

Invited minireview

Muscle-derived interleukin-6—A possible link between skeletal muscle, adipose tissue, liver, and brain

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Abstract

Accumulating evidence exists that regular exercise offers protection against chronic disorders such as cardiovascular diseases, type 2 diabetes, dementia, and depression. Although acute and chronic exercise has numerous consequences, it is still discussed how contracting skeletal muscles mediate metabolic and physiological effects of benefits on health. For years the search for the stimulus that initiates and maintains the change of excitability or sensibility of the regulating centers in exercise has been progressing. For lack of more precise knowledge, it has been called the ‘work stimulus,’ ‘the work factor’ or ‘the exercise factor.’ In other terms, the big challenge for muscle and exercise physiologists has been to determine how muscles signal to central and peripheral organs. Recently, we identified that muscle fibers produce and release the cytokine IL-6 into the circulation during exercise. We further 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.’ In line with that adipokines have been suggested as a term, which is restricted to cover cytokines and other peptides which are produced and secreted by adipocytes, we suggest that the term “myokines” should be used exclusively to describe cytokines or other peptides, which are produced and released by muscle fibers per se. Myokines may represent the link from working muscle to other organs such as the adipose tissue, the liver, and the vascular compartments. Here, we review the literature on muscle- and brain-derived IL-6. We further suggest that myokines may also provide an explanation as to how regular muscle activity influences mood, performance, and cognitive function.

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1. Introduction

Regular exercise offers protection against all causes of mortality, primarily by protection against atherosclerosis, type 2 diabetes, colon cancer, and breast cancer (Blair et al., 2001). In addition, physical training is effective in the treatment of patients with ischemic heart disease (Jolliffe et al., 2000), heart failure (Piepoli et al., 2004), and type 2 diabetes (Boule et al., 2001). Although

the evidence is less clear, it appears that regular physical activity also protects against cognitive impairment and depression. At least one large-scale study suggests that engaging in regular physical activity, among other health benefits, may delay or prevent the onset of cognitive impairment, Alzheimer’s disease and dementia of any kind in the elderly, especially in women (Laurin et al., 2001). Among Harvard alumni, incidence-rates of physician-diagnosed depression were examined during a 25-year follow-up period. Depression rates were lower among the physically active and sport players (Paffenbarger et al., 1994). Exercise training has also been dem-

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onstrated to have a potential role in the treatment of patients with disturbed brain function. A recent meta-analysis concluded that exercise training increases fitness, physical function, cognitive function, and positive behaviour in persons with dementia and related cognitive impairment (Heyn et al., 2004). The effectiveness of exercise as an intervention in the management of depression seems promising, although it is premature to conduct firm conclusions (Lawlor and Hopker, 2001). Even though it is not clear whether the pathogenesis of the metabolic syndrome, dementia, and depression shares common mechanisms, it is of interest that these disorders co-exist (Anderson et al., 2001; Perlmutter et al., 2000; Vinkers et al., 2004). Some of the beneficial effects of regular exercise are mediated through an improved lipid profile (Kraus et al., 2002), elevated insulin sensitivity (Dela et al., 1993), and lower blood pressure (Whelton et al., 2002). Less is known about the mechanisms whereby exercise influences brain function. This effect may be related to its effect of exercise on serotonin level in the brain (Dwyer and Flynn, 2002) and its effect on brain-derived neurotrophic factor (BDNF), a predictor of learning efficacy (Molteni et al., 2004).

Although acute and chronic exercise has numerous consequences for health, it is still discussed how contracting skeletal muscles mediate metabolic and physiological effects of benefits on health. For most of the last century, researchers have searched for a muscle contraction-induced factor, which could mediate some of the exercise-induced changes in other organs (Winocour et al., 1992). Due to lack of more precise knowledge, it has been called the “work stimulus” or “the work factor” or the “exercise factor” (Pedersen et al., 2003), although “exercise factors” would be more compatible since multiple metabolic changes are induced by exercise. The concept of an exercise factor builds on the fact that contracting skeletal muscle mediates metabolic and physiologic responses in other organs, which is not mediated by nerve impulses. Since the signalling pathways from contracting skeletal muscles to other organs are not the nervous system has been demonstrated by the fact that electrical stimulation of paralysed muscles in spinal cord injured patients with no afferent and efferent nerve impulses induces in essence the same physiological changes as in intact human beings. Therefore, contracting skeletal muscles clearly communicate to other organs via humoral factors = exercise factors, which are produced and released into the circulation during physical activity. Such factors might directly or indirectly induce functional changes in other organs such as the adipose tissue, the liver, the cardiovascular system, and the brain. Thereby, exercise factors may contribute to mediate the health beneficial effects of exercise.

