HUMAN MOVEMENT
2012, vol. 13 (4), 372–379

INTERLEUKIN-6 AS AN ADIPOKINE AND MYOKINE: THE REGULATORY ROLE OF CYTOKINE IN ADIPOSE TISSUE AND SKELETAL MUSCLE METABOLISM

doi: 10.2478/v10038-012-0045-y

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ABSTRACT
Purpose. Interleukin-6 (IL-6) belongs to the IL-6-type cytokine family, which, besides IL-6, comprises of IL-11, leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary neurotrophic factor (CNTF), cardiotrophin-1 (CT) and cardiotrophin-like cytokine (CLC). The metabolic effects of IL-6 differ markedly depending on the nature of the target cell with positive action on nerve cells' differentiation and hematopoesis, but negative in the etiology of autoimmune disease such as rheumatoid arthritis. In a target cell, IL-6 can simultaneously generate functionally distinct or sometimes contradictory signals depending on the in vivo environment, and the final physiological effect is a consequence of the orchestration of the diverse signals. Thus, its physiological effects are characterized by pleiotropy and redundancy. At present, it has been well documented that in obese individuals, IL-6, as an adipokine secreted into circulation by adipose tissue in proportion to body fat content and an elevated level of the cytokine in the plasma, adversely affects insulin signaling and glucose disposal in skeletal muscles and liver. Moreover, several lines of evidence indicated that IL-6 is a myokine synthesized in skeletal muscle and secreted into the bloodstream in response to exercise. In this way muscular work has a potential to stimulate adipose tissue lipolysis and provides an energy to working muscle. Furthermore, muscle-originated IL-6 acts locally, positively affecting intramuscular fat utilization. It has also been postulated that IL-6 is inevitable for satellite cell stimulation and muscle hypertrophy and repair.

Key words: interleukin-6, adipose tissue, skeletal muscle, exercise

Introduction

Interleukin-6 (IL-6) belongs to the IL-6-type cytokine family which besides of IL-6 comprises IL-11, leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary neurotrophic factor (CNTF), cardiotrophin-1 (CT) and cardiotrophin-like cytokine (CLC) [1].

The members of this family bind to specific receptors and have pro- as well as anti-inflammatory properties and also play an important role in acute phase and immune responses and haematopoiesis. However, the effects of IL-6 differ markedly depending on the nature of the target cell with positive action on nerve cells differentiation and hematopoesis, but negative in the etiology of autoimmune disease such as, e.g., rheumatoid arthritis [2].

In addition, in a target cell, IL-6 can simultaneously generate functionally distinct or sometimes contradictory signals depending on the *in vivo* environment and the final physiological effect is a consequence of the orchestration of the diverse signals [3, 4]. Moreover, the unique structure of the IL-6 receptor consisting of two polypeptide chains, a ligand-binding chain (IL-6r) and non-ligand-binding, signal transducing chain (gp130-glycoprotein 130) explain its redundancy and pleiotropy [5]. In consequence, many studies concerning IL-6 action in living systems are ambiguous or even contradictory.

Interleukin-6 as an adipokine

Until the discovery of leptin in 1994, adipose tissue was recognized as an energy store providing free fatty acids to different tissues (e.g., skeletal muscle, liver and heart). At present, it is well documented that adipose tissue is an endocrine organ with autocrine and paracrine function due to the secretion of many adipokines – leptin, adponectin, resistin and many others including IL-6 [for a review see 6, 7].

IL-6 relationship with body fat, glucose disposal and insulin sensitivity

IL-6 release from subcutaneous adipose tissue in the post-absorptive state in humans has been demonstrated by Mohamed-Ali et al. [8], with a significant relationship between the arterial IL-6 level and body mass index. Similarly, a significant association between plasma concentrations of IL-6 and the percentage of body mass has been found by other authors [9–11].

Moreover, several lines of evidence have demonstrated that both serum and adipose tissue IL-6 are reduced in response to weight loss [12–15]. Thus, it has been suggested that IL-6 is involved in the regulation of body fat stores. This assumption was supported at least in animal studies, since IL-6-deficient mice developed mature-onset obesity [16].

More detailed studies have noted that, in humans, subcutaneous injection of recombinant human IL-6

induces dose-dependent elevation in circulating glucose and glucagon levels under fasting conditions with no effect on plasma levels of C-peptide and insulin [17]. In consequence, it has been postulated that circulating IL-6 contributes to the regulation of glucose plasma levels either by induction of its release from the liver or by cytokine effects on insulin sensitivity.

