JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 2006, 57, Suppl 10, 43–51
www.jpp.krakow.pl

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THE ROLE OF IL-6 IN MEDIATING THE ANTI-INFLAMMATORY EFFECTS OF EXERCISE

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Regular exercise offers protection against all cause mortality and there is evidence from randomised intervention studies that physical training is effective as a treatment in patients with chronic heart diseases, type 2 diabetes and symptoms related to the metabolic syndrome. Chronic diseases such as cardiovascular disease, type 2 diabetes and cancer are associated with chronic low-grade systemic inflammation. It has been demonstrated that regular exercise induces anti-inflammatory effects with elevated levels of anti-inflammatory cytokines and suppression of TNF-α production. Thereby, exercise offers protection against TNF-α-induced insulin resistance. Otherwise, the exercise-induced production and release of IL-6 from myofibers may contribute to abrogate an atherogenic lipid profile, which is often associated with chronic diseases. This review focuses on the anti-inflammatory effects of exercise and how this may contribute to mediate the beneficial health effects of exercise training in patients with chronic diseases associated with chronic low-grade inflammation.

Key words: *anti-inflammation, cytokines, exercise, atherosclerosis, diabetes*

INTRODUCTION

Regular physical activity, independently of BMI, is associated with lower risk of all cause mortality (1). Moreover, physical inactivity has been identified as a stronger predictor than risk factors such as hypertension, hyperlipidemia, diabetes, and obesity for all-cause mortality (2).

Over the past decade, there has been an increasing focus on the role of inflammation in the pathogenesis of atherosclerosis (3). Furthermore, inflammation has been suggested to be a key factor in insulin resistance (4). Low-grade chronic inflammation is characterised by increased systemic levels of some cytokines (5) and C-reactive protein (CRP). Several reports investigating various markers of inflammation have confirmed an association between low-grade systemic inflammation on one hand and atherosclerosis and type 2 diabetes on the other (6). Recent findings demonstrate that physical activity induces an increase in the systemic levels of a number of cytokines with anti-inflammatory properties (7) and skeletal muscle has recently been identified as an endocrine organ, which produces and releases cytokines (also called myokines) (7 - 10).

Given that skeletal muscle is the largest organ in the human body, the discovery of contracting muscle as a cytokine producing organ opens a new paradigm: Skeletal muscle is an endocrine organ which by contraction stimulates the production and release of cytokines, which can influence metabolism and modify cytokine production in tissue and organs.

The protective effects of regular exercise against diseases such as cardiovascular disease, type 2 diabetes, colon cancer and breast cancer has been extensively reviewed (11 - 13).

This review discusses to what extent anti-inflammatory activity induced by regular exercise may exert the beneficial health effects of exercise in patients with chronic diseases.

Chronic low-grade systemic inflammation, insulin resistance and atherosclerosis

The initial cytokines as they appear in the circulation in relation to an acute infections consist of (named in order): TNF-α, IL-1β, IL-6, interleukin-1 receptor antagonist (IL-1ra), and soluble TNF-α-receptors (sTNF-R) and IL-10. IL-1ra inhibits IL-1 signal transduction, and sTNF-R represents the natural occurring inhibitors of TNF-α. Chronic low-grade systemic inflammation has been introduced as a term for conditions in which a 2 to 3 fold increase in the systemic concentrations of TNF-α, IL-1, IL-6, IL-1ra, sTNF-R and CRP is reflected. In the latter case, the stimuli for the cytokine production are not known, but the likely origin of TNF in chronic low-grade systemic inflammation is mainly the adipose tissue.