Cytokines are biologically active low molecular weight proteins that possess several endocrine and metabolic functions, and are known products of the im-

mune system and inflammation. White adipose tissue is now recognised to be a multifunctional organ; in addition to the central role of lipid storage, it has a major endocrine function secreting several hormones, notably leptin, adiponectin, TNF- α , IL-6, plasminogen activator inhibitor-1, and a diverse range of other protein factors. These various protein signals have been given the collective name ‘adipocytokines’ or ‘adipokines.’ It has been recommended that the term ‘adipokine’ is universally adopted to describe a protein that is secreted from (and synthesised by) adipocytes. It is suggested that the term is restricted to proteins secreted from adipocytes, excluding signals released only by the other cell types (such as macrophages) in adipose tissue (Trayhurn and Wood, 2004).

We recently pointed at IL-6 as an exercise factor and suggested that IL-6 and other cytokines, which are produced and released by skeletal muscles exerting their effects on other organs of the body, should be named “myokines” (Pedersen et al., 2003, 2004). In line with that adipokines have been suggested as a term to cover cytokines and other peptides, which are produced and secreted by adipocytes, we suggest that the term “myokines” should be restricted as a collective term to describe cytokines or other peptides, which are produced and released by muscle fibers per se. Accordingly, IL-6 is a cytokine, which can be classified as both an adipokine and a myokine as it is produced and secreted by both adipocytes and myofibers. Here, we provide an updated review on muscle-derived IL-6 and suggest that the concept of “myokines” could represent a link between skeletal muscle work, adipose tissue, liver, and brain. (See Fig. 1.)

2. IL-6 is released from muscle during exercise

IL-6 is markedly increased after exercise without muscle damage. This fact has been documented in numerous studies. Plasma IL-6 increases in an exponential fashion with exercise and is related to exercise intensity, duration, the mass of muscle recruited, and endurance capacity (reviewed in (Febbraio and Pedersen, 2002; Pedersen and Hoffman-Goetz, 2000; Pedersen et al., 2001, 2003)). The latter review articles summarize the following findings: IL-6 mRNA is upregulated in contracting skeletal muscle and the transcriptional rate of the IL-6 gene is markedly enhanced by exercise. In addition, the IL-6 protein is expressed in contracting muscle fibers and IL-6 is released from skeletal muscle during exercise. Studies have reported that carbohydrate ingestion attenuates elevations in plasma IL-6 during both running and cycling. Pre-exercise intramuscular glycogen content appears to be an important stimulus for the IL-6 gene transcription and muscle-IL-6 is further regulated by an autocrine mechanism.

