effects.

1. Introduction

Over the past several decades, numerous large cohort studies have attempted to quantify the protective effect of physical activity on cardiovascular and all-cause mortality. A recent meta-analysis included a total of 33 studies with 883,372 participants with a followup time of up to more than 20 years [1]. Concerning cardiovascular mortality, physical activity was associated with a risk reduction of 35%, whereas all-cause mortality was reduced by 33%. Taken together, there is no doubt that physical activity is independently associated with a marked decrease in risk of cardiovascular disease (CVD) as well as CVD mortality in both men and women.

Randomised controlled trials including people with impaired glucose tolerance have found that lifestyle modification (diet and moderate physical activity) protects against the development of type 2 diabetes. A Finnish trial randomised 522 overweight middle-aged people with impaired glucose tolerance to physical training combined with diet or to control and followed them for 3.2 years [2]. The risk of type 2 diabetes was reduced by 58% in the intervention group. The effect was largest in the patients who made the greatest lifestyle modification. An American trial randomised 3,234 people with impaired glucose tolerance to treatment with metformin, lifestyle modification entailing dietary change and at least 150 minutes of physical exercise weekly, or placebo and followed them for 2.8 years [3]. The lifestyle modification reduced the risk of type 2 diabetes by 58%. The reduction was, thus, the same as in the Finnish trial [2], whereas treatment with metformin only reduced the risk of diabetes by 31%. After a median of 4 years of active intervention period, participants in the Finnish study who were still free of diabetes were further followed up for a median of 3 years. During the total followup, the incidence of type 2 diabetes was 4.3 and 7.4 per 100 person-years in the intervention and control groups, respectively, indicating 43% reduction in relative risk. The risk reduction was related to the success in achieving the intervention goals of weight loss, reduced intake of total and saturated fat and increased intake of dietary fibre, and increased physical activity [4].

In humans, type 2 diabetes are associated with impaired cognitive function, including learning, memory, and processing speed [5]. Large longitudinal population-based studies show that the rate of cognitive decline is accelerated in elderly people with type 2 diabetes [6]. A recent review [7] showed that the incidence of 'any dementia' was higher in individuals with type 2 diabetes than in those without. This high risk included both Alzheimer's disease and vascular dementia. Interestingly, a couple of studies suggest that regular exercise also protects against dementia [8–10].

Type 2 diabetes, cardiovascular diseases, colon cancer, breast cancer, and dementia constitute a cluster of diseases that defines "a diseasome of physical inactivity" [11]. Both physical inactivity and abdominal adiposity, reflecting accumulation of visceral fat mass, are associated with the occurrence of the diseases within the diseasome. We recently suggested that physical inactivity leads to accumulation of visceral fat and consequently the activation of a network of inflammatory pathways, which promote the development of insulin resistance, atherosclerosis, neurodegeneration, tumour growth, and thereby the development of the diseases belonging to the "diseasome of physical inactivity" [11].

Chronic inflammation accompanies the diseases within the "diseasome of physical inactivity", potentially explaining the clustering of these chronic disorders in epidemiological studies. The aim of the present review is to summarize the evidence suggesting that regular exercise creates an anti-inflammatory environment, and thereby offers protection against a vast number of chronic diseases.

2. Inflammation as a Cause of Chronic Diseases

Systemic low-grade inflammation is defined as two- to four-fold elevations in circulating levels of proinflammatory and anti-inflammatory cytokines, naturally occurring cytokine antagonists, and acute-phase proteins, as well as minor increases in counts of neutrophils and natural killer cells [12–14]. Chronic inflammation contributes to the development of atherosclerosis, insulin resistance, tumour growth, and neurodegenation [15], and thus directly influences pathogenesis of key importance for the development of the chronic diseases within the "diseasome of physical inactivity" [11].

It appears that TNF-α may play a direct role in the metabolic syndrome, recently reviewed in [16]. In vitro studies demonstrate that TNF-α has direct inhibitory effects on insulin signalling. Moreover, TNF-α infusion in healthy humans induces insulin resistance in skeletal muscle, without an effect on endogenous glucose production [17].

It has also been proposed that TNF-α causes insulin resistance indirectly in vivo by increasing the release of free fatty acids (FFAs) from adipose tissue. TNF-α increases lipolysis in human and 3T3-L1 adipocytes. However, TNF-α has no effect on muscle protein turnover or fatty acid oxidation but increases fatty acid incorporation into diacylglycerol, which may be involved in the development of the TNF-α-induced insulin resistance in skeletal muscle [18, 19]. Moreover, evidence suggests that TNF-α plays a direct role in linking insulin resistance to vascular disease [20, 21]. Several downstream mediators and signalling pathways seem to provide the crosstalk between inflammatory and metabolic signalling. These include the discovery of c-Jun N-terminal kinase (JNK) and I kappa beta kinase (IKK) as critical regulators of insulin action activated by TNF-α [22]. In human TNF-α infusion studies, TNF-α increases phosphorylation of p70 S6 kinase, extracellular signal-regulated kinase-1/2, and c-Jun NH(2)-terminal kinase, concomitantly with increased serine and reduced tyrosine phosphorylation of insulin receptor substrate-1[21]. These signalling effects are associated with impaired phosphorylation of Akt substrate 160, the most proximal step identified in the insulin signalling cascade regulating GLUT4 translocation and glucose uptake [21].

