Kenneth Ostrowski · Peter Schjerling
Bente Klarlund Pedersen

Physical activity and plasma interleukin-6 in humans – effect of intensity of exercise

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Abstract The present study included data from three marathon races to investigate the hypothesis that a relationship exists between running intensity and elevated concentrations of interleukin (IL)-6 in plasma. The study included a total of 53 subjects whose mean age was 30.6 [95% confidence interval (CI) 1.4] years, mean body mass 77.7 (95% CI 2.0) kg, mean maximal oxygen uptake ($\dot{V}O_2$max) 59.3 (95% CI 1.4) ml·min$^{-1}$·kg$^{-1}$, and who had participated in the Copenhagen Marathons of 1996, 1997 or 1998, achieving a mean running time of 206 (95% CI 7) min. Running intensity was calculated as running speed divided by $\dot{V}O_2$max. The concentration of IL-6 in plasma peaked immediately after the run. There was a negative correlation between peak IL-6 concentration and running time ($r = -0.30, P < 0.05$) and a positive correlation between peak IL-6 concentration and running intensity ($r = 0.32, P < 0.05$). The IL-1 receptor antagonist (IL-1ra) plasma concentration peaked 1.5 h after the run and there was a positive correlation between the peak plasma concentrations of IL-6 and IL-1ra ($r = 0.39, P < 0.01$). Creatine kinase (CK) plasma concentration peaked on the 1st day after the run, but no association was found between peak concentrations of IL-6 and CK. In conclusion, the results confirmed the hypothesized association between plasma IL-6 concentration and running intensity, but did not confirm the previous finding of a connection between IL-6 plasma concentration and muscle damage.

Key words Cytokine · Running · Marathon

Introduction

Interleukin(IL)-6 is a key cytokine in the acute phase response. It is produced by many different cell types of which the primary sources are stimulated monocytes, fibroblasts and endothelial cells. The main stimuli for the production of IL-6 are lipopolysaccharide, IL-1 and tumour necrosis factor. Initially, IL-6 was thought to be a pro-inflammatory cytokine but recent results have suggested that IL-6 has an inflammation-controlling role and is important for the return to homeostasis after an inflammatory challenge (Tilg et al. 1997; Xing et al. 1998). Plasma IL-6 concentration has been found to be elevated in a variety of conditions where system homeostasis is threatened or compromised such as in sepsis or multiple trauma (Hack et al. 1997; Giannoudis et al. 1998). Interestingly, recent findings have shown that strenuous exercise is also a powerful inducer of elevated concentrations of IL-6 in plasma (Drenth et al. 1995; Castell et al. 1997; Nehlsen-Cannarella et al. 1997; Ostrowski et al. 1998a, b, 1999).

In a previous study, involving trained athletes running for 2.5 h on a treadmill, a strong positive correlation was found between the peak plasma IL-6 concentration reached at the end of running and plasma lactate concentration at the same time point (Ostrowski et al. 1998b). This led us to the idea that the concentration of IL-6 could be related to either running intensity or duration (or both), since plasma lactate concentration has been shown to increase with both intensity and duration of exercise (Jacobs 1986). Furthermore, we have noted that marathon running resulted in a 100-fold increase in plasma IL-6 concentration (Ostrowski et al. 1999), whereas a less strenuous (shorter duration and slightly lower intensity) treadmill run (Ostrowski et al. 1998b) resulted in only a 25-fold increase. We therefore hypothesize that there is an association between running intensity and/or duration and the concentration of plasma IL-6 immediately after running. In this study we investigated whether there is an association between plasma...
IL-6 concentration and running intensity, by combining data collected from runners participating in the Copenhagen Marathons of 1996, 1997 or 1998.

The intensity of exercise is often defined as the oxygen uptake ($\dot{V}O_2$) during exercise as a percentage of maximal oxygen uptake ($V_2O_\text{max}$). In field studies, however, $\dot{V}O_2$ measurements cannot easily be obtained during exercise. In the present study – given the fixed length of the run – we therefore calculated the intensity of exercise (running intensity) as running speed divided by $V_2O_\text{max}$. The expression is simple and might not represent a physiological quantity, but the parameter appeared to be a reasonable compromise, which took into account each subject’s effort to complete the marathon race (running speed) relative to their exercise capacity ($V_2O_\text{max}$).

**Methods**

**Subjects**

The present study combined the data from three previous studies involving subjects participating in the Copenhagen Marathons of 1996, 1997 and 1998 (17, 19 and 17 subjects, respectively). Part of the data (approximately half) has been published previously (Ostrowski et al. 1998a, 1999) but is included to increase the size of the data-set, and thereby allow stronger conclusions. The 53 subjects were male athletes, whose mean age was 30.6 [95% confidence interval CI ± 1.4] years, body mass 77.7 [95%CI ± 2.0] kg and $V_2O_\text{max}$ 59.3 [95%CI ± 1.4] ml min$^{-1}$ kg$^{-1}$. The athletes were all experienced runners, who were participating regularly in running competitions, and it is therefore assumed that they ran at a largely constant pace throughout the marathon race. For each subject, the $V_2O_\text{max}$ was determined prior to the experiment during an incremental exercise test.

The experiment protocol for each study was approved by the local Ethics Committee and all subjects were informed about the purpose and risks of the study before their written, informed consent was obtained. The mean running time was 206 (95%CI ± 7 min).

**Sampling and analysis of blood**

Blood samples were (in each of the three studies) drawn from an antecubital vein 1 week prior to running, immediately after running and at various times during the rest after running (see Fig. 1). On each occasion two samples of 10 ml of blood were drawn into glass tubes containing 35 µmol dipotassium-ethylenediaminetetra-acetic acid and 1,500 kallikrein inactivator units Trasylol (Bayer, Leverkusen, Germany). Tubes were kept on ice until centrifuged at 2,150g for 15 min, at 4 °C. Plasmas were separated from the cells and stored at −80 °C until analysed by commercially available enzyme-linked immunosorbent assay (ELISA; R&D systems, Minneapolis, Minn., USA). The pre blood sample was taken 1 week prior to the race in order not to influence the performance of the runners, but the subjects prepared for this sample in a similar way as they prepared for the marathon, which involved refraining from exercise for 2 days before the blood sampling and eating the same carbohydrate-high diet as they planned to eat before the marathon race. In the marathon 1996, blood samples were taken at 2 h after the run (instead of 1.5 h) and these were combined with the 1.5 h samples from the marathons 1997 and 1998.

**Enzyme-linked immunosorbent assay**

All measurements were performed in duplicate, and a high sensitivity kit (R&D Systems) was used for the determination of concentrations of IL-6 but not IL-1 receptor antagonist (IL-1ra).

According to information provided by R&D Systems the IL-6 ELISA is insensitive to addition of the recombinant form of the soluble receptor, and the measurement therefore probably corresponds to both soluble and receptor-bound IL-6. The detection limits for the IL-6 and IL-1ra ELISA were below 0.1 pg ml$^{-1}$ and