Interleukin-6 in acute exercise and training: what is the biological relevance?

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ABSTRACT

It is now recognized that contracting skeletal muscle may synthesize and release interleukin-6 (IL-6) into the interstitium as well as into the systemic circulation in response to a bout of exercise. Although several sources of IL-6 have been demonstrated, contracting muscles contributes to most of the IL-6 present in the circulation in response to exercise. The magnitude of the exercise-induced IL-6 response is dependent on intensity and especially duration of the exercise, while the mode of exercise has little effect. Several mechanisms may link muscle contractions to IL-6 synthesis: Changes in calcium homeostasis, impaired glucose availability, and increased formation of reactive oxygen species (ROS) are all capable of activating transcription factors known to regulate IL-6 synthesis. Via its effects on liver, adipose tissue, hypothalamic-pituitary-adrenal (HPA) axis and leukocytes, IL-6 may modulate the immunological and metabolic response to exercise. However, prolonged exercise involving a significant muscle mass in the contractile activity is necessary in order to produce a marked systemic IL-6 response. Furthermore, exercise training may reduce basal IL-6 production as well as the magnitude of the acute exercise IL-6 response by counteracting several potential stimuli of IL-6. Accordingly, a decreased plasma IL-6 concentration at rest as well as in response to exercise appears to characterize normal training adaptation.
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INTRODUCTION

Since the first study in 1991 (115), several studies have consistently reported that the plasma interleukin-6 (IL-6) concentration increases in response to exercise

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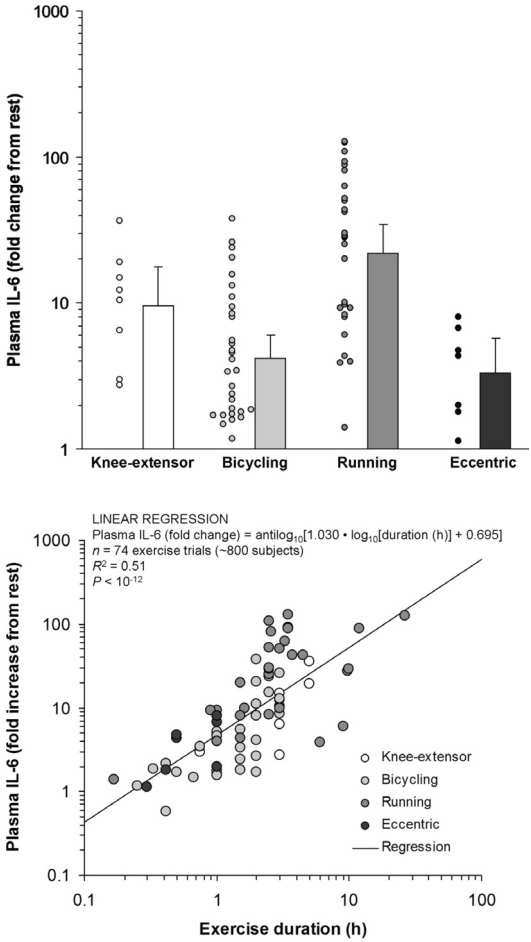

Fig. 1. Effect of mode and duration of exercise on post-exercise plasma IL-6.
Different modes of exercise (dynamic knee-extensor, bicycling, running, eccentric) and the corresponding increase in plasma IL-6 (fold change from pre-exercise level), based on the 67 exercise trials listed in Table 1 as well as 7 trials representing various eccentric exercise protocols (17, 53, 90, 144, 182, 194). Accordingly, the graphs represent approximately 800 subjects. Each dot represents one exercise trial, while the corresponding bars show geometric means with 95% confidence intervals (A). The overall $\log_{10}$-$\log_{10}$ linear relation (straight solid line) between exercise duration and increase in plasma IL-6 (fold change from pre-exercise level) indicates that 51% of the variation in fold plasma IL-6 increase can be explained by the duration of exercise (B).

(Table 1 & Fig. 1). Although the plasma concentration of several other cytokines may be affected by exercise, IL-6 increases more dramatically than any other cytokine investigated to date (120, 126). But what determines the magnitude and time course of the increase of IL-6 with exercise? What is the effect of exercise training on IL-6? And what is the possible biological relevance of IL-6 in acute and chronic physical activity? These are some of questions addressed in this review.

Two decades ago, IL-6 was first sequenced and described as a cytokine facilitating the differentiation of B-lymphocytes into immunoglobulin-secreting plasma cells (55, 56). Later, several other immunological properties was ascribed to this pleiotropic cytokine, which received its present name in 1987 (139). IL-6 belongs to a family of cytokines that also includes leukemia inhibitory factor, interleukin-11, ciliary neurotrophic factor, cardiotrophin-1, and oncostatin M. In addition to structural similarities, these cytokines share the gp130 receptor subunit (76).

