J Appl Physiol 98: 1154–1162, 2005;
doi:10.1152/japplphysiol.00164.2004.

The anti-inflammatory effect of exercise

Anne Marie W. Petersen and Bente Klarlund Pedersen

Centre of Inflammation and Metabolism at The Copenhagen Muscle Research Centre and The Department of Infectious Diseases, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Petersen, Anne Marie W., and Bente Klarlund Pedersen. The anti-inflammatory effect of exercise. *J Appl Physiol* 98: 1154–1162, 2005; doi:10.1152/japplphysiol.00164.2004.—Regular exercise offers protection against all-cause mortality, primarily by protection against cardiovascular disease and Type 2 diabetes mellitus. The latter disorders have been associated with chronic low-grade systemic inflammation reflected by a two- to threefold elevated level of several cytokines. Adipose tissue contributes to the production of TNF-α, which is reflected by elevated levels of soluble TNF-α receptors, IL-6, IL-1 receptor antagonist, and C-reactive protein. We suggest that TNF-α rather than IL-6 is the driver behind insulin resistance and dyslipidemia and that IL-6 is a marker of the metabolic syndrome, rather than a cause. During exercise, IL-6 is produced by muscle fibers via a TNF-independent pathway. IL-6 stimulates the appearance in the circulation of other anti-inflammatory cytokines such as IL-1ra and IL-10 and inhibits the production of the proinflammatory cytokine TNF-α. In addition, IL-6 enhances lipid turnover, stimulating lipolysis as well as fat oxidation. We suggest that regular exercise induces suppression of TNF-α and thereby offers protection against TNF-α-induced insulin resistance. Recently, IL-6 was introduced as the first myokine, defined as a cytokine that is produced and released by contracting skeletal muscle fibers, exerting its effects in other organs of the body. Here we suggest that myokines may be involved in mediating the health-beneficial effects of exercise and that these in particular are involved in the protection against chronic diseases associated with low-grade inflammation such as diabetes and cardiovascular diseases.

cytokines; atherosclerosis; diabetes; aging; physical activity

CHRONIC DISEASES ARE THE LARGEST cause of death in the world, led by cardiovascular disease (17 million deaths in 2002) followed by cancer (7 million deaths), chronic lung diseases (4 million), and diabetes mellitus (almost 1 million) (160). Not only are cardiovascular disease and Type 2 diabetes leading causes of death and illness in developed countries, but these chronic diseases are becoming the dominating health problem worldwide (79).

Regular exercise offers protection against all-cause mortality, primarily by protection against atherosclerosis, Type 2 diabetes, colon cancer, and breast cancer (7). In addition, physical training is effective in the treatment of patients with ischemic heart disease (55), heart failure (108), Type 2 diabetes (11), and chronic obstructive pulmonary disease (66).

Atherosclerosis is characterized by the accumulation of lipids and fibrous elements in the large arteries. The current views of the pathophysiology of atherosclerosis are changing. The link between lipids and atherosclerosis dominated our thinking until the 1970s (119). The emerging knowledge of vascular biology led to a focus on growth factors and the proliferation of smooth muscle cells in the 1970s and 1980s (119). Over the past decade, however, there has been much focus on the role of inflammation in the pathogenesis of atherosclerosis (68, 69). Furthermore, inflammation has been suggested to be a key factor in insulin resistance (24).

Address for reprint requests and other correspondence: B. K. Pedersen, Dept. of Infectious Diseases, Rigshospitalet, Section 7641, Blegdamsvej 9, DK-2100, Copenhagen, Denmark (E-mail: bkp@rh.dk).

Low-grade chronic inflammation is reflected by increased C-reactive protein (CRP) concentrations and increased systemic levels of some cytokines (118) and several reports investigating various markers of inflammation in different population groups have confirmed an association between low-grade systemic inflammation on one hand and the metabolic syndrome, Type 2 diabetes, and atherosclerosis on the other (5, 30, 36, 39, 40, 48, 70, 80, 110, 152).

Given that chronic low-grade systemic inflammation may be involved in atherosclerosis and diabetes pathogenesis (24, 69) and given the recent finding that physical activity induces an increase in the systemic levels of a number of cytokines with anti-inflammatory properties, we discuss the possibility that physical exercise exerts anti-inflammation and thereby protects against chronic medical disorders associated with low-grade systemic inflammation.

THE PLAYERS IN CHRONIC LOW-GRADE INFLAMMATION

The local response to infections or tissue injury involves the production of cytokines that are released at the site of inflammation. Cytokines are small polypeptides, which were originally discovered to have immunoregulatory roles (2, 3). Some of these cytokines facilitate an influx of lymphocytes, neutrophils, monocytes, and other cells. The local inflammatory response is accompanied by a systemic response known as the acute-phase response. This response includes the production of a large number of hepatocyte-derived acute phase proteins, such as CRP and can be mimicked by the injection of the cytokines TNF-α, IL-1β, and IL-6 into laboratory animals or

humans (2, 3, 25, 25). The initial cytokines in the cytokine cascade are (named in order) TNF-α, IL-1β, IL-6, IL-1 receptor antagonist (IL-1ra), and soluble TNF-α receptors (sTNF-R). IL-1ra inhibits IL-1 signal transduction and sTNF-R represents the naturally occurring inhibitors of TNF-α (2, 3, 25). In response to an acute infection or trauma, the cytokines and cytokine inhibitors may increase severalfold and decrease when the infection or trauma is healed. Chronic low-grade systemic inflammation has been introduced as a term for conditions in which a typically two- to threefold 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 it is assumed that the origin of TNF in chronic low-grade systemic inflammation is mainly the adipose tissue (23, 54).

CHRONIC LOW-GRADE INFLAMMATION IN AGING AND DISEASE

Chronic low-grade inflammation accompanies aging as well as some chronic medical disorders. During aging, increased plasma levels of TNF-α (13, 17, 28, 96), IL-6, IL-1ra (28), sTNF-R (13, 15, 22), and CRP (4) have been demonstrated. These cytokines work in a network, and their levels are found to intercorrelate, e.g., plasma levels of TNF-α were positively correlated with IL-6, sTNF-R, and CRP in centenarians. However, although a linear relationship was found for TNF-α and IL-6, high levels of TNF-α, but not IL-6, were associated with dementia and atherosclerosis (13). Also, elevated levels of circulating IL-6 have been associated with several disorders. Increased levels of both TNF-α and IL-6 have been observed in obese individuals, in smokers, and in patients with Type 2 diabetes mellitus (150), and plasma concentrations of IL-6 have been shown to predict all-cause mortality as well as cardiovascular mortality (49, 151). Furthermore, plasma concentrations of IL-6 and TNF-α have been shown to predict the risk of myocardial infarction in several studies (114, 115), and recently it was shown that the CRP level is a stronger predictor of cardiovascular events than the low-density lipoprotein cholesterol level and that CRP adds prognostic information to that conveyed by the Framingham risk score (116).

LINKING INFLAMMATION, INSULIN RESISTANCE, AND ATHEROSCLEROSIS

Given that low-grade systemic inflammation is found in patients with obesity, insulin resistance, Type 2 diabetes, and atherosclerosis, the question is whether a causal link exists between inflammation on one hand and insulin resistance and dyslipidemia on the other. In the following, we will discuss the individual roles of TNF-α and IL-6.

There is accumulating data to suggest that TNF-α plays a direct role in the metabolic syndrome. Patients with diabetes demonstrate high expression of TNF-α in skeletal muscle (122) and in plasma (35, 74, 159), and it is likely that adipose tissue, which produces TNF-α, is the main source of the circulating TNF-α (23, 54). Accumulating data point to an effect of TNF-α on insulin signaling. TNF-α impairs insulin-stimulated rates of glucose storage in cultured human muscle cells (47) and impairs insulin-mediated glucose uptake in rats (161). Obese mice with a gene knockout of the TNF-α are protected from insulin resistance (147), and inhibition of TNF-α with an anti-TNF-α antibody treatment improves the insulin sensitivity in the insulin resistance rat model (9). TNF-α has direct inhibitory effects on insulin signaling (52, 53, 104), and in addition it has been proposed that TNF-α causes insulin resistance in vivo indirectly by increasing the release of free fatty acids from adipose tissue (10, 44, 46, 125, 126). TNF-α increases lipolysis in human (121, 162), rat (10, 44, 46), and 3T3-L1 adipocytes (90, 113, 125, 126). Recently, it was found that TNF-α had no effect on muscle fatty acid oxidation but increased fatty acid incorporation into diacylglycerol, which may be involved in the development of TNF-induced insulin resistance in skeletal muscle (12).