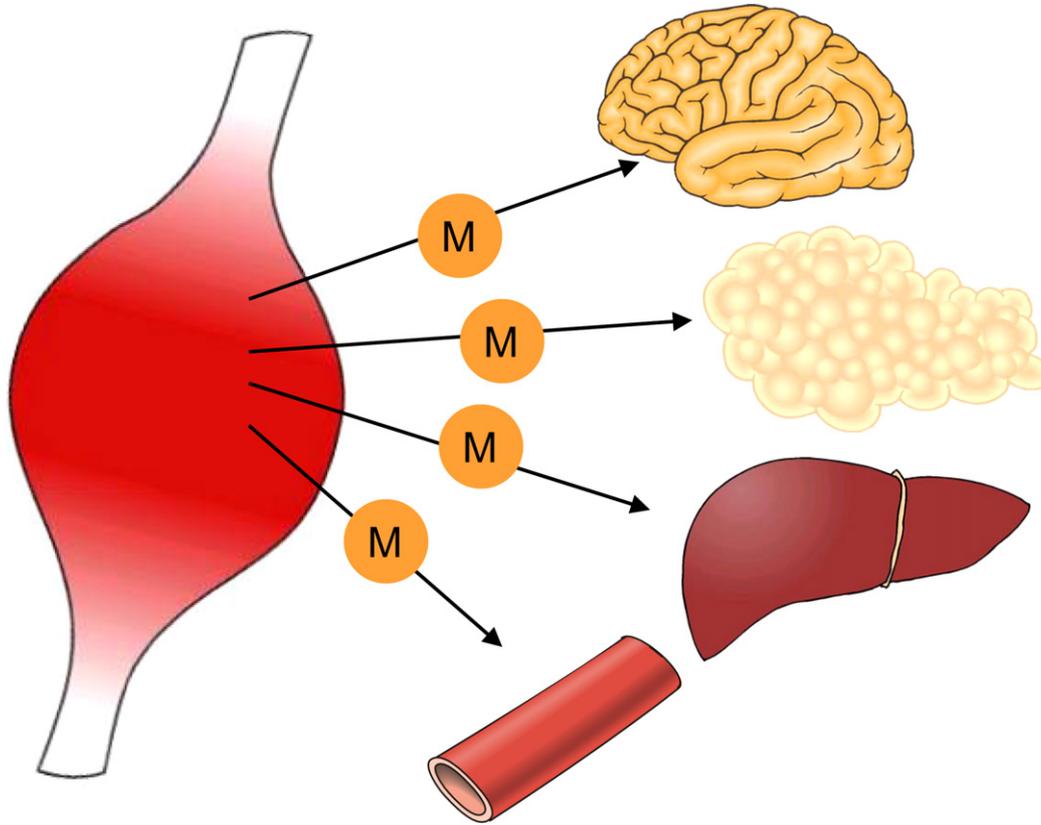


Fig. 1. Schematic presentation of a model suggesting that muscle-derived factors “myokines” (M) are produced and released from working muscle and exert their effects in other organs such as the brain, the adipose tissue, the liver, and the cardiovascular system.

3. IL-6 is released from the brain during exercise

Besides skeletal muscle, other tissues may also contribute to the systemic increase in IL-6 concentration during exercise. Studies have demonstrated that during exercise IL-6 is to a minor degree produced from adipose tissue and peritendon tissue. However, there is a decrease in the number of monocytes producing IL-6 and these cells are therefore not likely to contribute to the systemic increase in IL-6 during exercise—reviewed in (Febbraio and Pedersen, 2002; Pedersen and Hoffman-Goetz, 2000; Pedersen et al., 2001, 2003).

Blood glucose homeostasis is also important for the metabolic function of the central nervous system (CNS), which stimulated us to investigate whether IL-6 is released from the brain during exercise (Nybo et al., 2002).

Within the CNS IL-6 levels remain low under normal conditions, but during brain injury, inflammation, hypoxia, and certain diseases, the IL-6 level becomes elevated and the predominant source of IL-6 production in CNS appears to be activated astrocytes (Van Wagoner and Benveniste, 1999). IL-6 is also expressed in hypothalamic nuclei, where its synthesis and secretion may be enhanced after long-term stress (Schobitz et al., 1993). It furthermore appears that centrally acting IL-6

plays a role in the regulation of appetite, energy expenditure, and body composition. Thus, IL-6-deficient mice increase their food intake and develop mature-onset obesity, while intracerebroventricular injection of IL-6 in rats induces an acute increase in whole body oxygen consumption (Wallenius et al., 2002). We speculated that IL-6 could be released from the brain as a stimulus for increased hepatic glucose output, similar to the observation from the skeletal muscles, or IL-6 could be released during exercise as a consequence of an increased production in brain regions activated during exercise.

The cerebral IL-6 response was determined on the basis of internal jugular venous to arterial IL-6 differences and global cerebral blood flow (Nybo et al., 2002). There was no net release or uptake of IL-6 in the brain at rest or after 15 min of exercise, but a small release of IL-6 was observed after 60 min of exercise. When subjects performed a second bout of exercise, this release of IL-6 from the brain was fivefold greater at the end of the second bout. The study demonstrated that IL-6 is released from the brain during prolonged exercise in humans although to a much lesser degree than the amount of IL-6 released from skeletal muscle. The release of IL-6 appears to be influenced by the duration of exercise rather than by the increase in body tempera-

ture. A role for IL-6 in central fatigue was not supported, as the arterial and cerebral IL-6 responses were similar during normothermia and hyperthermia, although hyperthermia is associated with central fatigue.

4. IL-6—a role in glucose and lipid metabolism?

Skeletal muscle contraction is a powerful stimulus for glucose disposal and a key-question in exercise physiology has been: how is glucose homeostasis regulated during exercise? The glucose uptake in contracting skeletal muscle would lead to hypoglycemia if the endogenous glucose production (EGP) and glucose output from the liver was not stimulated during exercise. Regulation of the contraction-induced increase in EGP has been the focus of a vast number of studies over the past 40 years. In general, it is accepted that during exercise at a moderate intensity, glucoregulation is primarily mediated by an increase in the portal venous glucagon-to-insulin ratio, but studies have been unable to fully elucidate the precise mediator(s) of contraction-induced EGP. As far back as in the 1960s it was suggested that muscle cells possess a “humoral” component, and since this time, many studies have concluded that an as yet unidentified factor released from contracting muscle cells may contribute to the increase in hepatic glucose production. We recently tested the hypothesis that IL-6 is involved in mediating EGP during exercise. Humans performed 2 h of bicycle exercise on three separate occasions at a relatively high intensity or at a low intensity with or without an infusion of recombinant human IL-6 that matched the circulating concentration of IL-6 seen during high intensity exercise (Febbraio et al., 2004). Using stable isotopes we observed that throughout exercise at the low intensity with IL-6 infusion, glucose appearance and disappearance were higher than exercise at the low intensity without IL-6. Moreover, glucoregulatory hormones were identical when comparing these trials. These data suggest that although IL-6 has no effect on EGP at resting conditions, it is involved in mediating glucose homeostasis during exercise.