Transcription and translation of the human gene encoding IL-6 – consisting of a ~5 kilobase long sequence containing 5 exons located on chromosome 7 (155) – leads to the synthesis of a propeptide containing 212 amino acids, which is cleaved in

order to obtain the mature IL-6 peptide containing 184 amino acids (56). Interestingly, a variant IL-6 peptide lacking the sequence encoded by exon II – thus unable to signal via the gp130 receptor – may be released from stimulated lymphocytes and monocytes in concert with the full-length IL-6 (74). Further post-translational modifications include varying degrees of glycosylation and phos-

Exercise mode											
Knee-extensor				Bicycling				Running			
n	Duration (h)	IL-6 (fold change)	Ref	*n*	Duration (h)	IL-6 (fold change)	Ref	*n*	Duration (h)	IL-6 (fold change)	Ref
7	3.0	3	(38)	9	0.4	1	(33)	12	0.2	1	(195)
7	0.8	3	(52)	9	0.3	1	(188)	19	6.0	4	(30)
7	3.0	6	(127)	16	0.7	1	(96)	7	1.0	4	(113)
6	3.0	11	(71)	7	1.0	2	(12)	8	1.5	4	(178)
7	3.0	12	(37)	17	1.0	2	(186)	6	9.1	6	(132)
6	3.0	15	(168)	6	2.0	2	(59)	8	1.5	8	(179)
6	5.0	19	(172)	9	0.5	2	(17)	30	2.5	8	(102)
7	5.0	36	(165)	8	1.0	2	(87)	7	1.0	9	(163)
				9	1.5	2	(86)	12	0.9	9	(114)
				7	0.3	2	(42)	10	1.6	10	(159)
				7	0.3	2	(42)	16	3.0	10	(107)
				8	0.4	2	(33)	10	1.5	20	(134)
				8	1.5	2	(177)	10	2.5	25	(119)
				6	2.0	3	(59)	13	9.8	28	(108)
				11	1.5	3	(181)	7	9.9	29	(110)
				6	0.8	3	(189)	7	2.5	29	(170)
				8	2.0	4	(11)	9	2.5	30	(169)
				8	1.0	5	(89)	50	4.5	42	(112)
				7	1.0	5	(163)	18	3.7	43	(21)
				9	1.0	5	(146)	6	3.0	50	(84)
				7	1.5	6	(164)	10	2.5	52	(109)
				6	2.0	8	(31)	16	3.3	63	(121)
				18	3.0	8	(128)	10	2.6	80	(175)
				8	1.0	9	(118)	18	3.5	88	(18)
				8	2.0	11	(60)	10	3.5	92	(183)
				8	3.0	13	(69)	16	2.5	109	(176)
				15	2.5	16	(106)	60	26.3	126	(111)
				6	2.0	20	(162)	10	3.5	128	(120)
				10	2.5	24	(109)				
				6	3.0	26	(117)				
				8	2.0	38	(47)				

Table 1. Effect of acute exercise on plasma IL-6 in humans.
Shown is the relation between exercise mode (dynamic knee-extensor, bicycling, and running), exercise duration, and plasma IL-6 increase (fold change from pre-exercise level). In studies investigating the effect of an intervention on the IL-6 response to exercise, e.g. carbohydrate supplementation, only the result from the control group (exercise without intervention) is presented. Hence, the n value may be lower than the n value presented in the original study.

phorylation, and several isoforms ranging from 21-30 kDa have been described (7, 46, 51, 95). Whether the biological effects *in vivo* of these isoforms differ is not established.

The plasma IL-6 concentration is ~1 pg/ml or even lower in resting healthy subjects (17, 121). In contrast, the plasma IL-6 concentration may reach 10000 pg/ml in response to severe systemic infections (40). Less dramatic increases of plasma IL-6 are found in numerous inflammatory and infectious diseases. A pathogenic role for IL-6 in the development of the metabolic syndrome has been suggested, in part because the presence of a chronic low-level increase of plasma IL-6 (usually <10 pg/ml) is associated with obesity (6), low physical activity (36, 123), insulin-resistance (13), type 2 diabetes (67), cardiovascular disease (39) and may serve as a predictor of mortality (15).

Downstream signaling requires that IL-6 binds to the heterodimeric receptor complex consisting of the ubiquitously expressed gp130 receptor and the specific receptor IL-6Rα (50). This event triggers tyrosine-phosphorylation of gp130 by Janus-activated kinases (Jak) on the intracellular domain, whereby at least two distinct signalling pathways are activated: 1) the signal transducers and activators of transcription (STAT) 1 and 3, and 2) the mitogen-activated protein kinases (MAPK) (49). The two pathways are characterized by distinct effects; thus, the effect of IL-6 may vary in different tissues depending on the balance between the two pathways (54). A negative feedback mechanism of STAT activation involves transcription and translation of the suppressor of cytokine signaling 3 (SOCS3).

THE IL-6 RESPONSE TO ACUTE EXERCISE

Following exercise, the basal plasma IL-6 concentration may increase up to 100 fold, but less dramatic increases are more frequent (Table 1, Fig. 1A). Thus, the 8000-fold increase of plasma IL-6 following a 246 km "Spartathlon" race (92) represents an atypical and extreme response. Of note, the exercise-induced increase of plasma IL-6 is not linear over time; repeated measurements during exercise show an accelerating increase of the IL-6 in plasma in an almost exponential manner (37, 119, 172). Furthermore, the peak IL-6 level is reached at the end of the exercise or shortly thereafter (37, 119), followed by a rapid decrease towards pre-exercise levels.

Where does the exercise-induced IL-6 come from?