Mounting evidence suggests that TNF-α plays a direct role in the metabolic syndrome (14). Patients with diabetes demonstrate high mRNA and protein expression of TNF-α in skeletal muscle and increased TNF-α levels in plasma, and it is likely that adipose tissue, which produces TNF-α, is the main source of the circulating TNF-α. Mounting evidence points to an effect of TNF-α on insulin signaling. TNF-α impairs insulin-stimulated rates of glucose storage in cultured human muscle cells and impairs insulin mediated glucose uptake in rats. Obese mice with a gene knock-out of TNF-α are protected from insulin

resistance, and inhibition of TNF-α with an anti-TNF-α antibody treatment improves the insulin sensitivity in the insulin resistance rat model. *In vitro* studies demonstrate that TNF-α has direct inhibitory effects on insulin signalling. Recently, it was demonstrated that TNF-α infusion in healthy humans induces insulin resistance in skeletal muscle without an effect on endogenous glucose production. TNF-α directly impaired glucose uptake and metabolism by altering insulin signal transduction. These data provide a *direct* molecular link between low-grade systemic inflammation and insulin resistance (14).

At resting conditions, acute IL-6 administration at physiological concentrations did not impair whole-body glucose disposal, net leg-glucose uptake, or increased endogenous glucose production in resting healthy young humans (15 - 17). In patients with type 2 diabetes, plasma-insulin decreased in response to IL-6 infusion, suggesting an insulin sensitizing effect of IL-6 (17). Recently, we demonstrated that IL-6 increased glucose infusion rate (18) and glucose oxidation without affecting the suppression of endogenous glucose production during a hyperinsulinemic euglycemic clamp in healthy humans. Infusion of rhIL-6 into healthy humans to obtain physiological concentrations of IL-6, increased lipolysis in the absence of hypertriacylglyceridemia or changes in catecholamines, glucagon, insulin or any adverse effects in healthy individuals (16, 17, 19) and in patients with type 2 diabetes (17). These findings together with cell culture experiments demonstrating that IL-6 alone markedly increases both lipolysis and fat oxidation identify IL-6 as a novel lipolytic factor. Blocking IL-6 in clinical trials with patients with rheumatoid arthritis leads to enhanced cholesterol and plasma glucose levels, indicating that functional lack of IL-6 may lead to insulin resistance and an atherogenic lipid profile rather than the opposite (20 - 22). In accordance, IL-6KO mice develop late onset obesity and impaired glucose tolerance (23).

Given that TNF-α mainly works locally, TNF-α transcription may not always be reflected in enhanced systemic levels of TNF-α. Rather, TNF-α may stimulate IL-6 production and consequently IL-1ra and CRP. A body of evidence points at TNF as a driver in the metabolic syndrome. In our view, chronically elevated levels of IL-6, IL-1ra and CRP are likely to reflect local ongoing TNF-α production.

The anti-inflammatory effects of acute exercise

Typically, 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 level of circulating IL-6 increases in an exponential fashion (up to 100 fold) in response to exercise, and declines in the post-exercise period (24 - 27). The fact that the classical pro-inflammatory cytokines, TNF-α and IL-1β, in general do not increase with exercise indicates that the cytokine cascade induced by exercise markedly differs

from the cytokine cascade induced by infections. Another finding in relation to exercise is increased circulating levels of well-known anti-inflammatory cytokines, cytokine inhibitors such as IL-1ra and sTNF-R (28, 29). Taken together, exercise provokes an increase primarily in IL-6, followed by an increase in IL-1ra and IL-10.

The IL-6 response to exercise has recently been reviewed (10, 24 - 26). A marked increase in circulating levels of IL-6 after exercise without muscle damage has been a remarkably consistent finding. Plasma-IL-6 increases in an exponential fashion with exercise and is related to exercise intensity, duration, the mass of muscle recruited, and one's endurance capacity (10, 24 - 26).

Research within the past few years have demonstrated that IL-6 mRNA is upregulated in contracting skeletal muscle (30 - 35), and that the transcriptional rate of the IL-6 gene is markedly enhanced by exercise (36). In addition, it has been demonstrated that the IL-6 protein is expressed in contracting muscle fibers (37, 38), and that IL-6 is released (33) from skeletal muscle during exercise whereas this is not the case for TNF-α (33, 39). Even moderate exercise has major effects on muscle-derived IL-6 (40, 41).