The relationship between insulin sensitivity and circulating IL-6 has been further supported by Fernandez-Real et al. [18], who have demonstrated a close correlation between circulating IL-6 and the calculated index of insulin resistance (FIRI) in healthy subjects. Furthermore, in vitro studies have noted that exposure of mouse hepatocytes and human hepatocarcinoma cells to IL-6 disturbs the insulin signaling pathway and brings about cellular insulin resistance [19]. Similarly, five-day constant subcutaneous IL-6 infusion into mice markedly destroyed insulin signaling in mouse liver [20]. Moreover, IL-6 has been found to negatively affect insulin signaling in 3T3-L1 adipocytes, together with a reduced expression of glucose transporter 4 (GLUT-4) [21]. These data together with increased expression of IL-6 in adipose tissue of obese, insulin-resistant subjects clearly demonstrate a close relationship between body fat, this cytokine and disturbed insulin action [22].

However, it should be stressed that short-term IL-6 infusion (2 h) does not affect insulin signaling or whole-body glucose metabolism in rats [23]. Thus, it cannot be excluded that chronic exposure to IL-6 is needed for adverse effects of this cytokine on insulin action and glucose disposal. This seems feasible since recent data have noted that IL-6 overexpression in mice leads to hyperinsulinaemia, liver inflammation and a depressed amount of GLUT-4 transporters in the muscle [24].

On the other hand, several lines of evidence suggest a positive effect of IL-6 on insulin action and glucose disposal. Human studies have demonstrated that acute IL-6 infusion improves glucose disposal with no effect on endogenous glucose production during a hyperinsulinemic-euglycemic clamp [25]. In the same study, it was noted that *in vitro* IL-6 infusion stimulates GLUT-4 transporter translocation into cell membrane in myotubes, thus positively influencing muscle glucose uptake. Similarly, in rats treated for 14 days with recombinant human IL-6, enhanced glucose clearance during a glucose tolerance test and increased insulin sensitivity were noted [26].

To shed more light on the relationship between IL-6, insulin, and glucose disposal, studies concerning the effects of circulating insulin on plasma IL-6 have been performed and indicated that hyperinsulinaemia *per se* raises plasma IL-6 concentration and this rise was significantly and adversely correlated with BMI and WHR [27, 28].

Thus, it could be postulated that there is a mutual relationship between circulating IL-6, insulin and body fat stores in healthy subjects. An elevation in circulating IL-6 has an adverse effect on insulin action and glucose disposal, but hyperinsulinaemia, as observed in obese individuals, markedly stimulates IL-6 secretion and plasma levels.

IL-6 and adipose tissue lipolysis

Early studies have demonstrated that a 2.5 h IL-6 infusion at a dose giving a rise of circulating cytokine up to 35 ng/L causes marked elevation in glycerol release from subcutaneous fat in healthy volunteers with no change in circulating free fatty acids (FFA) [29], while in the splanchnic region IL-6 elicits a significant uptake of FFA and gluconeogenic precursors – lactate and glycerol – indicating lipolytic IL-6 action but also its influence on gluconeogenesis. It has been also demonstrated that recombinant human IL-6 infusion markedly increases circulating free fatty acid (FFA) and the endogenous FFA rate of appearance, with no changes in circulating triacylglycerols in young, healthy men [30]. In consequence, it has been postulated that IL-6 stimulates both lipolysis and fat oxidation.

These findings have been further supported by an *in vivo* study on elderly men that indicated pronounced stimulation of palmitate turnover in response to an infusion of recombinant human IL-6 [31]. Additionally, in isolated adipocytes, the IL-6 effect on palmitate metabolism was independent from other hormones such as growth hormone and/or cortisol.

Interesting data concerning the relationship between fat metabolism and IL-6 have been provided by Ji et al. [32], who demonstrated that adipocytes treated with IL-6 release more glycerol into the medium and were characterized by lower lipids content, which indicates a marked lipolytic action of this adipokine. However, IL-6 exerted an adverse effect on adipocyte mitochondria, decreasing membrane potential and ATP synthesis but increasing reactive oxygen species (ROS) production. Moreover, mitochondria from IL-6-treated adipocytes were swollen with reduced or missing cristae, but insulin-stimulated glucose uptake by adipocytes was not disturbed, possibly due to increased mitochondrial biogenesis.