Importantly, the contracting skeletal muscle *per se* appears to be one of the main sources of the IL-6 in the circulation in response to exercise: In resting human skeletal muscle, the IL-6 mRNA content is very low, while small amounts of IL-6 protein predominantly in type I fibers may be detected using sensitive immunohistochemical methods (137). In response to exercise, an increase of the IL-6 mRNA content in the contracting skeletal muscle is detectable after 30 minutes of exercise, and up to 100-fold increases of the IL-6 mRNA content may be present at the end of the exercise bout (71, 168). Recently, further evidence that contracting muscle fibers themselves are a source of IL-6 mRNA and protein has been achieved by analysis of biopsies from the human *vastus lateralis using in situ* hybridization and immunohistochemistry (58, 128). In addition, assessment of the

interstitial IL-6 concentration using microdialysis indicates that the concentration of IL-6 within the contracting skeletal muscle may be 5-100 fold higher than the levels found in the circulation (84, 147). Accordingly, IL-6 appears to accumulate within the contracting muscle fibers as well in the interstitium during exercise. However, it has been the simultaneous measurement of arterio-venous IL-6 concentrations and blood flow across the leg that has demonstrated that large amounts of IL-6 can be released from the exercising leg (172). In the same study, the authors also estimated that the net release from the exercising leg could account for the systemic increase of plasma IL-6, assuming that IL-6 is distributed in the extracellular compartment and that IL-6 content in blood is the same in plasma and the cellular fraction. Since IL-6 appears to be transported solely in the non-cellular fraction of the blood (20), the net release of IL-6 from the exercising leg probably was overestimated. Yet, a simpler approach based on the close log-log linear relationship between recombinant human IL-6 (rhIL-6) dose and resulting steady state plasma IL-6 concentration (Fig. 2) supports the concept that IL-6 released from the exercising limb may account for systemic plasma IL-6 increase following exercise: At the end of the exercise, the average release of IL-6 from the contracting leg was 15 ng/min, while the systemic plasma IL-6 concentration was 14 pg/ml (172). Based on the dose-response relationship, the expected systemic plasma IL-6 concentration corresponding to an IL-6 dose of 15 ng/min is 16 pg/ml ($\text{antilog}_{10}[1.05 \cdot \log_{10}[15 \text{ ng/ml}] + 0.07]$), which corresponds well to the observed value.

However, although IL-6 released from the contracting muscles may account for most of the IL-6 found in the circulation, other studies have demonstrated that skeletal muscle is not the sole source of exercise-induced IL-6. Using oral supplementation with vitamins C and E for 4 weeks, the IL-6 net release from the exercising legs was almost blocked completely, yet the systemic increase of plasma IL-6 was only reduced by 50% (37). Very high concentrations of IL-6 along the Achilles' tendon has been detected using microdialysis in response to prolonged running (84), but since the muscle mass involved in exercise is much higher than the mass comprised by tendons, the mutual contribution of peritendinous versus muscle-derived IL-6 to the systemic IL-6 is unclear. In addition, a small net release of IL-6 from the internal jugular vein has been reported, suggesting that the central nervous system may contribute to the IL-6 found in the circulation (118). In contrast, a contribution from peripheral blood mononuclear cells to the IL-6 found in the circulation of healthy subjects is detected consistently neither at rest nor in response to exercise (121, 162, 186, 189). The adipose tissue may contribute markedly to IL-6 in the circulation at rest (98, 160), but measurement of arterio-venous plasma IL-6 differences across the abdominal subcutaneous adipose tissue bed shows that this compartment does not contribute to the exercise-induced IL-6 in the circulation until the recovery phase (88). However, since almost any cell type may synthesize IL-6 upon adequate stimulation (3), further studies may discover other sites contributing to the IL-6 in the circulation in response to exercise.

How is the exercise-induced IL-6 response regulated?

Overall, the combination of mode, intensity and duration of the exercise determines the magnitude of the exercise-induced increase of plasma IL-6. However,

although it was suggested that the IL-6 response was related to muscle damage (17), it now has become clear that eccentric exercise is not associated with more marked increases of plasma IL-6 than compared to exercise involving concentric muscle contractions (Fig 1A). Thus, muscle damage is not required in order to increase plasma IL-6 during exercise. Rather, eccentric exercise may result in a delayed peak and a slower decrease of plasma IL-6 during recovery (53, 90, 194).

In contrast, the IL-6 response is sensitive to the exercise intensity (122), which again indirectly represents the muscle mass involved in the contractile activity. Since contracting skeletal muscle *per se* is an important source of IL-6 found in the plasma (37, 172), it is therefore not surprising that exercise involving a limited muscle mass, e.g. the muscles of the upper extremities, may be insufficient in order to increase plasma IL-6 above pre-exercise level (8, 57, 116). In contrast, running – which involves several large muscle groups – is the mode of exercise where the most dramatic plasma IL-6 increases have been observed (Table 1, Fig. 1A).

Regardless, exercise duration is the single most important factor determining the post-exercise plasma IL-6 amplitude (Table 1, Fig. 1B); more than 50% of the variation in plasma IL-6 following exercise can be explained by exercise duration alone ($P < 10^{-12}$). Since exercise at high intensity often is associated with shorter duration of the exercise and *vice versa*, the relationship between the plasma IL-6 increase and the duration may be even more pronounced if adjusted for the exercise intensity. In accordance, 6 minutes of maximal rowing ergometer exercise may increase plasma IL-6 two-fold (105), but more than 10-fold increases of plasma IL-6 has not been observed in response to exercise lasting less than 1 h (Fig. 1B). Based on the log-log linear relationship between time and fold increase of plasma IL-6 (Fig. 1B), a 10-fold increase of plasma IL-6 requires exercise for 1.9 h (95% confidence interval, CI, 1.6 - 2.9 h, $P < 0.0001$) of exercise, while a 100-fold increase of plasma IL-6 requires exercise lasting 6.0 h (CI 4.5 - 8.1 h, $P < 0.0001$). This relationship is remarkably insensitive to the mode of exercise, although the highest increases of plasma IL-6 generally are found in response to running.

↑, increase; ↓, decrease; ↔ no effect of the intervention.

