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Exercise, Cytokines, and Lymphocytes

Nutritional and Metabolic Aspects

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1. INTRODUCTION

Recent studies suggest that the beneficial effects of exercise may, in part, be mediated by exercise-induced changes in cytokine responses, which, in turn, have several effects, including effects on metabolism and on the cellular immune system (1). The mechanisms underlying exercise-induced immune changes also include neuroendocrinological factors (2). Thus, nutritional intervention may influence the immune response to exercise on several levels. When the immune system is studied at rest in trained vs. untrained humans, few differences are found. However, the so-called natural immunity mediated by natural killer (NK) cells is slightly enhanced in trained subjects (2). Whereas little changes are found in trained vs. untrained subjects at rest, an acute bout of exercise induces dramatic immune system changes. Regarding lymphocyte changes (number and function), the findings are highly consistent. The intensity and duration of the exercise affect the magnitude of changes, whereas the mode of exercise has little influence (2). However, if the exercise includes an eccentric component and thereby muscle damage and cell infiltration, this has some effect, which is described later. In general, both moderate and intense exercise (even if only for a few minutes) induce mobilization of lymphocytes to the blood. After intense exercise (more than 70% of VO$_{2\text{max}}$) of long duration (more than 45 min), immune impairment occurs (2). The nature of these changes, the mechanisms of action, and the influence of nutritional intervention are described in this chapter.

2. EFFECTS OF EXERCISE

Recent studies show that several cytokines can be detected in plasma during and after strenuous exercise (1,2). However, in relation to exercise interleukin (IL)-6 is produced in larger amounts than any other cytokine examined. The IL-6 increase is followed by increases in other antiinflammatory cytokines, such as IL-1 receptor antagonist (IL-1ra), tumor necrosis factor-α (TNF-α) receptors, and IL-10. It has recently been demonstrated that contracting skeletal muscles produce IL-6. Initially, it was believed that the cytokine response to exercise represented a reaction to exercise-induced muscle injury. Thus, we found that peak IL-6 was associated with prolonged muscle damage using an eccentric
exercise model in which the creatine kinase (CK) level peaked at day 4 after exercise (3). However, later studies from our group using exercise models in which CK peaked 1 d after exercise failed to show an association between peak IL-6 and peak CK levels (4,5). Furthermore, using an eccentric exercise model, we recently demonstrated that CK levels increased up to 1000-fold, with only a fourfold increase in plasma-IL-6 during subsequent days (6). The latter findings suggest that the huge increase in IL-6 plasma levels in exercise models where the CK level does not change or is enhanced a few-fold only is related to mechanisms other than muscle damage. Also, a recent study (7) failed to find an association between increases in IL-6 and biochemical markers for muscle damage. The latter study (7) showed that training reduced the myoglobin increase and decreased delayed onset muscle soreness in response to a bout of eccentric exercise, whereas the IL-6 increase was not influenced by a training effect. It is most likely that the huge and immediate IL-6 increase in response to long-duration exercise is independent of muscle damage, whereas muscle damage is followed by repair mechanisms, including macrophage invasion into the muscle, leading to IL-6 production by the macrophages. The IL-6 production in relation to muscle damage occurs later and is less intense compared to the IL-6 production related to muscle contractions.

The finding of markedly increased IL-6 levels after strenuous exercise has consistently been found in many studies (4,5,8–17). A twofold increase in plasma IL-6 was demonstrated after 6 min of intense exercise (18). In treadmill running, the IL-6 level in blood was significantly enhanced 30 min after the start of running, with IL-6 peaking in the end of 2.5 h of running (4). In other studies, in which IL-6 was not measured during the running but at several time points after, maximum IL-6 levels were found immediately after the exercise, followed by a rapid decline. Thus, after a marathon run, maximum IL-6 levels (100-fold increase) were measured immediately after the 3–3.5 h race (5,16).

In contrast, using a prolonged eccentric one-legged exercise model lasting 1 h (14) or a two-legged high-intensity eccentric exercise leg model lasting 30 min (3), the IL-6 level did not peak until 1–1.5 h after exercise. In another study, subjects performed five bouts of one-legged eccentric exercise. The plasma IL-6 concentration peaked 90 min after exercise and remained elevated for 4 d (15). It is clear that IL-6 kinetics differ from those induced by concentric muscle contractions and those induced by eccentric exercise associated with muscle damage (3,5,14,16). In relation to concentric exercise, the IL-6 increase is related to exercise duration (4), and there is a logarithmic relationship between the increase in IL-6 and exercise duration. The IL-6 levels decline after the concentric exercise to reach prevalues within a few hours. In contrast, eccentric exercise induces only a modest increase in plasma IL-6, and the IL-6 level peaks some time after exercise cessation and remains elevated for several days.

Data from the Copenhagen Marathon race (1996, 1997, and 1998, n = 56) suggest that there is a correlation intensity between exercise intensity and plasma IL-6 increase (19). Furthermore, a correlation between peak IL-6 levels and heart rate was demonstrated (4). An animal study suggested that the increase in epinephrine (adrenaline) during stress was responsible for the increase in IL-6 (20). However, recent data from our group showed that when epinephrine was infused to volunteers, which closely mimicked the increase in plasma-epinephrine during 2.5 h of running exercise, plasma-IL-6 increased only fourfold during the infusion but 30-fold during the exercise (21). Thus, epinephrine plays only a minor role in the exercise-induced plasma IL-6 increase. A study was performed to test