With regard to IL-6, its role in insulin resistance is highly controversial. In humans, circulating IL-6 levels may (6, 107) or may not (18, 106) be associated with insulin resistance. 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 (71, 132), although IL-6 contributes to the contraction-induced increase in endogenous glucose production (32).

When diabetes patients were given rhIL-6 infusion, plasma concentrations of insulin declined to levels comparable with that in age and body mass index-matched healthy controls, indicating that the IL-6 enhanced insulin sensitivity (105). In vitro studies demonstrate that IL-6 can induce insulin resistance in isolated 3T3-L1 adipocytes (120) and in mice (61). However, the IL-6 concentrations applied in the latter studies were highly supraphysiological with possibly little relevance for human physiology. With regard to the effect of IL-6 on glucose uptake in myotubes, a recent publication by Weigert et al. (157) demonstrated no inhibitory effect of IL-6 on insulin action and glycogen synthesis. Interestingly, IL-6 knockout mice develop impaired glucose tolerance, which is reverted by IL-6 (153).

AMP-activated protein kinase (AMPK) activity stimulates a variety of processes that increase ATP generation, including fatty acid oxidation and glucose transport in skeletal muscle (19). Incubation with IL-6 increases the phosphorylation of AMPK (an indicator of its activation) and that of its target molecule, acetyl CoA carboxylase, in skeletal muscles. In addition, AMPK activity and acetyl CoA carboxylase levels were very low in IL-6 knockout mice, suggesting a role of IL-6 in the regulation of AMPK activity. These data suggest that IL-6 activation of AMPK is dependent on the presence of IL-6 (60).

A number of studies indicate that IL-6 enhances lipolysis (12, 87, 97, 105, 136).

To assess whether IL-6 increases fat oxidation, L6 myotubes were treated with IL-6 or 5-aminoimidazole-4-carboxamide riboside (AICAR), a compound known to increase lipid oxidation. Both IL-6 and AICAR markedly increased oxidation of [^{14}C]palmitate compared with control (105). In accordance, Wallenius et al. (153) 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 patients with Type 2 diabetes (105, 149). The latter studies identified IL-6 as a

potent modulator of fat metabolism in humans, increasing lipolysis and fat oxidation without causing hypertriacylglycerolemia.

Of note, whereas it is known that both TNF-α and IL-6 induce lipolysis, there is only published evidence to suggest that IL-6 induces fat oxidation. A recent clinical trial demonstrated that anti-TNF-α treatment enhanced high-density lipoprotein without influencing low-density lipoprotein, indicating that TNF-α causes a risk lipid profile (109). In contrast, anti-IL-6 receptor treatment induced increase of both high-density and low-density lipoprotein (86).

High levels of IL-6 and TNF-α in patients with the metabolic syndrome are associated with truncal fat mass (101), and both TNF-α and IL-6 are produced in adipose tissue (23, 41, 76, 145). Given the different biological profiles of TNF-α and IL-6 and given that TNF-α can trigger IL-6 release, one theory holds that it is adipose tissue-derived TNF-α that actually is the "driver" behind the metabolic syndrome and that locally produced TNF-α causes increased systemic levels of IL-6.

In this line, we find that genetic epidemiology also supports a differential role for IL-6 and TNF-α. IL-6 is largely regulated at the level of expression, because of the rapid plasma clearance of this cytokine (20). Four polymorphisms exist in the IL-6 promoter, although most population-based studies focus on the G-174-C, where the C allele shows lower IL-6 expression than the G allele (141). The G-174-C genotype is a disease "risk genotype" associated with cardiovascular disease and all-cause mortality in old humans (14), as well as insulin resistance and low energy expenditure (65). Compared with the G-308G genotype, the -308A allele of the TNF-α gene has been shown to increase transcription twofold and, therefore, TNF-α concentration (63, 158). Subjects with risk genotypes for both TNF-α (AA) and IL-6 (CC) have the highest incidence of diabetes (64), favoring the theory that high levels of TNF-α and low production of IL-6 are determining factors in the metabolic syndrome. 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. In our view, chronically elevated levels of IL-6, IL-1ra, and CRP are likely to reflect local ongoing TNF-α production (Fig. 1).

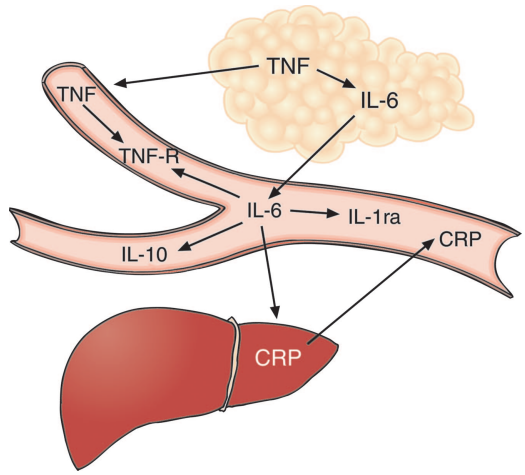

Fig. 1. Chronic low-grade systemic inflammation. The cytokine TNF-α is produced in adipose tissue. TNF-α stimulates the production of IL-6 in adipose tissue and blood mononuclear cells. IL-6 enhances the systemic levels of IL-1 receptor antagonist (IL-1ra), soluble TNF receptor (TNF-R), IL-10, and C-reactive protein (CRP).

CYTOKINE RESPONSES TO SEPSIS AND EXERCISE

Mostly, studies on cytokines come from sepsis research. In sepsis and experimental models of sepsis, the cytokine cascade consists of (named in order) TNF-α, IL-1β, IL-6, IL-1ra, sTNF-R, and IL-10 (3). The first two cytokines in the cytokine cascade are TNF-α and IL-1β, which are produced locally. These cytokines are usually referred to as proinflammatory cytokines (26). TNF-α and IL-1 stimulate the production of IL-6, which has been classified as both a pro- and an anti-inflammatory cytokine (142). The cytokine response to exercise differs from that elicited by severe infections (33, 98, 100, 138). The fact that the classic proinflammatory 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. Typically, IL-6 is the first cytokine present in the circulation during exercise. The level of circulating IL-6 increases in an exponential fashion (up to 100-fold) in response to exercise and declines in the postexercise period (33, 98, 100, 138).

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 (93, 95).

Taken together, exercise provokes an increase primarily in IL-6, followed by an increase in IL-1ra and IL-10. The appearance of IL-6 in the circulation is by far the most marked and its appearance precedes that of the other cytokines (Fig. 2).

IL-6 RESPONSE TO EXERCISE

The IL-6 response to exercise has recently been reviewed (33, 98–100). A marked increase in circulating levels of IL-6 after exercise without muscle damage has been a remarkably consistent finding (21, 29, 43, 50, 81, 82, 84, 85, 88, 91–95, 117, 128, 129, 130, 134, 135, 139, 144). 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 (33, 98–100).

Research within the past few years has demonstrated that IL-6 mRNA is upregulated in contracting skeletal muscle (34, 56, 83, 94, 130, 133) and that the transcriptional rate of the IL-6 gene is markedly enhanced by exercise (58). In addition, it has been demonstrated that the IL-6 protein is expressed in contracting muscle fibers (51, 103) and that IL-6 is released (133) from skeletal muscle during exercise whereas this is not the case for TNF-α (133, 135). Even moderate exercise has major effects on muscle-derived IL-6. Young healthy individuals performed 3 h of dynamic two-legged knee-extensor exercise at 50% of their individual maximal power output. This exercise induced an only moderate increase in heart rate (113 to 122 beats/min) but induced a 16-fold increase in IL-6 mRNA, a 20-fold increase in plasma-IL-6, and a marked IL-6 release from working muscle (38). When the same model was applied in elderly healthy untrained subjects, even higher amounts of IL-6 were released from working muscle during exercise at the same relative intensity (102).