Intervention	Effect on exercise-induced IL-6	References
Reduction of pre-exercise glycogen content	Muscle IL-6 mRNA ↑ Plasma IL-6 ↑	(24, 71, 171)
Supplementation with carbohydrates	Muscle IL-6 mRNA ↔ Plasma IL-6 ↓	(37, 179, 189)
Hyperglycemia in Type 1 diabetes	Plasma IL-6 ↑	(42)
Nicotinic acid (inhibits lipolysis)	Muscle IL-6 mRNA ↔ Adipose tissue IL-6 mRNA ↑ Plasma IL-6 ↑	(62)
Hot environment	Plasma IL-6 ↑	(164)
Indomethacin (NSAID)	Plasma IL-6 ↓	(143)
O_2 supplementation to COPD patients	Plasma IL-6 ↓	(188)
Supplementation with antioxidants	Muscle IL-6 mRNA ↔ Plasma IL-6 ↓	(37, 179, 189)

Table 2. Some interventions influencing the exercise-induced IL-6 response.

What mechanisms may explain why contractile activity leads to increased synthesis of IL-6? Since IL-6 is synthesized and released only from the contracting muscles and not from the resting muscles exposed to the same hormonal changes (66, 172), circulating systemic factors alone does not explain why contracting muscles synthesize and release IL-6. Instead, local factors seem necessary, although systemic factors may modulate the response.

The promoter region of the IL-6 gene contains binding sites for the nuclear factor kappa B (NF-κB) and nuclear factor interleukin-6 (NFIL6) (93). Additional transcription factors such as the nuclear factor of activated T cells (NFAT) (1) and heat shock factors 1 and 2 (HSF1 and HSF2) (141) may contribute to the activation of IL-6 gene transcription. *In vitro*, calcium activates both NFAT and NF-κB (29, 83), and incubation of muscle cell cultures with a calcium ionophore (ionomycin) increases IL-6 secretion in a p38 MAPK dependent manner (24). Human studies have shown increased total and nuclear content of phosphorylated p38 MAPK, but unaltered nuclear content of NFAT in muscle biopsies after 1 h of bicycling (97), while mRNA content of calcineurin A – which is involved in calcium signalling – is increased in muscle biopsies 6 h post 3 h of knee-extensor exercise (136). Activation of NF-κB has been demonstrated in rat skeletal muscle after exercise (65), but not consistently in humans (97). Noteworthy, NF-κB is a redox-sensitive transcription factor (154) that may be activated by reactive oxygen species (ROS). Increased ROS formation in exercising skeletal muscle following exercise has been demonstrated directly in animals (27, 63) and indirectly in humans (4). *In vitro*, murine skeletal myotubes release IL-6 when exposed to oxidative stress in a NF-κB-dependent way (81). In addition, supplementation with different antioxidants attenuates the systemic increase of IL-6 in response to exercise (179, 189). Using arterio-venous differences of IL-6 across the leg, we observed that the reduced systemic increase of IL-6 during exercise was due to an almost complete inhibition of the net leg release of IL-6 in the group pre-treated with vitamin C and E for 4 weeks (37). The observation that indomethacin – a member of the non-steroid anti-inflammatory drugs (NSAID), which are known to inhibit NF-κB activity – reduces the exercise-induced increase of IL-6 further supports that NF-κB is likely to serve as a link between contractile activity and IL-6 synthesis (80, 143). On the other hand, increased oxidative stress, as well as low glucose availability, low glycogen content, catecholamines, increased intracellular calcium levels, hyperthermia, ischemia-reperfusion are all features of exercise capable of inducing heat shock proteins (HSPs) (9, 22, 34, 125, 190, 193), which may in turn activate IL-6 synthesis via HSF1 and HSF2 (141). Accordingly, several regulators of IL-6 transcription are likely to be activated by an altered intramuscular milieu in response to exercise (Fig. 4). This point of view is supported by the various interventions that have demonstrated an effect on the exercise-induced IL-6 response (Table 2). For instance, reduction of intramuscular glycogen content prior to exercise results increased accumulation of IL-6 mRNA within the contracting muscle as well as increased release of IL-6 from the contracting muscle (24, 71, 171). This effect of glycogen reduction on the exercise-induced IL-6 response may be mediated through activation of p38 MAPK (24) and AMPK (89). In contrast, supplementation with carbohydrates during exercise inhibits the exercise-induced increase of IL-6 in plasma, whereas IL-6 mRNA expression within the contracting muscle is unaffected (32, 102, 109,

163). While glucose availability may interfere with IL-6 gene expression through AMPK (2), other mechanisms regulating IL-6 at a posttranslational level appear to exist.

To make it even more complex, IL-6 appears to be capable of enhancing its own transcription (72), which may partly explain the almost exponential increase of IL-6 towards the end of exercise (Fig. 3). However, it should be noted that the IL-6 released into the circulation is cleared very quickly, thus the 'area under the curve' for plasma IL-6 in response is limited in particular in response to short bouts of exercise (Fig. 3). In mice, the halflife of ^{125}I-labelled IL-6 in the circulation is 2 minutes (99), which is accordance with the rapid decline of plasma IL-6 following rhIL-6 infusion from human studies (187). Most of the IL-6 is cleared by the kidneys and the liver (31, 99).

What are the effects of IL-6 in acute exercise?

Exercise is known to cause major physiological, hormonal, metabolic, and immunological effects. The question is whether exercise-induced IL-6 mediates some of these effects. Of note, IL-6 may act locally within the contracting muscle during exercise or within the adipose tissue during recovery, while most other cells and target organs are exposed only to IL-6 released into the systemic circulation. Regarding the systemic effects of IL-6, the dose-response relationship and timing has to be considered. First, it should be noted that marked increases of plasma IL-6 only occur if the exercise involves a considerable muscle mass working for a considerable amount of time at a considerable intensity. Otherwise, a systemic IL-6 increase may be small or absent. Regardless, the exercise-induced peak plasma IL-6 concentration will usually not exceed 100 pg/ml. Second, the peak plasma IL-6 concentration occurs at the cessation of the exercise (or shortly after), thus the systemic effects induced by IL-6 are for the most part expected to occur during recovery from exercise.