The role of IL-6 in insulin resistance is highly controversial, as reviewed in [16]. Infusion of recombinant human (rh)IL-6 into resting healthy humans does not impair whole body, lower limb, or subcutaneous adipose tissue glucose uptake or endogenous glucose production (EGP), although IL-6 contributes to the contraction-induced increase in endogenous glucose production [16]. A number of studies indicate that IL-6 enhances lipolysis, as well as fat oxidation, via an activation of AMP-activated protein kinase (AMPK), reviewed in [16]. Consistent with this idea, Wallenius et al. [23] demonstrated that IL-6 deficient mice developed mature-onset obesity and insulin resistance. In addition, when the mice were treated with IL-6, there was a significant decrease in body fat mass in the IL-6 knockout, but not in the wild-type mice. To determine whether physiological concentrations of IL-6 affected lipid metabolism, our group administered physiological concentrations of rhIL-6 to healthy young and elderly humans as well as to patients with type 2 diabetes [24, 25]. The latter studies identified IL-6 as a potent modulator of fat metabolism in humans, increasing lipolysis as well as fat oxidation without causing hypertriacylglycerolaemia.

Of note, whereas it is known that both TNF-α and IL-6 induce lipolysis, only IL-6 appears to induce fat oxidation [18, 25]. Although circulating levels of TNF-α and IL-6 coexist in epidemiological studies [26], the biological profiles of these cytokines are very different. TNF-α stimulates the release of IL-6 and one theory holds that it is TNF-α derived from adipose tissue that is actually the major "driver" behind inflammation-induced insulin resistance and atherosclerosis.

Importantly, also tumour progression is stimulated by systemic elevation of proinflammatory cytokines [15, 27]. In addition, a number of neurodegenerative diseases are linked to a local inflammatory response in the brain (neuroinflammation) and systemic inflammation may further exacerbate the progression of neurodegeneration [28].

In summary, inflammation is *directly* involved in the pathogenesis of insulin resistance, atherosclerosis, neurodegeneration, and tumour growth. Therefore, the finding that type 2 diabetes, cardiovascular diseases, Alzheimer's disease and cancer is associated with chronic inflammation suggests that inflammatory mechanisms contribute as causative factors in the development of these disorders.

3. The Myokine Concept

The protective effect of exercise against diseases associated with chronic inflammation may to some extent be ascribed to an anti-inflammatory effect of regular exercise.

In line with the acceptance of adipose tissue as an endocrine organ, we came up with the innovative idea that also skeletal muscle should be viewed as an endocrine organ. We have suggested that cytokines and other peptides that are produced, expressed, and released by muscle fibres and exert paracrine or endocrine effects should be classified as "myokines". This paradigm provides a conceptual basis explaining the multiple consequences of a physically inactive lifestyle. If the endocrine and paracrine functions of the muscle are not stimulated through contractions, this will cause dysfunction of several organs and tissues of the body as well as an increased risk of cardiovascular disease, cancer, and dementia.

Today, it appears that skeletal muscle has the capacity to express several myokines. The list includes IL-6, IL-8, IL-15 [29], BDNF [30], and LIF [31]. In addition, Kenneth Walsh, Boston, has recently identified the myokines FGF21 and Follistatin-like-1 [32, 33].

The prototype myokine, IL-6, appears to be able to mediate metabolic effects as well as anti-inflammatory effects. IL-6 was the first identified and to date most studied myokine. The gp130 receptor cytokine IL-6 was discovered as a myokine because of the observation that it increases up to 100-fold in the circulation during physical exercise. Identification of IL-6 production by skeletal muscle during physical activity generated renewed interest in the metabolic role of IL-6 because it created a paradox. On one hand, IL-6 is markedly produced and released in the post-exercise period when insulin action is enhanced but, on the other hand, IL-6 has also been associated with obesity and reduced insulin action. However, a number of studies during the past decade have revealed that in response to muscle contractions both type I and type II muscle fibres express the myokine IL-6, which subsequently exerts its effects both locally within the muscle (e.g., through activation of AMPK) and—when released into the circulation—peripherally in several organs in a hormone-like fashion. Within skeletal muscle, IL-6 acts locally to signal through gp130Rβ/IL-6Rα, resulting in activation of AMPK and/or PI3-kinase to increase glucose uptake and fat oxidation. IL-6 may also work in an endocrine fashion to increase hepatic glucose production during exercise or lipolysis in adipose tissue, reviewed in [16].