IL-6 influences glucose homeostasis during exercise and provides potential new insights into factors that mediate glucose production and disposal, implicating IL-6 in the so-called “work factor.” However, whereas IL-6 release from the skeletal muscles is attenuated by glucose ingestion (Febbraio and Pedersen, 2002; Pedersen and Hoffman-Goetz, 2000; Pedersen et al., 2001, 2003), the brain shows an inverse response. Thus, the brain contributes to the elevated level of circulating IL-6 during carbohydrate administration, while hypoglycaemia abolishes the cerebral IL-6 release (Nybo et al., 2003). Therefore, exercise-induced IL-6 production and release from the brain appears to have a different function from muscle-derived IL-6.

There is strong evidence that IL-6 may also affect lipid metabolism. Recently, studies have demonstrated that IL-6 infusion or incubation results in lipolysis and fat oxidation both in humans in vivo and in skeletal muscle in vitro. In accordance to this, IL-6 deficient mice developed mature-onset obesity (reviewed in (Febbraio and Pedersen, 2002; Pedersen and Hoffman-Goetz, 2000; Pedersen et al., 2001, 2003)).

5. The anti-inflammatory effects of IL-6

The anti-inflammatory profile of IL-6 represents yet another important biological effect of this cytokine. Both an acute bout of exercise as well as rhIL-6 infusion inhibits the endotoxin-induced increase in circulating levels of TNF- α in healthy humans (Starkie et al., 2003). TNF- α has direct inhibitory effects on insulin signalling (Hotamisligil et al., 1996) and the ability of IL-6 to inhibit TNF- α production may represent a mechanism whereby exercise enhances insulin sensitivity. Given that several chronic disorders such as cardiovascular diseases, type 2 diabetes, dementia, and depression are associated with chronic low-grade systemic inflammation, the anti-inflammatory effects of IL-6 may represent a mechanism whereby exercise protects against these disorders (Petersen and Pedersen, 2005).

6. Exercise and brain function

The acute mood effects associated with participation in single sessions of exercise and the effect of regular exercise has been demonstrated in a number of publications (reviewed by Yeung (1996)). It is well known that adipose tissue secretes peptides that regulate appetite and that receptors for adipokines are distributed in the brain (Ahima and Flier, 2000). Regular physical exercise and muscle metabolism is likely to influence brain function (Nybo and Secher, 2004), although there presently are more hypotheses than evidence.

The identification of skeletal muscle as an endocrine peptide-releasing organ opens the possibility that contracting skeletal muscle may influence brain metabolism. Such a regulation could be mediated via muscle-derived IL-6 or other yet unidentified myokines. In accordance, IL-6 has been demonstrated to cross the blood–brain barrier (Banks et al., 1994, 1995).

IL-6 represents thus one mechanism for a direct interaction between muscle and brain. IL-6 has been demonstrated to have numerous effects on brain function. It influences the activity and functions of the neurons and following brain pathology, it activates different signalling cascades, whereby it can counteract certain detrimental molecules such as the pro-inflammatory

cytokine TNF- α and reactive oxygen radicals (Penkowa et al., 2003). In addition, IL-6 is a strong inducer of metallothionin, which possesses strong anti-inflammatory, anti-oxidative, and anti-apoptotic effects (Penkowa et al., 2003). Robson-Ansley et al. (Robson-Ansley et al., 2004) demonstrated that athletic performance during an exercise challenge consisting of a 10-km running time trial was impaired in trained male runners following the administration of a low dose of rhIL-6. Therefore, as previously suggested by Gleeson (Gleeson, 2000), one theory holds that IL-6 may be taken up by the brain during exercise and that the large release of IL-6 from skeletal muscle during prolonged exercise might act as a feedback mechanism contributing to the development of so called “central fatigue.” Presently, this hypothesis lacks experimental evidence, but does not contradict the possibility of IL-6 to be released by the brain during physical activity.

7. Conclusion

Regular exercise offers primary and secondary protection against chronic diseases such as cardiovascular diseases, type 2 diabetes, dementia, and depression. The long-term effect of exercise may to some extent be ascribed to the anti-inflammatory response elicited by an acute bout of exercise, which is partly mediated by muscle-derived IL-6. Although, other tissues such as the brain and the adipose tissue also release IL-6 during exercise it is not known whether these tissues contribute substantially to the increased systemic concentration of IL-6. Recently, we 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 (Pedersen et al., 2003). Given that IL-6 crosses the blood–brain barrier, this concept may be extended to explain not only the effect of exercise on metabolism, but may also explain how regular muscle activity influences mood, performance, and cognitive function.

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