Metabolic and hormonal effects of exercise-induced IL-6. Whole body oxygen consumption and carbondioxide production increases in response to rhIL-6 infusion in the postabsorptive state as well as during a euglycemic hyperinsulinemic clamp (19, 184). This increase in energy turnover may occur without significant changes in body temperature, though a moderate increase in body temperature – which occurs when the plasma IL-6 concentration is 300 pg/ml or higher (174, 184, 185) – may *per se* be associated with an augmented energy turnover. However, since a relatively high plasma IL-6 concentration apparently is required in order to increase body temperature, it seems unlikely that the systemic increase of IL-6 in response to exercise modulates metabolism through changes in body temperature.

In rats, IL-6 injection may deplete hepatic glycogen content (173). *In vitro* and *in vivo* in animals, several studies have indicated that IL-6 interferes with insulin-signalling in hepatocytes and liver tissue (68, 77, 78, 156, 157), whereby hepatic glucose output may increase. However, even marked elevations of plasma IL-6 has little effect on glucose metabolism in resting humans: In subjects both with and without type 2 diabetes, an acute elevation of plasma IL-6 has no effect glucose rate of appearance (R_a), glucose disappearance (R_d) or plasma glucose in the postabsorptive state (133, 167). When combined with a euglycemic hyperinsulinemic clamp, an acute increase of plasma IL-6 to ~50 pg/ml has no effect on

plasma glucose, glucose R_a or R_d (82), while an acute increase of plasma IL-6 to ~200 pg/ml increases glucose R_d and glucose oxidation (19). However, a much lower increase of plasma IL-6 increases both glucose R_a and R_d during exercise (35). The mechanism behind the apparent discrepancy between the effect of IL-6 at rest and during exercise is unknown, but the presence of additional "exercise cofactors" capable of modulating the effect of IL-6 has been suggested (35). Alternatively, the effect of IL-6 on glucose metabolism is only detectable when glucose fluxes are high as in response to exercise or insulin stimulation. Accordingly, a systemic increase IL-6 in response to exercise may augment hepatic glucose output, while other tissues increase the uptake of glucose, whereby the plasma glucose concentration is unaffected. Thus, it is possible that the enhanced hepatic output is balanced by increased glucose uptake in the contracting skeletal muscle during exercise. However, conflicting results regarding the effect of IL-6 on glucose uptake in skeletal muscle exist: In mice, IL-6 decreases insulin-mediated glucose uptake in skeletal muscle (75), while L6 myotubes exposed to IL-6 *in vitro* demonstrate increased insulin-sensitivity (19).

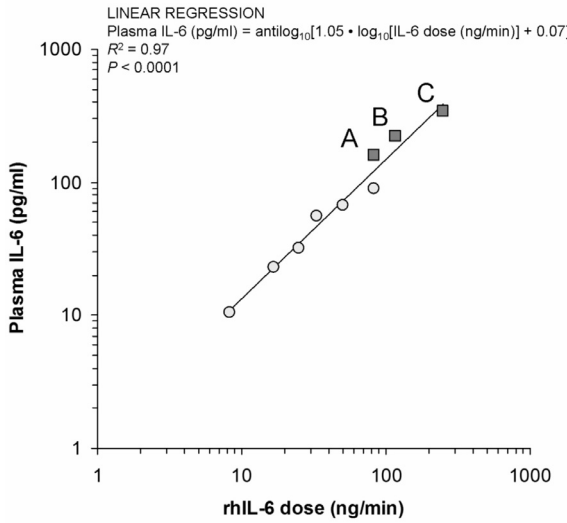

Fig. 2. Dose-response curve for rhIL-6.
Shown is the plasma IL-6 concentration in response to different infusion rates of rhIL-6 diluted in saline containing human albumin. The equation describes the log10-log10 linear regression (straight solid line). The light grey circles represent data from a pilot study, while the dark grey squares represent published data: A, (72); B, (133); C, (187). Although the shown dose-response relationship has been established in resting subjects, it has been proven useful also in exercise trials (35).

Infusion of rhIL-6 increases lipolysis and fat oxidation after 2 h in healthy subjects (187) and in subjects with type 2 diabetes (133). The lipolytic effect of IL-6 is also observed in cultured adipocytes, suggesting a direct effect of IL-6 on adipose tissue (133). Increased IL-6 mRNA content in the adipose tissue is observed in response to exercise (69), and this increase appears to be mediated by catecholamines (73). If the IL-6 mRNA is translated into protein, an additive effect together with the IL-6 derived from the circulation is possible. Accordingly, IL-6 and adrenaline may enhance the lipolytic capacity of each other in response to exercise. As for the liver, the effect of IL-6 in adipocytes may partly be due to a decrease in insulin-signalling (148, 158). Although adipose tissue mRNA expression of the hormone-sensitive lipase (HSL) is increased by rhIL-6 infusion, the corresponding HSL protein is not affected (192).