Data suggest that IL-6 exerts inhibitory effects on TNF-α and IL-1production. IL-6 inhibits lipopolysaccharide (LPS)-induced TNF-α production both in cultured human monocytes and in the human monocytic line U937 (42), and levels of TNF-α are markedly elevated in anti-IL-6-treated mice and in IL-6 deficient knock-out mice (43, 44), indicating that circulating IL-6 is involved in the regulation of TNF-α levels. In addition, rhIL-6 infusion as well as exercise inhibits the endotoxin-induced increase in circulating levels of TNF-α in healthy humans (45). The anti-inflammatory effects of IL-6 are also demonstrated by IL-6 stimulating the production of IL-1ra and IL-10 (46). Whereas IL-10 influences multiple cytokines, (47 - 49), the biological role of IL-1ra is to inhibit signalling transduction through the IL-1 receptor complex (50). The IL-1ra is a member of the IL-1 family that binds to IL-1 receptors but does not induce any intracellular response. Studies have demonstrated that IL-1ra is also an acute phase protein (51) as both cultured human hepatocytes and the human hepatoma cell line HepG2 produce sIL-1ra in response to stimulation with IL-6. A small increase of CRP levels is seen the day after acute exercise of longer duration (26).

The anti-inflammatory effects of regular exercise

Cross-sectional studies demonstrate an association between physical inactivity and low-grade systemic inflammation in healthy subjects (52 - 59) in elderly people (60), as well as in patients with intermittent claudication (61). These correlational data do, however, not provide any information with regard to a possible causal relationship. The finding in two longitudinal studies that regular training induces a reduction in CRP level (52, 53) suggests that physical activity as such may suppress systemic low-grade inflammation.

Mechanism underlying the anti-inflammatory response of acute exercise

Following exercise, the high circulating levels of IL-6 are followed by an increase in IL-1ra and IL-10, and the latter two anti-inflammatory cytokines can be induced by IL-6 (46).

Therefore, IL-6 induces an anti-inflammatory environment by inducing the production of IL-1ra and IL-10, but it also inhibits TNF-α production as suggested by *in vitro* (62) and animal studies (43, 44). In addition, rhIL-6 infusion, which causes an increase in plasma IL-6 mimicking the exercise-induced IL-6 response, inhibited endotoxin-induced increase in plasma-TNF-α in humans (45). However, exercise is likely to suppress TNF-α also *via* IL-6 independent pathways as demonstrated by the finding of a modest decrease of TNF-α following exercise in IL-6 knock-out mice (63). High levels of epinephrine are provoked by exercise and epinephrine infusion has been shown to blunt the appearance of TNF-α in response to endotoxin *in vivo* (64). As epinephrine infusion induces only a small increase in IL-6 (65), the mechanism whereby epinephrine inhibits TNF-α production is not clear. However, it appears that epinephrine and IL-6 inhibit endotoxin-induced appearance of TNF-α *via* independent mechanisms.

It is suggested 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 link between the acute effects of exercise and the long-term benefits has not yet been proven. Given that the atherosclerotic process is characterised by inflammation, one alternative explanation would be that regular exercise, which offers protection against atherosclerosis, indirectly offers protection against vascular inflammation and hence systemic low-grade inflammation.

CONCLUSION

Regular exercise protects against diseases associated with chronic low-grade systemic inflammation. Muscle contraction-induced factors, so-called myokines, may be involved in mediating the health beneficial effects of exercise and play important roles in the protection against diseases associated with low-grade inflammation such as cardiovascular diseases, type 2 diabetes and symptoms related to the metabolic syndrome as well as cancer. In particular, the long-term effect of exercise may to some extent be ascribed to the anti-inflammatory response elicited by an acute bout of exercise, which is partly mediated by muscle-derived IL-6.

Acknowledgements: The Centre of Inflammation and Metabolism is supported by a grant from the Danish National Research Foundation (# 02-512-55).

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Received: October 13, 2006
Accepted: November 20, 2006

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