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The anti-inflammatory effect of exercise

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00164.2004.—Regular exercise offers protection against all-cause mortality, pri-
marily by protection against cardiovascular disease and Type 2 diabetes mellitus.
The latter disorders have been associated with chronic low-grade systemic inflam-
mation 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-inflamma-
tory 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, stim-
ulating 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 mortal-
ity, 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).

Low-grade chronic inflammation is reflected by increased
C-reactive protein (CRP) concentrations and increased sys-
temic 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 meta-
bolic 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 inflam-
mation. Cytokines are small polypeptides, which were origi-
nally discovered to have immunoregulatory roles (2, 3). Some
of these cytokines facilitate an influx of lymphocytes, neutro-
phils, 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).

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
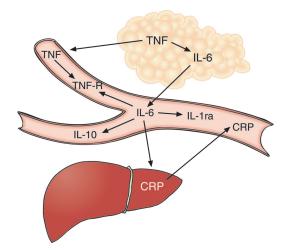

Fig. 1. Chronic low-grade systemic inflammation. The cytokine TNF-α is produced in adipose tissue. TNF-α stimulates the production of IL-6 in adipose tissue and blood mononuclear cells. IL-6 enhances the systemic levels of IL-1 receptor antagonist (IL-1ra), soluble TNF receptor (TNF-R), IL-10, and C-reactive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

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).

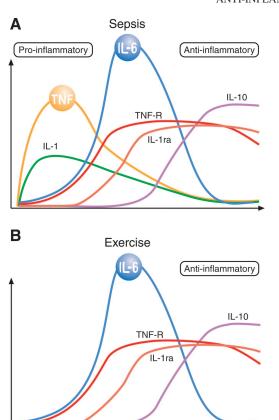Several studies have reported that carbohydrate ingestion attenuates elevations in plasma IL-6 during both running and

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.

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-

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)-
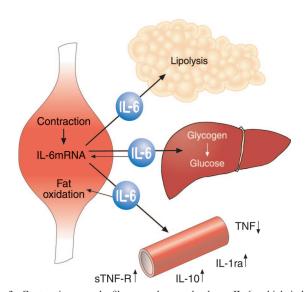

Fig. 3. Contracting muscle fibers produce and release IL-6, which induces several metabolic effects. IL-6 induces lipolysis and fat oxidation and is involved in glucose homeostasis during exercise. In addition, IL-6 has strong anti-inflammatory effects and may inhibit TNF-induced insulin resistance.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

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