Several studies have reported that carbohydrate ingestion attenuates elevations in plasma IL-6 during both running and

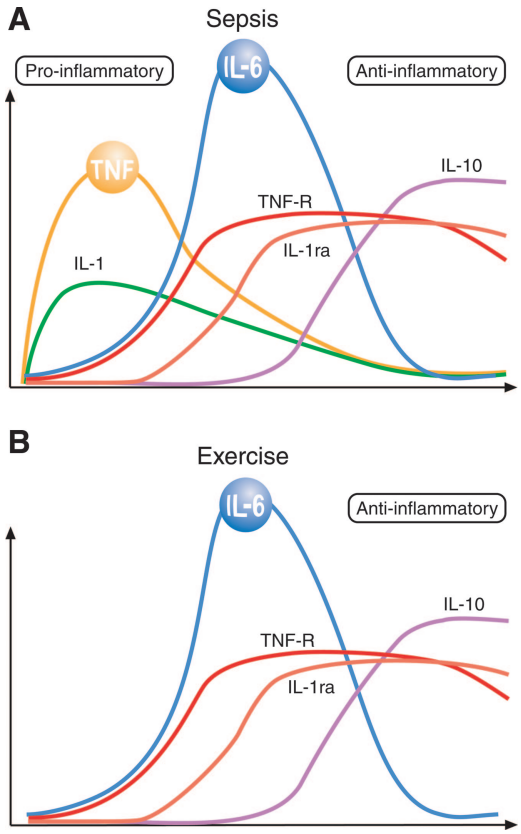

Fig. 2. In sepsis (*A*), the cytokine cascade within the first few hours consists of TNF-α, IL-1β, IL-6, IL-1ra, TNF-R, and IL-10. The cytokine response to exercise (*B*) does not include TNF-α and IL-1 but does show a marked increase in IL-6, which is followed by IL-1ra, TNF-R, and IL-10. Increased CRP levels do not appear until 8–12 h later.

cycling (81, 85). During exercise, carbohydrate ingestion exerts its effect at the posttranscriptional level of IL-6 (34, 128), whereas low muscle glycogen concentration further enhances IL-6 mRNA and transcription rate for IL-6 (58, 130). Therefore, preexercise intramuscular glycogen content appears to be an important stimulus for the IL-6 gene transcription, and it appears that muscle-derived IL-6 acts as an energy sensor. Recent data from our group have demonstrated that infusion of rhIL-6 in human subjects can exert an increase in IL-6 gene expression in skeletal muscle (59), thus demonstrating that muscle-derived IL-6 is regulated by an autocrine mechanism. A number of studies (77, 129, 146) have demonstrated that monocytes are not major contributors to the IL-6 response to exercise. However, small amounts of IL-6 are also produced and released from adipose tissue (71), and studies indicate that also the brain (89) and peritendon tissue (67) may release IL-6 in response to exercise. Although we have yet to determine the precise biological action of muscle-derived IL-6, accumulating data support the hypothesis that the role of IL-6 released from contracting muscle during exercise is to act in a hormonelike manner to mobilize extracellular substrates and/or augment substrate delivery during exercise. In addition, IL-6 has important anti-inflammatory effects (Fig. 3).

ANTI-INFLAMMATORY EFFECTS OF IL-6

Data suggest that IL-6 exerts inhibitory effects on TNF-α and IL-1 production. IL-6 inhibits lipopolysaccharide (LPS)-induced TNF-α production both in cultured human monocytes and in the human monocytic line U937 (123), and levels of TNF-α are markedly elevated in anti-IL-6-treated mice and in IL-6-deficient knockout mice (72, 75), indicating that circulating IL-6 is involved in the regulation of TNF-α levels. In addition, rhIL-6 infusion inhibits the endotoxin-induced increase in circulating levels of TNF-α in healthy humans (127). The anti-inflammatory effects of IL-6 are also demonstrated by the fact that IL-6 stimulates the production of IL-1ra and IL-10 (131). Furthermore, IL-6 stimulates the release of soluble TNF-α receptors, but not IL-1β and TNF-α (142), and appears to be the primary inducer of the hepatocyte-derived acute-phase proteins, many of which have anti-inflammatory properties (2).

ANTI-INFLAMMATORY EFFECTS OF IL-10, IL-1RA, AND CRP

The appearance of IL-10 and IL-1ra in the circulation after exercise also contributes to mediating the anti-inflammatory effects of exercise. The concept that IL-10 acts as an anti-inflammatory molecule was suggested primarily by studies showing inhibition of the synthesis of a large spectrum of proinflammatory cytokines by different cells, particularly of the monocytic lineage. Thus IL-10 inhibits the production of IL-1α, IL-1β, and TNF-α as well as the production of chemokines, including IL-8 and macrophage inflammatory protein-α from LPS-activated human monocytes (78, 111). These cytokines and chemokines play a critical role in the activation of granulocytes, monocytes/macrophages, natural killer cells, and T and B cells and in their recruitment to the sites of inflammation. Taken together, these observations suggested that IL-10 plays an important role in orchestrating the inflammatory reaction involving macrophage/monocyte activation in particular. Addition of IL-10 to LPS-stimulated human mononuclear cells and neutrophils suppresses cytokine synthesis, mainly via the inhibition of the transcription of their corresponding genes (154, 155). IL-10 also prevents cytokine synthesis by posttran-

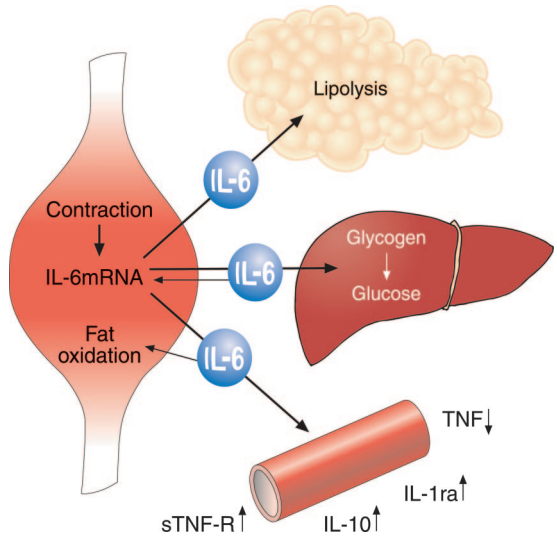

Fig. 3. Contracting muscle fibers produce and release IL-6, which induces several metabolic effects. IL-6 induces lipolysis and fat oxidation and is involved in glucose homeostasis during exercise. In addition, IL-6 has strong anti-inflammatory effects and may inhibit TNF-induced insulin resistance. sTNF-R, soluble TNF receptor.

scriptional mechanisms, as shown in human macrophages where the inhibition of IL-1α, IL-1β, and TNF-α release induced by LPS is a direct consequence of mRNA degradation of their corresponding genes (8).

Whereas IL-10 influences multiple cytokines, the biological role of IL-1ra is to inhibit signaling transduction through the IL-1 receptor complex (27). 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 (42) because both cultured human hepatocytes and the human hepatoma cell line HepG2 produce IL-1ra in response to stimulation with IL-6.

A small increase of CRP levels is seen the day after exercise of longer duration (98). CRP has a role both in the induction of anti-inflammatory cytokines in circulating monocytes and in the suppression of the synthesis of proinflammatory cytokines in tissue macrophages (112).

ANTI-INFLAMMATORY EFFECTS OF EXERCISE

Cross-sectional studies demonstrate an association between physical inactivity and low-grade systemic inflammation in healthy subjects (1, 31, 45, 62, 73, 124, 140, 156) in elderly people (16), as well as in patients with intermittent claudication (143). 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 (31, 73) suggests that physical activity as such may suppress systemic low-grade inflammation. To study whether acute exercise induces a true anti-inflammatory response, our laboratory developed a model of "low-grade inflammation" in which we injected a low dose of *Escherichia coli* endotoxin to healthy volunteers, who had been randomized to either rest or exercise before endotoxin administration. In resting subjects, endotoxin induced a two- to threefold increase in circulating levels of TNF-α. In contrast, when the subjects performed 3 h of ergometer cycling and received the endotoxin bolus at 2.5 h, the TNF-α response was totally blunted (127). The finding that exercise suppresses endotoxin-induced TNF-α production was supported by a recent study demonstrating that exercise normalizes overexpression of TNF-α in TNF-R knockout mice (57).

MECHANISM UNDERLYING THE ANTI-INFLAMMATORY RESPONSE OF ACUTE EXERCISE

After 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 (131).