IL-15 is expressed in human skeletal muscle, and has been identified as an anabolic factor in muscle growth, and appears also to play a role in lipid metabolism [34]. Recently, we demonstrated that IL-15 mRNA levels were upregulated in human skeletal muscle following a bout of strength training [35], suggesting that IL-15 may accumulate within the muscle as a consequence of regular training. Interestingly, a negative association exists between plasma IL-15 concentration and trunk fat mass. In support of the human data, we found a decrease in visceral fat mass, but not subcutaneous fat mass, when IL-15 was overexpressed in murine muscle [36]. Quinn et al. found that elevated circulating levels of IL-15 resulted in significant reductions in body fat and increased bone mineral content, without appreciably affecting lean body mass or levels of other cytokines [37]. These findings lend support to the idea that muscle-expressed IL-15 may be involved in the regulation of visceral fat mass.

BDNF is recognized as playing a key role in regulating survival, growth, and maintenance of neurons [38], and BDNF plays a role in learning and memory [39]. Hippocampal samples from Alzheimer's disease donors show decreased BDNF expression [40] and individuals with Alzheimer's disease have low plasma levels of BDNF [41]. Also, patients with major depression have lower levels of serum BDNF than normal control subjects [42]. Other studies suggest that plasma BDNF is a biomarker of impaired memory and general cognitive function in ageing women [43] and a low circulating BDNF level was recently shown to be an independent and robust biomarker of mortality risk in old women [44]. Interestingly, we found low levels of circulating BDNF also in individuals with both obesity and type 2 diabetes [45]. Thus, BNDF is low in people with Alzheimer's disease, major depression, impaired cognitive function, CVD, type 2 diabetes, and obesity.

We studied whether skeletal muscle would produce BDNF in response to exercise [46]. It was found that BDNF mRNA and protein expression was increased in human skeletal muscle after exercise; however; muscle-derived BDNF appeared not to be released into the circulation. In addition, BDNF mRNA and protein expression was increased in muscle cells that were electrically stimulated. Interestingly, BDNF increased phosphorylation of AMPK and Acetyl Co-carboxylase (ACC) and enhanced fat oxidation both in vitro and ex vivo. Thus, we have been able to identify BDNF as a novel contraction-induced muscle cell-derived protein that may increase fat oxidation in skeletal muscle in an AMPK-dependent fashion. BDNF appears to be a myokine that works in an autocrine or paracrine fashion with strong effects on peripheral metabolism, including fat oxidation with a subsequent effect on the size of adipose tissue [30].

In summary, contracting skeletal muscles release myokines, which create a systemic anti-inflammatory environment and exert specific endocrine effects on visceral fat. Such myokines may also work locally within the muscle and exert their effects on signalling pathways involved in fat oxidation and glucose uptake. Taken together, myokines may be involved in mediating the anti-inflammatory effects of exercise.

4. The Anti-inflammatory Effects of an Acute Bout of Exercise

Regular exercise appears to induce anti-inflammatory effects, suggesting that physical activity per se may suppress systemic low-grade inflammation [47]. Several studies show that markers of inflammation are reduced following longer-term behavioural changes involving both reduced energy intake and increased physical activity, reviewed in [48]. However,

the mediators of this effect are unresolved. A number of mechanisms have been identified. Exercise increases the release of epinephrine, cortisol, growth hormone, prolactin, and other factors that have immunomodulatory effects [15, 49].

IL-6 is the first cytokine present in the circulation during exercise and the appearance of IL-6 in the circulation is by far the most marked and its appearance precedes that of the other cytokines. The fact that the classical pro-inflammatory cytokines, TNF-α and IL-1β, in general do not increase with exercise, whereas exercise provokes an increase in circulating levels of IL-1ra, IL-10, and sTNF-R [50, 51], suggests that exercise provokes an environment of anti-inflammatory cytokines. Importantly, we showed that rhIL-6 infusion as well as exercise inhibited the endotoxin-induced increase in circulating levels of TNF-α in healthy humans [52]. The anti-inflammatory effects of IL-6 have also been demonstrated by IL-6 stimulating the production of the classical anti-inflammatory cytokines IL-1ra and IL-10 [53].

Recent work has shown that both upstream and downstream signalling pathways for IL-6 differ markedly between myocytes and macrophages. It appears that unlike IL-6 signalling in macrophages, which is dependent upon activation of the NFκB signalling pathway, intramuscular IL-6 expression is regulated by a network of signalling cascades, including the Ca2+/NFAT and glycogen/p38 MAPK pathways. Thus, when IL-6 is signalling in monocytes or macrophages, it creates a pro-inflammatory response, whereas IL-6 activation and signalling in muscle is totally independent of a preceding TNF-response or NFκB activation.

In summary, the possibility exists that with regular exercise the anti-inflammatory effects of an acute bout of exercise will protect against chronic systemic low-grade inflammation, but such a direct link between the acute effects of exercise and the long-term benefits has yet to be established.

5. Conclusion

The authors suggest that the beneficial effects of regular exercise may be due to the anti-inflammatory effects of muscle contractions. Such exercise effects may be mediated via long-term effects on abdominal adiposity and/or by the anti-inflammatory environment that is created by each acute bout of exercise.

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