Does IL-6 affect other hormones, which in part may explain the apparent metabolic effects of IL-6? Table 3 summarizes some of the effects of an acute increase of plasma IL-6 on some major hormones in humans. IL-6 injection increases adrenocorticotropic hormone (ACTH) in a corticotropin-releasing hormone (CRH) dependent manner in rats (101), while injection of an anti-IL-6 antibody abrogate the endotoxin-induced increase of ACTH in mice (131). Since the IL-6 receptor present in the human pituitary gland (48) and adrenal cortex (45), alternative pathways by which IL-6 can stimulate cortisol release in humans may exist. A dose-dependent relationship between the IL-6 and cortisol in humans has been demonstrated (184). In fact, a consistent increase of cortisol has been reported when plasma IL-6 is ~50 pg/ml or higher (Table 3). Conversely, the post-exercise increase of cortisol is attenuated if the release of IL-6 from the exercising leg is inhibited by supplementation with vitamins C and E (37). However, the increase of cortisol by IL-6 is abrogated during a euglycemic hyperinsulinemic clamp (19). Taken together, it seems likely that an exercise-induced systemic increase of IL-6 may reach concentrations capable of inducing cortisol secretion, although other factors contributing to an exercise-induced activation of the HPA axis not should be excluded. Of note, an increase of cortisol may contribute further to the increased lipolysis and hepatic glucose output induced by IL-6. Interestingly, the increase of cortisol may be involved in a negative feedback regulation of IL-6, at least when present in higher concentrations (124).

While cortisol is induced by even modest plasma IL-6 increases, somewhat higher plasma IL-6 concentrations appear to be necessary in order to increase plasma glucagon and growth hormone (GH) levels consistently (Table 3). During exercise, a low-level increase of IL-6 has no effect on either glucagon or GH (35). Plasma concentrations of both adrenaline and noradrenaline are increased when plasma IL-6 is ~300 pg/ml or higher (187). In healthy subjects, even very high IL-6 doses have no acute effect on fasting postabsorptive plasma insulin levels (Table 3). However, IL-6 infusion may decrease plasma insulin in subjects with type 2 diabetes without concomitant changes in glucose turnover (133). Of note, the increase of catecholamines and the decrease of insulin in response to exercise comprise two highly potent stimuli for lipolysis (28, 64), while GH and cortisol may further enhance the lipolysis (43, 151). Accordingly, IL-6 *per se* may induce lipolysis but more likely IL-6 may stimulate lipolysis in concert with catecholamines and cortisol. In type 2 diabetes, an additional decrease of plasma insulin may contribute to the lipolytic effect of IL-6 (133).

Immunoregulatory effects of exercise-induced IL-6. In humans, infusion of rhIL-6 increases plasma cortisol, IL-1 receptor antagonist (IL-1ra), IL-10, soluble TNF-α receptors (sTNF-R), and C-reactive protein (CRP) (149, 166, 180). Conversely, the increase of cortisol, IL-1ra and CRP after exercise is abrogated if the release of IL-6 from the contracting muscles is reduced by supplementation with antioxidants (37), suggesting that IL-6 from the contracting skeletal muscle in part accounts for the increase of cortisol, IL-Ira and CRP.

The anti-inflammatory properties of cortisol are well characterized (5). In response to rhIL-6 infusion, a significant increase of cortisol occurs within one hour (166). While moderate exercise increase number as well as antimicrobial capacity of the neutrophils in the circulation, intense exercise is associated with a reduced antimicrobial capacity of the neutrophils (126), which is likely to be

mediated by cortisol (91). In addition, cortisol may reduce the number of lymphocytes by enhancing the apoptosis. Thus, higher systemic increases of IL-6 – as observed after prolonged intense exercise – may in part be responsible for the changes in leukocyte subpopulations and antimicrobial capacity.

IL-1ra is a cytokine produced primarily by macrophages, but a further contribution may come from hepatocytes and monocytes (41, 180). IL-1ra attenuates the effect of the pro-inflammatory cytokine IL-1 by reducing the signal transduction through the IL-1 receptor (41). Plasma IL-1ra is increased after rhIL-6 infusion for one hour (166). In contrast to IL-1ra, IL-10 is capable of inhibiting the LPS-stimulated production of several pro-inflammatory cytokines including TNF-α, IL-1α and IL-1β (100, 140). The anti-inflammatory effect of IL-10 is exerted at both the transcriptional and posttranslational level (10, 191). Lymphocytes and monocytes are the primary sources of IL-10, which increases in plasma in response to rhIL-6 infusion for 2 hours (166).

IL-6 infusion also induces a delayed increase of CRP from the liver via activation of the STAT3 pathway (166, 196). CRP was originally characterized as an acute phase protein involved in precipitation of the somatic C-polysaccharide of *Streptococcus pneumoniae* (130). Whether CRP has pro-inflammatory effects or not is being debated (129). When purified adequately, even high doses of recombinant CRP do not induce a pro-inflammatory response (129). Rather, CRP may contribute to the increase of plasma IL-1ra during late recovery from exercise by enhancing the release of IL-1ra from monocytes (142).

Furthermore, while the pro-inflammatory cytokine TNF-α can stimulate IL-6 production (138), IL-6 does not stimulate the production of TNF-α (166). Rather, IL-6 attenuates the LPS-stimulated production of TNF-α in cultured monocytes (153) as well as *in vivo* in humans (161), while treatment with anti-IL-6 antibodies augment the TNF-α response following challenge with staphylococcal enterotoxin B in mice (94). In addition, IL-6 may attenuate the effect of TNF-α by induction of sTNF-R (180).

Taken together, the release of IL-6 from the contracting muscles may facilitate a broad anti-inflammatory response via effects on liver as well as on different leukocyte subpopulations.

IL-6 AND TRAINING ADAPTATION

Exercise training involves multiple adaptations including increased pre-exercise skeletal muscle glycogen content, enhanced activity of key enzymes involved in the beta-oxidation (152), increased sensitivity of adipose tissue to adrenaline-stimulated lipolysis (26), increased oxidation of intramuscular triglycerides (135), whereby the capacity to oxidize fat is increased (61, 150). As a consequence, the trained skeletal muscle is less dependent on plasma glucose and muscle glycogen as substrate during exercise (135).