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 (37) and animal studies (72, 75). 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 (127). 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 after exercise in IL-6 knockout mice (57). 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 (148). Because epinephrine infusion induces only a small increase in IL-6 (134), 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.

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 link between the acute effects of exercise and the long-term benefits has not yet been proven. Given that the atherosclerotic process is characterized 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.

In conclusion, regular exercise protects against diseases associated with chronic low-grade systemic inflammation. This long-term effect of exercise may be ascribed to the anti-inflammatory response elicited by an acute bout of exercise, which is partly mediated by muscle-derived IL-6. Physiological concentrations of IL-6 stimulate the appearance in the circulation of the anti-inflammatory cytokines IL-1ra and IL-10 and inhibit the production of the proinflammatory cytokine TNF-α. Moreover, IL-6 stimulates lipolysis as well as fat oxidation. The anti-inflammatory effects of exercise may offer protection against TNF-induced insulin resistance. Recently, our group proposed that IL-6 and other cytokines, which are produced and released by skeletal muscles, exerting their effects in other organs of the body, should be named myokines (99). Here we suggest that 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.

GRANTS

The study was supported by grants from The Danish Research Agency (22-01-0019), Rigshospitalet, H:S-Copenhagen Hospital Corporation, Apotekerfonden af 1991, Augustinus Fonden, the Lundbeck Foundation, the Novo Nordisk Foundation, and The Copenhagen Muscle Research Center, which is supported by grants from The University of Copenhagen, The Faculties of Science and of Health Sciences at this University, and the Danish National Research Foundation (504-14).

REFERENCES

1. **Abramson JL and Vaccarino V.** Relationship between physical activity and inflammation among apparently healthy middle-aged and older US adults. *Arch Intern Med* 162: 1286–1292, 2002.
2. **Akira S and Kishimoto T.** IL-6 and NF-IL6 in acute-phase response and viral infection. *Immunol Rev* 127: 25–50, 1992.
3. **Akira S, Taga T, and Kishimoto T.** Interleukin-6 in biology and medicine. *Adv Immunol* 54: 1–78, 1993.
4. **Ballou SP, Lozanski FB, Hodder S, Rzewnicki DL, Mion LC, Sipe JD, Ford AB, and Kushner I.** Quantitative and qualitative alterations of acute-phase proteins in healthy elderly persons. *Age Ageing* 25: 224–230, 1996.
5. **Barzilay JI, Abraham L, Heckbert SR, Cushman M, Kuller LH, Resnick HE, and Tracy RP.** The relation of markers of inflammation to the development of glucose disorders in the elderly: the Cardiovascular Health Study. *Diabetes* 50: 2384–2389, 2001.
6. **Bastard JP, Maachi M, Van Nhieu JT, Jardel C, Bruckert E, Grimaldi A, Robert JJ, Capeau J, and Hainque B.** Adipose tissue IL-6 content correlates with resistance to insulin activation of glucose uptake both in vivo and in vitro. *J Clin Endocrinol Metab* 87: 2084–2089, 2002.
7. **Blair SN, Cheng Y, and Holder JS.** Is physical activity or physical fitness more important in defining health benefits? *Med Sci Sports Exerc* 33: S379–S399, 2001.