On the other hand, there are data suggesting that during low-intensity exercise, recombinant human IL-6 infusion affects neither lipolysis in adipose tissue nor fat oxidation in humans [33]. Thus, IL-6 action in adipocytes is far from being elucidated.

The above-mentioned studies concerning IL-6 influence on insulin action, glucose disposal and lipolysis do not take into account paracrine (local) IL-6 action in adipose tissue. It has been demonstrated that IL-6 concentration in the interstitial fluid of adipose tissue is about 100 times higher than in plasma, suggesting its importance in the regulation of local metabolic processes [34]. In consequence, IL-6 infusion or knockout brings about significant changes in secretion of many

other adipokines from adipose tissue (e.g., adiponectin, tumor necrosis factor-α, visfatin), which have the potential to affect insulin sensitivity, glucose disposal and lipolysis [35–40].

Moreover, IL-6 release from adipocytes is stimulated by adrenaline, growth hormone, by IL-6 *per se* and inhibited by glucocorticoids [41–43]. Besides, it has been found that dopamine positively affects IL-6 secretion from adipose tissue, since its receptors were identified in adipocytes [44].

The schedule of metabolic effects of IL-6 on insulin action, glucose disposal and lipolysis is even more complicated due to the potent influence of dietary habits and genotype on IL-6 secretion and plasma levels [45, 46].

Interleukin-6 (IL-6) as myokine

Skeletal muscle plays a central role in many biological processes, such as movement and metabolism and alterations in its mass and composition (e.g., during aging), can markedly affect health and disease [47]. During the last few years the concept of regulatory function of skeletal muscle was strengthened due to recognition of its secretory function and release of several myokines into circulation under stress conditions, such as physical exercise and/or training [48].

Muscle IL-6 synthesis in response to exercise

It is worth noting that the term "myokine" was proposed by Pedersen et al. [49] for factors synthesized in skeletal muscle and released into circulation, where IL-6 was the first identified myokine.

It has been established that physical activity brings about a significant elevation in circulating IL-6 in humans due to its production in skeletal muscles but not in monocytes [50, 51]. In addition, muscle contractions markedly stimulate muscle IL-6 mRNA expression and IL-6 synthesis in rats [52, 53].

Furthermore, at rest, IL-6 protein was distributed across all fiber type at low levels, but consistently with glycogen stores and was higher in type II than in type I fibers [54]. Consequently, in response to exercise, IL-6 production was higher in fast than in slow muscle fibers.

Despite the marked effect of physical exercise on IL-6 synthesis and content in the muscle, it has been demonstrated that elevated IL-6 significantly stimulates IL-6 receptor expression in humans [55].

Additionally, the intramuscular IL-6 mRNA level, in response to exercise, seems to be affected by energy availability, since this level as well as plasma concentrations of IL-6 are greater under conditions of depleted pre-exercise muscle glycogen stores [56]. In contrast, carbohydrate ingestion during exercise decreases circulating IL-6 but does not affect IL-6 mRNA levels, thus affecting IL-6 efflux from the muscle [57–60]. Thus, it could be postulated that carbohydrate availability is a potent regulator of IL-6 synthesis during exercise and in this way influences fat utilization during contraction.

Moreover, it has been found that, following a 36 km run, IL-6 concentrations were markedly (by fifty-fold) elevated in plasma, but to a much greater degree (hundred-fold) in peritendious tissue around the Achilles tendon [61]. This suggests that this tissue, together with skeletal muscle, contribute to an elevated plasma IL-6 level in response to muscular work.

However, it should be pointed out that elevation in muscle IL-6 production in contracting muscles depends on exercise duration and is more pronounced following long-term than after short-term muscular work and rapidly decreases after exercise cessation [62].

IL-6 and metabolic processes in the muscle

In early studies, muscle-secreted IL-6 was postulated to have an energy-sensitizing role acting in a hormone-like manner mobilizing extracellular substrates and their delivery to the muscle [63].

This assumption was supported by the above-mentioned studies concerning the lipolytic effect of IL-6 in adipose tissue. Moreover, in humans both at rest and exercise, an inverse relationship has been observed between lipolysis and circulating IL-6 and lipolysis suppression with nicotinic acid, which induced a marked elevation in blood IL-6 levels [64]. Moreover, Ives et al. [65] have indicated that, in eumenorrheic women, elevation in circulating IL-6 in response to 1 h treadmill running at 65% VO_2 max is related to energy expenditure from fat and total energy expenditure but not to the menstrual cycle phase.