Several epidemiological studies have reported a negative association between the amount of regular physical activity and the basal plasma IL-6 levels: the more physical active, the lower basal plasma IL-6 (23, 25, 123). Basal plasma IL-6 is closer associated with physical inactivity than other cytokines associated with the metabolic syndrome (36).

The epidemiological data are supported by findings from intervention studies, although these produce less consistent results. Basal levels of IL-6 are reduced after training in patients with coronary artery disease (44). Aerobic training of adults aged 64 ys or more for 10 months also decreases basal plasma IL-6 (79). In severely obese subjects, the combination of a hypocaloric diet and regular physical activity for 15 weeks reduces not only plasma IL-6, but also the IL-6 mRNA content in subcutaneous adipose tissue and in skeletal muscle (14). In addition, athlete skiers have lower basal plasma IL-6 during the training season than off-season (145). However, others have not observed changes in basal IL-6 levels in response to training (16, 85, 104).

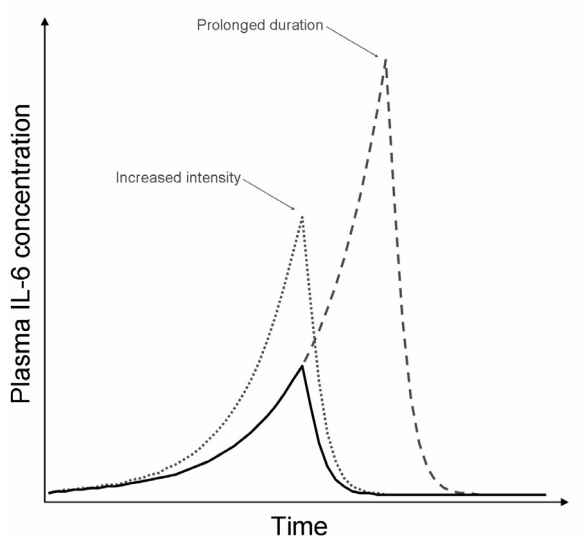

Fig. 3. The effect of exercise duration and intensity on the plasma IL-6 level.
Schematic presentation showing that in response to exercise, plasma IL-6 increases in a non-linear fashion over time (37, 119, 172) and peaks shortly after the cessation of the exercise (solid line). If the exercise intensity increases, plasma IL-6 is likely to increase faster resulting in a higher peak plasma IL-6 level (dotted line). If the exercise duration is extended, the peak plasma IL-6 occurs later but is also augmented (dashed line). From an "area under the curve" point of view, the cumulative systemic effect of IL-6 in response to exercise may accordingly be more prominent in response to prolonged exercise compared to an intense but shorter bout of exercise, even if the peak IL-6 values are similar.

At present, evidence that the exercise-induced increase of plasma IL-6 is affected by training is limited. Using knee-extensor exercise, 7 healthy men trained for 1 hour 5 times a week for 10 weeks (38). Before and after the training, the participants performed knee-extensor exercise for 3 h at 50% of the maximal workload. Due to a marked training response, the absolute workload was much higher after training compared to pre-training. Despite this, the increase in IL-6 mRNA content by acute exercise was 76-fold before training but only 8 fold after training. In addition, the exercise-induced increase of plasma IL-6 was similar before and after training, although the absolute workload was increased by 44% with training. Accordingly, it could be speculated that differences in training status may explain why elderly subjects release the same amount of IL-6 as young subjects from the leg during knee-extensor exercise at the exact same relative – but half the same absolute – workload (127).

Noteworthy, while IL-6 appears to be down-regulated by training, the IL-6 receptor appears to be up-regulated: In response to exercise training, the basal IL-

↑, increase; ↓, decrease; ↔ not affected by rhIL-6; GH, growth hormone; A, adrenaline; NA, noradrenaline.

[a] In response to rhIL-6 infusion, plasma insulin decreases in subjects with type 2 diabetes but not in healthy controls.

Plasma IL-6 level (pg/ml)	Insulin	Cortisol	Glucagon	GH	A, NA	References
< 50	↔	↔	↔	↔	↔	(35, 59, 184, 185)
~50	↔	↑				(82)
~100	↔			↑		(103)
~150	↔	↑	↔		↔	(166, 167, 187)
~200	↔/↓[a]	↑	↑	↑	↔	(133, 192)
~300	↔	↑	↔	↑	↑	(167, 184, 185, 187)
~500	↔	↑	↑		↑	(174)
~4000	↔	↑	↑	↔		(184, 185)

Table 3. Acute effects of rhIL-6 on hormone levels in humans.

6R mRNA content in trained skeletal muscle is increased by ~100% (70). Accordingly, it is possible that the downregulation of IL-6 is partially counteracted by enhanced expression of IL-6R, whereby the sensitivity to IL-6 is increased. However, it remains to be determined if the increased IL-6R mRNA content corresponds to an increased expression of the IL-6R protein. Furthermore, it is not known if the enhanced IL-6R expression following training occurs in several tissues or only locally within the trained skeletal muscle. In the circulation, the IL-6R concentration is affected neither by training nor acute exercise (70).

Thus, there is good evidence that low physical activity results in elevated basal IL-6 levels, while a high level of physical activity results in low basal IL-6 levels. Yet, there is limited evidence indicating that the exercise-induced increase of IL-6 in the contracting muscle as well as in the circulation is attenuated by training. Since training adaptation includes changes known to counteract potential stimuli for IL-6, it is, however, very likely that further studies will demonstrate alterations in the exercise-induced IL-6 response by training.