8. **Bogdan C, Paik J, Vodovotz Y, and Nathan C.** Contrasting mechanisms for suppression of macrophage cytokine release by transforming growth factor-beta and interleukin-10. *J Biol Chem* 267: 23301–23308, 1992.
9. **Borst SE and Bagby GJ.** Neutralization of tumor necrosis factor reverses age-induced impairment of insulin responsiveness in skeletal muscle of Sprague-Dawley rats. *Metabolism* 51: 1061–1064, 2002.
10. **Botion LM, Brasier AR, Tian B, Udupi V, and Green A.** Inhibition of proteasome activity blocks the ability of TNFα to down-regulate G_i proteins and stimulate lipolysis. *Endocrinology* 142: 5069–5075, 2001.
11. **Boule NG, Haddad E, Kenny GP, Wells GA, and Sigal RJ.** Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. *JAMA* 286: 1218–1227, 2001.
12. **Bruce CR and Dyck DJ.** Cytokine regulation of skeletal muscle fatty acid metabolism: effect of interleukin-6 and tumor necrosis factor-α. *Am J Physiol Endocrinol Metab* 287: E616–E621, 2004.
13. **Bruunsgaard H, Andersen-Ranberg K, Jeune B, Pedersen AN, Skinhoj P, and Pedersen BK.** A high plasma concentration of TNF-alpha is associated with dementia in centenarians. *J Gerontol A Biol Sci Med Sci* 54: M357–M364, 1999.
14. **Bruunsgaard H, Christiansen L, Pedersen AN, Schroll M, Jorgensen T, and Pedersen BK.** The IL-6 -174>C polymorphism is associated with cardiovascular diseases and mortality in 80-year-old humans. *Exp Gerontol* 39: 255–261, 2004.
15. **Bruunsgaard H, Jensen MS, Schjerling P, Halkjaer-Kristensen J, Ogawa K, Skinhoj P, and Pedersen BK.** Exercise induces recruitment of lymphocytes with an activated phenotype and short telomere lengths in young and elderly humans. *Life Sci* 65: 2623–2633, 1999.
16. **Bruunsgaard H, Ladelund S, Pedersen AN, Schroll M, Jorgensen T, and Pedersen BK.** Predicting death from tumour necrosis factor-alpha and interleukin-6 in 80-year-old people. *Clin Exp Immunol* 132: 24–31, 2003.
17. **Bruunsgaard H, Skinhoj P, Pedersen AN, Schroll M, and Pedersen BK.** Ageing, tumour necrosis factor-alpha (TNF-alpha) and atherosclerosis. *Clin Exp Immunol* 121: 255–260, 2000.
18. **Carey AL, Bruce CR, Sacchetti M, Anderson MJ, Olson D, Saltin B, Hawley JA, and Febbraio MA.** Interleukin-6 and tumor necrosis factor-alpha are not increased in patients with type 2 diabetes: evidence that plasma IL-6 is related to fat mass and not insulin responsiveness. *Diabetologia* 47: 1029–1037, 2004.
19. **Carling D.** The AMP-activated protein kinase cascade—a unifying system for energy control. *Trends Biochem Sci* 29: 18–24, 2004.
20. **Castell JV, Geiger T, Gross V, Andus T, Walter E, Hirano T, Kishimoto T, and Heinrich PC.** Plasma clearance, organ distribution and target cells of interleukin-6/hepatocyte-stimulating factor in the rat. *Eur J Biochem* 177: 357–361, 1988.
21. **Castell LM, Poortmans JR, Leclercq R, Brasseur M, Duchateau J, and Newsholme EA.** Some aspects of the acute phase response after a marathon race, and the effects of glutamine supplementation. *Eur J Appl Physiol* 75: 47–53, 1997.
22. **Catania A, Airagi L, Motta P, Manfredi MG, Annoni G, Pettenati C, Brambilla F, and Lipton JM.** Cytokine antagonists in aged subjects and their relation with cellular immunity. *J Gerontol A Biol Sci Med Sci* 52: B93–B97, 1997.
23. **Coppack SW.** Pro-inflammatory cytokines and adipose tissue. *Proc Nutr Soc* 60: 349–356, 2001.
24. **Dandona P, Aljada A, and Bandyopadhyay A.** Inflammation: the link between insulin resistance, obesity and diabetes. *Trends Immunol* 25: 4–7, 2004.
25. **Dinarello CA.** Interleukin-1 and interleukin-1 antagonism. *Blood* 77: 1627–1652, 1991.
26. **Dinarello CA.** Interleukin-1 and tumor necrosis factor: effector cytokines in autoimmune diseases. *Semin Immunol* 4: 133–145, 1992.
27. **Dinarello CA.** The role of the interleukin-1-receptor antagonist in blocking inflammation mediated by interleukin-1. *N Engl J Med* 343: 732–734, 2000.
28. **Dobbs RJ, Charlett A, Purkiss AG, Dobbs SM, Weller C, and Peterson DW.** Association of circulating TNF-alpha and IL-6 with ageing and parkinsonism. *Acta Neurol Scand* 100: 34–41, 1999.
29. **Drenth JP, van Uum SH, van Deuren M, Pesman GJ, van der ven Jongekrug J, and van der Meer J.** Endurance run increases circulating IL-6 and IL-1ra but downregulates ex vivo TNF-α and IL-1β production. *J Appl Physiol* 79: 1497–1503, 1995.
30. **Duncan BB, Schmidt MI, Pankow JS, Ballantyne CM, Couper D, Vigo A, Hoogeveen R, Folsom AR, and Heiss G.** Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study. *Diabetes* 52: 1799–1805, 2003.
31. **Fallon KE, Fallon SK, and Boston T.** The acute phase response and exercise: court and field sports. *Br J Sports Med* 35: 170–173, 2001.
32. **Febbraio MA, Hiscock N, Sacchetti M, Fischer CP, and Pedersen BK.** Interleukin-6 is a novel factor mediating glucose homeostasis during skeletal muscle contraction. *Diabetes* 53: 1643–1648, 2004.
33. **Febbraio MA and Pedersen BK.** Muscle-derived interleukin-6: mechanisms for activation and possible biological roles. *FASEB J* 16: 1335–1347, 2002.
34. **Febbraio MA, Steensberg A, Keller C, Starkie RL, Krustrup P, Ott P, Secher NH, and Pedersen BK.** Glucose ingestion attenuates interleukin-6 release from contracting skeletal muscle in humans. *J Physiol* 549: 607–612, 2003.
35. **Feingold KR and Grunfeld C.** Role of cytokines in inducing hyperlipidemia. *Diabetes* 41, *Suppl* 2: 97–101, 1992.
36. **Festa A, D'Agostino R Jr, Tracy RP, and Haffner SM.** Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes: the insulin resistance atherosclerosis study. *Diabetes* 51: 1131–1137, 2002.
37. **Fiers W.** Tumor necrosis factor. Characterization at the molecular, cellular and in vivo level. *FEBS Lett* 285: 199–212, 1991.
38. **Fischer CP, Hiscock NJ, Penkowa M, Basu S, Vessby B, Kallner A, Sjoberg LB, and Pedersen BK.** Supplementation with vitamins C and E inhibits the release of interleukin-6 from contracting human skeletal muscle. *J Physiol* 558: 633–645, 2004.
39. **Ford ES.** Leukocyte count, erythrocyte sedimentation rate, and diabetes incidence in a national sample of US adults. *Am J Epidemiol* 155: 57–64, 2002.
40. **Freeman DJ, Norrie J, Caslake MJ, Gaw A, Ford I, Lowe GD, O'Reilly DS, Packard CJ, and Sattar N.** C-reactive protein is an independent predictor of risk for the development of diabetes in the West of Scotland Coronary Prevention Study. *Diabetes* 51: 1596–1600, 2002.
41. **Fried SK, Bunkin DA, and Greenberg AS.** Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. *J Clin Endocrinol Metab* 83: 847–850, 1998.
42. **Gabay C, Smith MF, Eidlen D, and Arend WP.** Interleukin 1 receptor antagonist (IL-1Ra) is an acute-phase protein. *J Clin Invest* 99: 2930–2940, 1997.
43. **Gadient RA and Patterson PH.** Leukemia inhibitory factor, Interleukin 6, and other cytokines using the GP130 transducing receptor: roles in inflammation and injury. *Stem Cells* 17: 127–137, 1999.
44. **Gasic S, Tian B, and Green A.** Tumor necrosis factor alpha stimulates lipolysis in adipocytes by decreasing Gi protein concentrations. *J Biol Chem* 274: 6770–6775, 1999.
45. **Geffken DF, Cushman M, Burke GL, Polak JF, Sakkinen PA, and Tracy RP.** Association between physical activity and markers of inflammation in a healthy elderly population. *Am J Epidemiol* 153: 242–250, 2001.
46. **Green A, Dobias SB, Walters DJ, and Brasier AR.** Tumor necrosis factor increases the rate of lipolysis in primary cultures of adipocytes without altering levels of hormone-sensitive lipase. *Endocrinology* 134: 2581–2588, 1994.
47. **Halse R, Pearson SL, McCormack JG, Yeaman SJ, and Taylor R.** Effects of tumor necrosis factor-alpha on insulin action in cultured human muscle cells. *Diabetes* 50: 1102–1109, 2001.
48. **Han TS, Sattar N, Williams K, Gonzalez-Villalpando C, Lean ME, and Haffner SM.** Prospective study of C-reactive protein in relation to the development of diabetes and metabolic syndrome in the Mexico City Diabetes Study. *Diabetes Care* 25: 2016–2021, 2002.
49. **Harris TB, Savage PJ, Tell GS, Haan M, Kumanyika S, and Lynch JC.** Carrying the burden of cardiovascular risk in old age: associations of weight and weight change with prevalent cardiovascular disease, risk factors, and health status in the Cardiovascular Health Study. *Am J Clin Nutr* 66: 837–844, 1997.
50. **Hellsten Y, Frandsen U, Orthenblad N, Sjodin N, and Richter EA.** Xanthine oxidase in human skeletal muscle following eccentric exercise: a role of inflammation. *J Physiol* 498: 239–248, 1997.
51. **Hiscock N, Chan MH, Bisucci T, Darby IA, and Febbraio MA.** Skeletal myocytes are a source of interleukin-6 mRNA expression and

protein release during contraction: evidence of fiber type specificity. *FASEB J* 18: 992–994, 2004.