Thus, it seemed feasible that IL-6 secretion from the muscle during increased energy demands is targeted to activate extracellular energy stores. However, it has been also noted that IL-6 affects intramuscular fat metabolism. *In vitro* studies have demonstrated that this myokine stimulates free fatty acid oxidation and, that it attenuates insulin's ability to suppress fatty acid oxidation and stimulate lipogenesis in rat soleus muscle [66].

Interleukin-6 contribution to the regulation of fat metabolism in the muscle has been confirmed by Chabowski et al. [67], who demonstrated that IL-6 deficiency in mice increases muscle FFA transporters and intramuscular lipid content in mice red but not in white muscle. Moreover, it has been found that, in humans, IL-6 infusion resulting in high myokine levels (40 pg/ml) markedly (two-fold) increases systemic fatty acid oxidation with no effect on adipose tissue lipolysis [68]. Therefore, high IL-6 levels observed during exercise was postulated to activate intramuscular fat utilization

Numerous studies have focused on the role of IL-6 in the regulation of glucose homeostasis. Human IL-6 infusion during low intensity exercise up to a level observed during high-intensity effort markedly stimulated whole body glucose disposal and metabolic clearance with no effect on circulating insulin, glucagons and cate-

cholamines [69]. Moreover, resting plasma IL-6 levels in men were found to be negatively and significantly correlated with insulin resistance and insulin secretion, and positively with insulin-independent glucose uptake and its incorporation into glycogen [70, 71].

However, it should be noted that the association between IL-6 and insulin action and glucose disposal are not yet fully elucidated, since there are data indicating that IL-6 exerts its action on insulin sensitivity exclusively at a supraphysiological level [72]. Moreover, it has been noted that prolonged IL-infusion (2 weeks) has no effect on insulin sensitivity in mice [73]. However, it was found in the same study that IL-6 stimulated fat oxidation via mitochondrial uncoupling.

On the other hand, taking into account an inverse relationship between IL-6 and AMP-kinase (AMPK) activity, it should be pointed out that this cytokine has the potential to affect both fat and carbohydrate metabolism due to the regulatory function of AMPK in energy turnover [74, 75].

Taking together data concerning IL-6 generation in adipose tissue and skeletal muscle, it has been postulated that this cytokine enables a cross-talk between both tissues with fat-originating IL-6, inducing muscle insulin resistance in obesity and muscle IL-6 stimulating fat utilization during contraction [76] (Fig. 1).

Despite the above-mentioned effects of IL-6, it is worth noting that elevated levels of this cytokine in muscle in response to exercise exert an anti-inflammatory action by inhibition of pro-inflammatory tumor necrosis factor α (TNF-α) production and induction of anti-inflammatory cytokines (e.g., IL-10) [77]. However, it has been found that elevated plasma level of IL-6 in response to prolonged exercise brings about stimulation of C-reactive protein (CRP) synthesis in the liver and elevated plasma CRP concentration, which contributes to post-exercise fatigue [62, 78, 79].

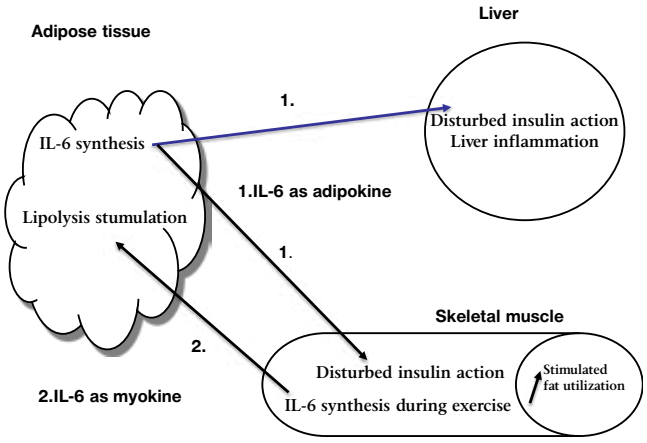

Figure 1. IL-6 contribution to the regulation of metabolism in adipose tissue, skeletal muscle and liver: 1. excessive body fat stores results in elevated IL-6 synthesis and secretion into circulation and adversely affect insulin sensitivity in skeletal muscle and liver, contributing to liver inflammation; 2. increased IL-6 synthesis and secretion from contracting muscle stimulate adipose tissue lipolysis to provide energy to the muscle, but also positively affects intramuscular fat utilization