SUMMARY AND CONCLUSION

Clearly, exercise may increase synthesis and subsequent release of IL-6 from contracting muscles, and this release may induce multiple effects in multiple tissues. IL-6 possesses somewhat catabolic features, indicated by the ability to increase energy expenditure, increase lipolysis, increase fat oxidation, increase endogenous glucose output (in part via reducing insulin-signalling in fat and liver), and increase cortisol. On the other hand, this mobilization of glucose and FFA from liver and fat to the circulation may result in enhanced substrate uptake by other tissues, e.g., the contracting skeletal muscle. The apparent discrepancy between tissues regarding the response to IL-6 may be due differences in downstream IL-6 signalling in different tissues. In addition, the IL-6 released from the contracting muscles may induce an anti-inflammatory response reflected by increase of IL-1ra, IL-10, CRP, and cortisol without concomitant increases in pro-inflammatory mediators.

The time and intensity required in order to accumulate IL-6 protein within the contracting muscle are not well characterized. In contrast, duration of exercise is the single most important factor that determines the magnitude of the systemic IL-6 response. The longer duration of the exercise, the more pronounced the systemic IL-6 response will be. Accordingly, short bouts of exercise or exercise at low intensity are not likely to increase IL-6 to an extent where systemic effects of IL-6 are expected. Independent of mode, exercise for less than one hour induces a peak plasma IL-6 concentration below 10 pg/ml (< 10 fold increase from pre-exercise level, Fig. 1B), and this for only a short period of time (Fig. 2). Several studies have demonstrated that pre-exercise glycogen depletion accelerates the exercise-induced IL-6 response, while carbohydrate supplementation reduces the increase of plasma IL-6. Thus, reduced availability of substrates fuelling the mus-

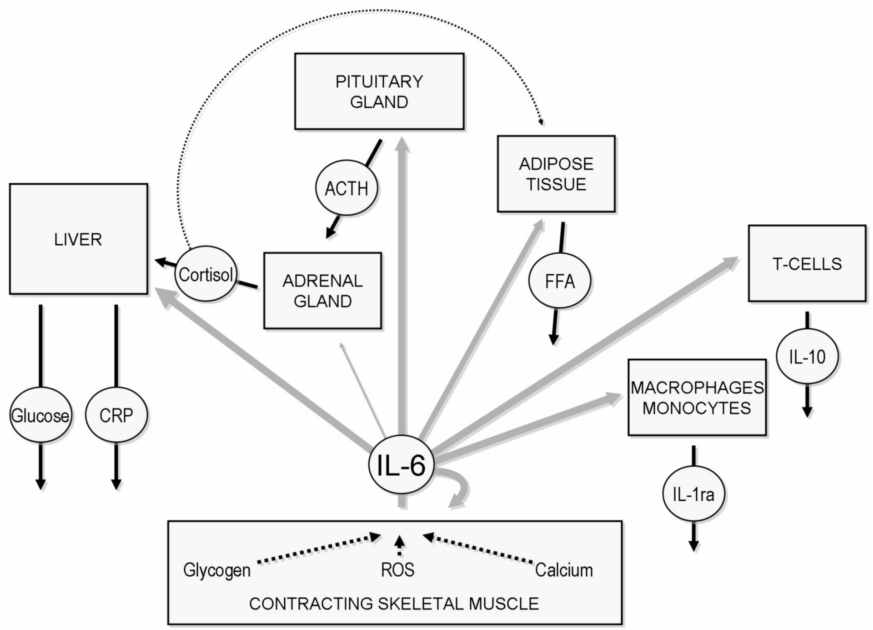

Fig. 4. Possible effects of IL-6 released from contracting skeletal muscle in response to exercise.
Several mechanisms may link muscle contractions to IL-6 synthesis. Changes in calcium homeostasis, impaired glucose availability, and increased formation of reactive oxygen species (ROS) are all capable of inducing transcription factors regulating IL-6 gene transcription. The synthesized IL-6 may act locally within the contracting skeletal muscle in a paracrine manner or be released into the circulation, thus able to induce systemic effects. In liver, the circulating IL-6 may increase hepatic glucose output and production of C-reactive protein (CRP). In adipose tissue, IL-6 produced locally and IL-6 from the circulation in concert may increase lipolysis. Via activation of the hypothalamic-pituitary-adrenal (HPA) axis, the circulating IL-6 may stimulate cortisol release, which may further enhance the lipolysis. In lymphocytes, macrophages, and monocytes, the circulating IL-6 may stimulate the production of IL-1ra and IL-10.

cle contractile activity appears to be one of the main triggers of IL-6 production. To reduce substrate availability, glycogen stores in liver and muscle have to be reduced markedly, which is process that takes time, although dependent on the intensity.

Low physical activity is associated with increased plasma IL-6 at rest. Exercise training dramatically reduces the exercise-induced accumulation of IL-6 mRNA within the contracting skeletal muscle. Training adaptation also includes increased glycogen content in the resting skeletal muscle and enhanced capacity to oxidize fat, whereby the contracting muscle becomes less dependent on plasma glucose as well as capable of performing more mechanical work before glycogen levels are reduced critically. Accordingly, exercise training may counteract several potential stimuli of IL-6 production. Therefore, a low plasma IL-6 concentration at rest as well as in response to exercise appears to characterize the IL-6 response after training adaptation. Interestingly, the training-induced downregulation of IL-6 may to some extent be compensated by an enhanced sensitivity to IL-6, at least within the trained skeletal muscle.

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