52. **Hotamisligil GS.** Mechanisms of TNF-alpha-induced insulin resistance. *Exp Clin Endocrinol Diabetes* 107: 119–125, 1999.
53. **Hotamisligil GS, Peraldi P, Budavari A, Ellis R, White MF, and Spiegelman BM.** IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-alpha- and obesity-induced insulin resistance. *Science* 271: 665–668, 1996.
54. **Hotamisligil GS, Shargill NS, and Spiegelman BM.** Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. *Science* 259: 87–91, 1993.
55. **Jolliffe JA, Rees K, Taylor RS, Thompson D, Oldridge N, and Ebrahim S.** Exercise-based rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* 4: CD001800, 2000.
56. **Jonsdottir IH, Schjerling P, Ostrowski K, Asp S, Richter EA, and Pedersen BK.** Muscle contractions induce interleukin-6 mRNA production in rat skeletal muscles. *J Physiol* 528: 157–163, 2000.
57. **Keller C, Keller P, Giralt M, Hidalgo J, and Pedersen BK.** Exercise normalises overexpression of TNF-alpha in knockout mice. *Biochem Biophys Res Commun* 321: 179–182, 2004.
58. **Keller C, Steensberg A, Pilegaard H, Osada T, Saltin B, Pedersen BK, and Neufer PD.** Transcriptional activation of the IL-6 gene in human contracting skeletal muscle: influence of muscle glycogen content. *FASEB J* 15: 2748–2750, 2001.
59. **Keller P, Keller C, Carey AL, Jauffred S, Fischer CP, Steensberg A, and Pedersen BK.** Interleukin-6 production by contracting human skeletal muscle: autocrine regulation by IL-6. *Biochem Biophys Res Commun* 319: 550–554, 2003.
60. **Kelly M, Keller C, Avilucea PR, Keller P, Luo Z, Xiang X, Giralt M, Hidalgo J, Saha AK, and Pedersen BK.** AMPK activity is diminished in tissues of the IL-6 knockout mice: the effect of exercise. *Biochem Biophys Res Commun* 320: 449–454, 2004.
61. **Kim HJ, Higashimori T, Park SY, Choi H, Dong J, Kim YJ, Noh HL, Cho YR, Cline G, Kim YB, and Kim JK.** Differential effects of interleukin-6 and -10 on skeletal muscle and liver insulin action in vivo. *Diabetes* 53: 1060–1067, 2004.
62. **King DE, Carek P, Mainous AG III, and Pearson WS.** Inflammatory markers and exercise: differences related to exercise type. *Med Sci Sports Exerc* 35: 575–581, 2003.
63. **Kroeger KM, Carville KS, and Abraham LJ.** The -308 tumor necrosis factor-alpha promoter polymorphism effects transcription. *Mol Immunol* 34: 391–399, 1997.
64. **Kubaszek A, Pihlajamaki J, Komarovski V, Lindi V, Lindstrom J, Eriksson J, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Tuomilehto J, Uusitupa M, and Laakso M.** Promoter polymorphisms of the TNF-alpha (G-308A) and IL-6 (C-174G) genes predict the conversion from impaired glucose tolerance to type 2 diabetes: the Finnish Diabetes Prevention Study. *Diabetes* 52: 1872–1876, 2003.
65. **Kubaszek A, Pihlajamaki J, Punnonen K, Karhapaa P, Vauhkonen I, and Laakso M.** The C-174G promoter polymorphism of the IL-6 gene affects energy expenditure and insulin sensitivity. *Diabetes* 52: 558–561, 2003.
66. **Lacasse Y, Brosseau L, Milne S, Martin S, Wong E, Guyatt GH, and Goldstein RS.** Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 3: CD003793, 2002.
67. **Langberg H, Olesen JL, Gemmer C, and Kjaer M.** Substantial elevation of interleukin-6 concentration in peritendinous tissue, in contrast to muscle, following prolonged exercise in humans. *J Physiol* 542: 985–990, 2002.
68. **Libby P.** Inflammation in atherosclerosis. *Nature* 420: 868–874, 2002.
69. **Libby P, Ridker PM, and Maseri A.** Inflammation and atherosclerosis. *Circulation* 105: 1135–1143, 2002.
70. **Lindsay RS, Funahashi T, Hanson RL, Matsuzawa Y, Tanaka S, Tataranni PA, Knowler WC, and Krakoff J.** Adiponectin and development of type 2 diabetes in the Pima Indian population. *Lancet* 360: 57–58, 2002.
71. **Lyngso D, Simonsen L, and Bulow J.** Interleukin-6 production in human subcutaneous abdominal adipose tissue: the effect of exercise. *J Physiol* 543: 373–378, 2002.
72. **Matthys P, Mitera T, Heremans H, Van Damme J, and Billiau A.** Anti-gamma interferon and anti-interleukin-6 antibodies affect staphylococcal enterotoxin B-induced weight loss, hypoglycemia, and cytokine release in D-galactosamine-sensitized and unsensitized mice. *Infect Immun* 63: 1158–1164, 1995.
73. **Mattusch F, Dufaux B, Heine O, Mertens I, and Rost R.** Reduction of the plasma concentration of C-reactive protein following nine months of endurance training. *Int J Sports Med* 21: 21–24, 2000.
74. **Mishima Y, Kuyama A, Tada A, Takahashi K, Ishioka T, and Kibata M.** Relationship between serum tumor necrosis factor-alpha and insulin resistance in obese men with Type 2 diabetes mellitus. *Diabetes Res Clin Pract* 52: 119–123, 2001.
75. **Mizuhara H, O'Neill E, Seki N, Ogawa T, Kusunoki C, Otsuka K, Satoh S, Niwa M, Senoh H, and Fujiwara H.** T cell activation-associated hepatic injury: mediation by tumor necrosis factors and protection by interleukin 6. *J Exp Med* 179: 1529–1537, 1994.
76. **Mohamed-Ali V, Goodrick S, Bulmer K, Holly JM, Yudkin JS, and Coppack SW.** Production of soluble tumor necrosis factor receptors by human subcutaneous adipose tissue in vivo. *Am J Physiol Endocrinol Metab* 277: E971–E975, 1999.
77. **Moldoveanu AI, Shephard RJ, and Shek PN.** Exercise elevates plasma levels but not gene expression of IL-1β, IL-6, and TNF-α in blood mononuclear cells. *J Appl Physiol* 89: 1499–1504, 2000.
78. **Moore KW, O'Garra A, de Waal MR, Vieira P, and Mosmann TR.** Interleukin-10. *Annu Rev Immunol* 11: 165–190, 1993.
79. **Murray CJ and Lopez AD.** Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet* 349: 1436–1442, 1997.
80. **Nakanishi N, Yoshida H, Matsuo Y, Suzuki K, and Tatara K.** White blood-cell count and the risk of impaired fasting glucose or Type II diabetes in middle-aged Japanese men. *Diabetologia* 45: 42–48, 2002.
81. **Nehlsen-Canarella SL, Fagoaga OR, and Nieman DC.** Carbohydrate and the cytokine response to 2.5 hours of running. *J Appl Physiol* 82: 1662–1667, 1997.
82. **Nielsen HB, Secher N, and Pedersen BK.** Lymphocytes and NK cell activity during repeated bouts of maximal exercise. *Am J Physiol Regul Integr Comp Physiol* 271: R222–R227, 1996.
83. **Nieman DC, Davis JM, Henson DA, Walberg-Rankin J, Shute M, Dumke CL, Utter AC, Vinci DM, Carson JA, Brown A, Lee WJ, McAnulty SR, and McAnulty LS.** Carbohydrate ingestion influences skeletal muscle cytokine mRNA and plasma cytokine levels after a 3-h run. *J Appl Physiol* 94: 1917–1925, 2003.
84. **Nieman DC, Nehlsen-Canarella SL, Fagoaga OR, Henson DA, Utter A, Davis JM, Williams F, and Butterworth DE.** Effects of mode and carbohydrate on the granulocyte and monocyte response to intensive prolonged exercise. *J Appl Physiol* 84: 1252–1259, 1998.
85. **Nieman DC, Nehlsen-Canarella SL, Fagoaga OR, Henson DA, Utter A, Davis JM, Williams F, and Butterworth DE.** Influence of mode and carbohydrate on the cytokine response to heavy exertion. *Med Sci Sports Exerc* 30: 671–678, 1998.
86. **Nishimoto N, Yoshizaki K, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Hashimoto J, Azuma J, and Kishimoto T.** Treatment of rheumatoid arthritis with humanized anti-interleukin-6 receptor antibody: a multicenter, double-blind, placebo-controlled trial. *Arthritis Rheum* 50: 1761–1769, 2004.
87. **Nonogaki K, Fuller GM, Fuentes NL, Moser AH, Staprans I, Grunfeld C, and Feingold KR.** Interleukin-6 stimulates hepatic triglyceride secretion in rats. *Endocrinology* 136: 2143–2149, 1995.
88. **Northoff H, Weinstock C, and Berg A.** The cytokine response to strenuous exercise. *Int J Sports Med* 15: 167–171, 1994.
89. **Nybo L, Nielsen B, Pedersen BK, Moller K, and Secher NH.** Interleukin-6 release from the human brain during prolonged exercise. *J Physiol* 542: 991–995, 2002.
90. **Ogawa H, Nielsen S, and Kawakami M.** Cachectin/tumor necrosis factor and interleukin-1 show different modes of combined effect on lipoprotein lipase activity and intracellular lipolysis in 3T3–L1 cells. *Biochim Biophys Acta* 1003: 131–135, 1989.
91. **Ostrowski K, Hermann C, Bangash A, Schjerling P, Nielsen JN, and Pedersen BK.** A trauma-like elevation in plasma cytokines in humans in response to treadmill running. *J Physiol* 508: 949–953, 1998.
92. **Ostrowski K, Rohde T, Asp A, Schjerling P, and Pedersen BK.** Chemokines are elevated in plasma after strenuous exercise in humans. *Eur J Appl Physiol* 84: 244–245, 2001.
93. **Ostrowski K, Rohde T, Asp S, Schjerling P, and Pedersen BK.** Pro- and anti-inflammatory cytokine balance in strenuous exercise in humans. *J Physiol* 515: 287–291, 1999.