IL-6 response to training

Data on circulating IL-6's response to training are scarce and ambiguous. In young, healthy men, 10 weeks of knee extensor endurance training markedly attenuated IL-6 mRNA expression in response to a single exercise bout with no effect on resting mRNA levels [80]. Similarly, after six weeks of high-intensity interval training plasma, IL-6 response to a single 50 min high-intensity run was lower than before training [81]. A positive effect of resistance training on circulating IL-6 after a single exercise was noted in previously sedentary elderly women and middle-aged men [82, 83]. Contrarily, no effect of resistance, endurance or concurrent training on IL-6 response to a single exercise session was noted following 16 weeks of training in a group of middle-aged men [84]. Moreover, 12 weeks of aerobic training (five days a week at 50 % of VO_2max) did not change plasma IL-6 concentrations in obese women despite the decrease in body fat and improvement in insulin sensitivity [85].

The above discrepancies are possibly due to genetic factors, since Oberbach et al. [86] have noted that genetic variants of the IL-6 gene significantly modify changes in circulating IL-6 after long-term (12-month) training.

Additionally, it has been demonstrated that the IL-6 gene and IL-6 receptor response to 10-week one leg knee extension training are attenuated by glucose ingestion [87]. Therefore, it could not be excluded that dietary habits and carbohydrate availability have a potential to affect the IL-6 response to training.

IL-6 and muscle mass

Several lines of evidence have indicated that IL-6 significantly contributes to muscle degeneration and IL-6 receptor antibody inhibits muscle atrophy and modulates muscle proteolytic system in IL-6 transgenic mice [88, 89]. Additionally, current studies have demonstrated that IL-6 is a key regulator of muscle wasting in cachexia [for a review see 90]. Moreover, in young rats, chronic exposure to IL-6 inhibits muscle growth, but this effect is attenuated by endurance exercise [91].

On the other hand, it has been noted that IL-6 is an essential regulator of skeletal muscle hypertrophy due to satellite cell activation [92]. In consequence, muscle growth in IL-6 null mice was markedly attenuated in comparison to their wild-type littermates. Furthermore, it has been noted that IL-6 mRNA expression in human muscle, but also in satellite cells, markedly increased in response to 300 maximal unilateral lengthening contractions, suggesting that IL-6 is an important signaling molecule associated with the satellite cells response to

muscle contraction [93]. Additionally, it has been suggested that IL-6 is associated with the proliferation of human muscle satellite cells following acute muscle damage in response to eccentric exercise [94].

Thus, it could not be excluded that muscle- and satellite cell-originated IL-6 plays a protective role against muscle damage.

As was mentioned earlier, many other cytokines belong to the IL-6 family and all of them utilize gp130 as a common signal transducer acting in a pleiotropic and redundant manner. Numerous experimental data suggest that they play an important role in the regulation of metabolic processes affecting adipocyte development and function [for a review, see 95]. For instance, leukemia inhibitory factor (LIF) expression in skeletal muscle was induced by exercise, thus LIF is recognized as a myokine [96].

On the other hand, a wealth of studies have demonstrated that skeletal muscle expressed many other myokines such as interleukins 8 and 15 (IL-8, IL-15), brain-derived neurotrophic factor (BDNF) and fibroblast growth factor 21 (FGF21), which have the potential to affect muscle growth and whole-body metabolic processes [97].

The above mentioned data clearly show a complicated mechanism of interactions between skeletal muscle secretory activity and metabolic processes; however, they support an early and intuitive hypothesis concerning the existence of a "muscle factor".

Summing up, IL-6, recognized as the first myokine, is an important factor in the regulation of both adipose tissue and skeletal muscle metabolic processes, thus contributing to the cross-talk between both tissues in the so-called adipose tissue-skeletal muscle axis. However, excessive IL-6 production and plasma levels in obesity disturb whole-body insulin sensitivity and glucose disposal. In contrast, exercise induced IL-6 expression in skeletal muscle and increased circulating IL-6 markedly stimulate adipose tissue lipolysis and fat utilization in the muscle and, in this way, mediate the beneficial effects of muscular work.

Moreover, it has been suggested that IL-6 expressed in skeletal muscle stimulates anti-inflammatory cytokine synthesis and satellite cell activity. At present, it has now been well-documented that IL-6 is not only a pro-inflammatory cytokine, and that skeletal muscles, besides their important role in movement, serve as an important secretory tissue.

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Paper received by the Editors: August 6, 2012
Paper accepted for publication: October 2, 2012

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