94. **Ostrowski K, Rohde T, Zacho M, Asp S, and Pedersen BK.** Evidence that IL-6 is produced in skeletal muscle during prolonged running. *J Physiol* 508: 949–953, 1998.
95. **Ostrowski K, Schjerling P, and Pedersen BK.** Physical activity and plasma interleukin-6 in humans—effect of intensity of exercise. *Eur J Appl Physiol* 83: 512–515, 2000.
96. **Paolisso G, Rizzo MR, Mazziotti G, Tagliamonte MR, Gambardella A, Rotondi M, Carella C, Giugliano D, Varricchio M, and D'Onofrio F.** Advancing age and insulin resistance: role of plasma tumor necrosis factor-α. *Am J Physiol Endocrinol Metab* 275: E294–E299, 1998.
97. **Path G, Bornstein SR, Gurniak M, Chrousos GP, Scherbaum WA, and Hauner H.** Human breast adipocytes express interleukin-6 (IL-6) and its receptor system: increased IL-6 production by beta-adrenergic activation and effects of IL-6 on adipocyte function. *J Clin Endocrinol Metab* 86: 2281–2288, 2001.
98. **Pedersen BK and Hoffman-Goetz L.** Exercise and the immune system: regulation, integration and adaptation. *Physiol Rev* 80: 1055–1081, 2000.
99. **Pedersen BK, Steensberg A, Fischer C, Keller C, Keller P, Plomgaard P, Febbraio M, and Saltin B.** Searching for the exercise factor: is IL-6 a candidate. *J Muscle Res Cell Motil* 24: 113–119, 2003.
100. **Pedersen BK, Steensberg A, and Schjerling P.** Muscle-derived interleukin-6: possible biological effects. *J Physiol* 536: 329–337, 2001.
101. **Pedersen M, Bruunsgaard H, Weis N, Hendel HW, Andreassen BU, Eldrup E, Dela F, and Pedersen BK.** Circulating levels of TNF-alpha and IL-6-relation to truncal fat mass and muscle mass in healthy elderly individuals and in patients with type-2 diabetes. *Mech Ageing Dev* 124: 495–502, 2003.
102. **Pedersen M, Steensberg A, Keller C, Osada T, Zacho M, Saltin B, Febbraio MA, and Pedersen BK.** Does the aging skeletal muscle maintain its endocrine function? *Exerc Immunol Rev* 10: 42–55, 2004.
103. **Penkowa M, Keller C, Keller P, Jauffred S, and Pedersen BK.** Immunohistochemical detection of interleukin-6 in human skeletal muscle fibers following exercise. *FASEB J* 17: 2166–2168, 2003.
104. **Peraldi P, Hotamisligil GS, Buurman WA, White MF, and Spiegelman BM.** Tumor necrosis factor (TNF)-alpha inhibits insulin signaling through stimulation of the p55 TNF receptor and activation of sphingomyelinase. *J Biol Chem* 271: 13018–13022, 1996.
105. **Petersen EW, Carey AL, Sacchetti M, Steinberg GR, Macaulay SL, Febbraio MA, and Pedersen BK.** Acute IL-6 treatment increases fatty acid turnover in elderly humans in vivo and in tissue culture in vitro: evidence that IL-6 acts independently of lipolytic hormones. *Am J Physiol Endocrinol Metab* 288: E155–E162, 2005.
106. **Petersen KF, Dufour S, Befroy D, Garcia R, and Shulman GI.** Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. *N Engl J Med* 350: 664–671, 2004.
107. **Pickup JC, Mattock MB, Chusney GD, and Burt D.** NIDDM as a disease of the innate immune system: association of acute-phase reactants and interleukin-6 with metabolic syndrome X. *Diabetologia* 40: 1286–1292, 1997.
108. **Piepoli MF, Davos C, Francis DP, and Coats AJ.** Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ* 328: 189–195, 2004.
109. **Popa C, Netea MG, Radstake T, van der Meer JW, Stalenhoef AF, Van Riel PL, and Barrera P.** Influence of anti-TNF treatment on the cardiovascular risk factors in patients with active rheumatoid arthritis. *Ann Rheum Dis* Jul 1 [Epub ahead of print]: 2004.
110. **Pradhan AD, Manson JE, Rifai N, Buring JE, and Ridker PM.** C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 286: 327–334, 2001.
111. **Pretolani M.** Interleukin-10: an anti-inflammatory cytokine with therapeutic potential. *Clin Exp Allergy* 29: 1164–1171, 1999.
112. **Pue CA, Mortensen RF, Marsh CB, Pope HA, and Wewers MD.** Acute phase levels of C-reactive protein enhance IL-1 beta and IL-1ra production by human blood monocytes but inhibit IL-1 beta and IL-1ra production by alveolar macrophages. *J Immunol* 156: 1594–1600, 1996.
113. **Rahn-Landstrom T, Mei J, Karlsson M, Manganiello V, and Degerman E.** Down-regulation of cyclic-nucleotide phosphodiesterase 3B in 3T3–L1 adipocytes induced by tumour necrosis factor alpha and cAMP. *Biochem J* 346: 337–343, 2000.
114. **Ridker PM, Hennekens CH, Buring JE, and Rifai NC.** Reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 342: 836–843, 2000.
115. **Ridker PM, Rifai N, Stampfer MJ, and Hennekens CH.** Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation* 101: 1767–1772, 2000.
116. **Ridker PM, Rifai N, Rose L, Buring JE, and Cook NR.** Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 347: 1557–1565, 2002.
117. **Rohde T, MacLean DA, Richter EA, Kiens B, and Pedersen BK.** Prolonged submaximal eccentric exercise is associated with increased levels of plasma IL-6. *Am J Physiol Endocrinol Metab* 273: E85–E91, 1997.
118. **Ross R.** Atherosclerosis—an inflammatory disease. *N Engl J Med* 340: 115–126, 1999.
119. **Ross R and Harker L.** Hyperlipidemia and atherosclerosis. *Science* 193: 1094–1100, 1976.
120. **Rotter V, Nagaev I, and Smith U.** Interleukin-6 (IL-6) induces insulin resistance in 3T3–L1 adipocytes and is, like IL-8 and tumor necrosis factor-alpha, overexpressed in human fat cells from insulin-resistant subjects. *J Biol Chem* 278: 45777–45784, 2003.
121. **Ryden M, Dicker A, van Harmelen V, Hauner H, Brunnberg M, Perbeck L, Lonnqvist F, and Arner P.** Mapping of early signaling events in tumor necrosis factor-alpha-mediated lipolysis in human fat cells. *J Biol Chem* 277: 1085–1091, 2002.
122. **Saghizadeh M, Ong JM, Garvey WT, Henry RR, and Kern PA.** The expression of TNF alpha by human muscle. Relationship to insulin resistance. *J Clin Invest* 97: 1111–1116, 1996.
123. **Schindler R, Mancilla J, Endres S, Ghorbani R, Clark SC, and Dinarello CA.** Correlations and interactions in the production of interleukin-6 (IL-6), IL-1, and tumor necrosis factor (TNF) in human blood mononuclear cells: IL-6 suppresses IL-1 and TNF. *Blood* 75: 40–47, 1990.
124. **Smith JK, Dykes R, Douglas JE, Krishnaswamy G, and Berk S.** Long-term exercise and atherogenic activity of blood mononuclear cells in persons at risk of developing ischemic heart disease. *JAMA* 281: 1722–1727, 1999.
125. **Souza SC, de Vargas LM, Yamamoto MT, Lien P, Franciosa MD, Moss LG, and Greenberg AS.** Overexpression of perilipin A and B blocks the ability of tumor necrosis factor alpha to increase lipolysis in 3T3–L1 adipocytes. *J Biol Chem* 273: 24665–24669, 1998.
126. **Souza SC, Yamamoto MT, Franciosa MD, Lien P, and Greenberg AS.** BRL 49653 blocks the lipolytic actions of tumor necrosis factor-alpha: a potential new insulin-sensitizing mechanism for thiazolidinediones. *Diabetes* 47: 691–695, 1998.
127. **Starkie R, Ostrowski SR, Jauffred S, Febbraio M, and Pedersen BK.** Exercise and IL-6 infusion inhibit endotoxin-induced TNF-α production in humans. *FASEB J* 17: 884–886, 2003.
128. **Starkie RL, Arkinstall MJ, Koukoulas I, Hawley JA, and Febbraio MA.** Carbohydrate ingestion attenuates the increase in plasma interleukin-6, but not skeletal muscle interleukin-6 mRNA, during exercise in humans. *J Physiol* 533: 585–591, 2001.
129. **Starkie RL, Rolland J, Angus DJ, Anderson MJ, and Febbraio MA.** Circulating monocytes are not the source of elevations in plasma IL-6 and TNF-α levels after prolonged running. *Am J Physiol Cell Physiol* 280: C769–C774, 2001.
130. **Steensberg A, Febbraio MA, Osada T, Schjerling P, van Hall G, Saltin B, and Pedersen BK.** Interleukin-6 production in contracting human skeletal muscle is influenced by pre-exercise muscle glycogen content. *J Physiol* 537: 633–639, 2001.
131. **Steensberg A, Fischer CP, Keller C, Moller K, and Pedersen BK.** IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. *Am J Physiol Endocrinol Metab* 285: E433–E437, 2003.
132. **Steensberg A, Fischer CP, Sacchetti M, Keller C, Osada T, Schjerling P, van Hall G, Febbraio MA, and Pedersen BK.** Acute interleukin-6 administration does not impair muscle glucose uptake or whole body glucose disposal in healthy humans. *J Physiol* 548: 631–638, 2003.
133. **Steensberg A, Keller C, Starkie RL, Osada T, Febbraio MA, and Pedersen BK.** IL-6 and TNF-α expression in, and release from, contracting human skeletal muscle. *Am J Physiol Endocrinol Metab* 283: E1272–E1278, 2002.
134. **Steensberg A, Toft AD, Schjerling P, Halkjaer-Kristensen J, and Pedersen BK.** Plasma interleukin-6 during strenuous exercise: role of adrenaline. *Am J Physiol Cell Physiol* 281: C1001–C1004, 2001.
135. **Steensberg A, van Hall G, Osada T, Sacchetti M, Saltin B, and Klarlund PB.** Production of interleukin-6 in contracting human skeletal

muscles can account for the exercise-induced increase in plasma interleukin-6. *J Physiol* 529: 237–242, 2000.

136. **Stouthard JM, Romijn JA, van der PT, Endert E, Klein S, Bakker PJ, Veenhof CH, and Sauerwein HP.** Endocrinologic and metabolic effects of interleukin-6 in humans. *Am J Physiol Endocrinol Metab* 268: E813–E819, 1995.
137. **Suzuki K, Nakaji S, Kurakake S, Totsuka M, Sato K, Kuriyama T, Fujimoto H, Shibusawa K, Machida K, and Sugawara K.** Exhaustive exercise and type-1/type-2 cytokine balance with special focus on interleukin-12 p40/p70. *Exerc Immunol Rev* 9: 48–57, 2003.
138. **Suzuki K, Nakaji S, Yamada M, Totsuka M, Sato K, and Sugawara K.** Systemic inflammatory response to exhaustive exercise. Cytokine kinetics. *Exerc Immunol Rev* 8: 6–48, 2002.
139. **Suzuki K, Yamada M, Kurakake S, Okamura N, Yamaya K, Liu Q, Kudoh S, Kowatari K, Nakaji S, and Sugawara K.** Circulating cytokines and hormones with immunosuppressive but neutrophil-priming potentials rise after endurance exercise in humans. *Eur J Appl Physiol* 81: 281–287, 2000.
140. **Taaffe DR, Harris TB, Ferrucci L, Rowe J, and Seeman TE.** Cross-sectional and prospective relationships of interleukin-6 and C-reactive protein with physical performance in elderly persons: MacArthur studies of successful aging. *J Gerontol A Biol Sci Med Sci* 55: M709–M715, 2000.
141. **Terry CF, Loukaci V, and Green FR.** Cooperative influence of genetic polymorphisms on interleukin 6 transcriptional regulation. *J Biol Chem* 275: 18138–18144, 2000.
142. **Tilg H, Dinarello CA, and Mier JW.** IL-6 and APPs: anti-inflammatory and immunosuppressive mediators. *Immunol Today* 18: 428–432, 1997.
143. **Tisi PV, Hulse M, Chulakadabba A, Gosling P, and Shearman CP.** Exercise training for intermittent claudication: does it adversely affect biochemical markers of the exercise-induced inflammatory response? *Eur J Vasc Endovasc Surg* 14: 344–350, 1997.
144. **Toft AD, Ostrowski K, Asp S, Møller K, Iversen S, Hermann C, Søndergaard SR, and Pedersen BK.** The effects of n-3 PUFA on the cytokine response to strenuous exercise. *J Appl Physiol* 89: 2401–2405, 2000.
145. **Tsigos C, Kyrou I, Chala E, Tsapogas P, Stavridis JC, and Raptis SA.** Circulating tumour necrosis factor alpha concentrations are higher in abdominal versus peripheral obesity. *Metabolism* 48: 1332–1335, 1999.
146. **Ullum H, Haahr PM, Diamant M, Palmo J, Halkjaer-Kristensen J, and Pedersen BK.** Bicycle exercise enhances plasma IL-6 but does not change IL-1α, IL-1β, IL-6, or TNF-α pre-mRNA in BMNC. *J Appl Physiol* 77: 93–97, 1994.
147. **Uysal KT, Wiesbrock SM, Marino MW, and Hotamisligil GS.** Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. *Nature* 389: 610–614, 1997.
148. **Van der Poll T, Coyle SM, Barbosa K, Braxton CC, and Lowry SF.** Epinephrine inhibits tumor necrosis factor-alpha and potentiates interleukin 10 production during human endotoxemia. *J Clin Invest* 97: 713–719, 1996.
149. **Van Hall G, Steensberg A, Sacchetti M, Fischer C, Keller C, Schjerling P, Hiscock N, Moller K, Saltin B, Febbraio MA, and Pedersen BK.** Interleukin-6 stimulates lipolysis and fat oxidation in humans. *J Clin Endocrinol Metab* 88: 3005–3010, 2003.
150. **Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, and Lin HM.** Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. *J Clin Endocrinol Metab* 85: 1151–1158, 2000.
151. **Volpato S, Guralnik JM, Ferrucci L, Balfour J, Chaves P, Fried LP, and Harris TB.** Cardiovascular disease, interleukin-6, and risk of mortality in older women: the women's health and aging study. *Circulation* 103: 947–953, 2001.
152. **Vozarova B, Weyer C, Lindsay RS, Pratley RE, Bogardus C, and Tataranni PA.** High white blood cell count is associated with a worsening of insulin sensitivity and predicts the development of type 2 diabetes. *Diabetes* 51: 455–461, 2002.
153. **Wallenius V, Wallenius K, Ahren B, Rudling M, Carlsten H, Dickson SL, Ohlsson C, and Jansson JO.** Interleukin-6-deficient mice develop mature-onset obesity. *Nat Med* 8: 75–79, 2002.
154. **Wang P, Wu P, Anthes JC, Siegel MI, Egan RW, and Billah MM.** Interleukin-10 inhibits interleukin-8 production in human neutrophils. *Blood* 83: 2678–2683, 1994.
155. **Wang P, Wu P, Siegel MI, Egan RW, and Billah MM.** IL-10 inhibits transcription of cytokine genes in human peripheral blood mononuclear cells. *J Immunol* 153: 811–816, 1994.
156. **Wannamethee SG, Lowe GD, Whincup PH, Rumley A, Walker M, and Lennon L.** Physical activity and hemostatic and inflammatory variables in elderly men. *Circulation* 105: 1785–1790, 2002.
157. **Weigert C, Brodbeck K, Staiger H, Kausch C, Machicao F, Haring HU, and Schleicher ED.** Palmitate, but not unsaturated fatty acids, induces the expression of interleukin-6 in human myotubes through proteasome-dependent activation of nuclear factor kappa B. *J Biol Chem* 279: 23942–23952, 2004.
158. **Wilson AG, Symons JA, McDowell TL, McDevitt HO, and Duff GW.** Effects of a polymorphism in the human tumor necrosis factor alpha promoter on transcriptional activation. *Proc Natl Acad Sci USA* 94: 3195–3199, 1997.
159. **Winkler G, Salamon F, Harmos G, Salamon D, Speer G, Szekeres O, Hajos P, Kovacs M, Simon K, and Cseh K.** Elevated serum tumor necrosis factor-alpha concentrations and bioactivity in Type 2 diabetics and patients with android type obesity. *Diabetes Res Clin Pract* 42: 169–174, 1998.
160. **Yach D, Hawkes C, Gould CL, and Hofman KJ.** The global burden of chronic diseases: overcoming impediments to prevention and control. *JAMA* 291: 2616–2622, 2004.
161. **Youd JM, Rattigan S, and Clark MG.** Acute impairment of insulin-mediated capillary recruitment and glucose uptake in rat skeletal muscle in vivo by TNF-alpha. *Diabetes* 49: 1904–1909, 2000.
162. **Zhang HH, Halbleib M, Ahmad F, Manganiello VC, and Greenberg AS.** Tumor necrosis factor-alpha stimulates lipolysis in differentiated human adipocytes through activation of extracellular signal-related kinase and elevation of intracellular cAMP. *Diabetes* 51: 2929–2935, 2002.