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Meeting Report

Exercise-induced immune changes – an influence on metabolism?

Bente Klarlund Pedersen, Jeffrey A. Woods and David C. Nieman

The International Society of Exercise and Immunology Fifth Convention was held in Baltimore, USA, on 29–30 May 2001.

It is clear that exercise-induced changes in the immune system might explain the increased susceptibility to infections in athletes. However, results presented at the convention indicate that the cytokine response to exercise might mediate important metabolic effects also.

Heat shock proteins

The primary role of heat shock proteins (HSPs) is to act as molecular chaperones by binding to denatured proteins and catalyzing the assembly of protein complexes within cells. A recent study demonstrated that exogenous HSP72 binds specifically to the cell surface of human monocytes *in vitro*[1]. Importantly, the resultant activation of the gene encoding interleukin-6 (IL-6) occurs by a CD14-dependent pathway. These data suggest that to induce the expression of IL-6 by monocytes, HSP72 must act by binding to the plasma membrane.

'…increased extracellular levels of HSPs, following necrotic cell death, facilitate the functions of innate immunity.'

Data presented at the Convention suggest that exercise-induced increases in the levels of HSPs could play a role in modulating immune function. M. Febbraio (Melbourne, Australia) found that HSP72 is released into the peripheral circulation during exercise, suggesting that HSPs might indeed provide a 'danger signal' to the immune system. Furthermore, A. Niess (Tuebingen, Germany) and colleagues found that exercise increased the level of HSP72 within monocytes themselves. By contrast, very stressful exercise decreased the intracellular production of IL-6 by monocytes *in vivo* (M. Febbraio). Therefore, it appears that for HSP72 to activate an IL-6 response within monocytes, it must be released by other cells first, before adhering to the surface of the monocyte to signal through the CD14-dependent pathway.

Increased intracellular levels of HSPs are protective against cellular stress. By contrast, increased extracellular levels of HSPs, following necrotic cell death, facilitate the functions of innate immunity. M. Fleshner (Boulder, CO, USA) demonstrated that physically active, stressed rats had increased levels of HSP70 in every tissue tested, whereas sedentary, stressed animals had increased levels of HSP70 in the blood, spleen, liver and adrenal glands only. Also, the increase in the level of HSP70 in these organs was

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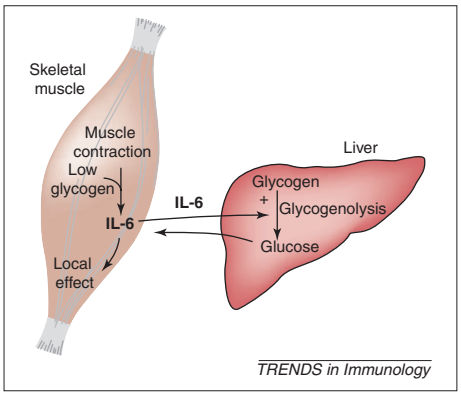

Fig. 1. Interleukin-6 (IL-6) is produced locally by working skeletal muscle and released into the circulation in large quantities. It is hypothesized that IL-6 might play a role in the maintenance of glucose homeostasis during long-term exercise.

smaller than in the physically active, stressed rats. In the physically active rats, the greater increase in levels of tissue (intracellular) HSP70 could protect lymphocytes from stress-induced immunosuppression, and the greater increase in the level of blood (extracellular) HSP70 could facilitate the stress-induced immunopotentiation of innate immunity.

'…exercise decreases the expansion of cell populations by an increase in the rate of apoptosis…'

Muscle-derived interleukin-6

Several researchers enlarged upon the finding that working muscle fibers produce IL-6, which is released into the circulation[2]. mRNA encoding IL-6 is present in muscle biopsies obtained after exercise, even though the level of mRNA encoding HSP72 is not increased in the muscle by exercise, suggesting that the induction of expression of IL-6 in the muscle is by an HSP-independent pathway. Measurements of the exercising limb indicate that skeletal muscle, rather than circulating monocytes, is the source of IL-6. C. Keller (Copenhagen, Denmark) determined the potential influence of normal versus low glycogen content of pre-exercise muscle on the muscle transcription rate of IL-6 mRNA and the total level of IL-6 mRNA during exercise. Nuclei were isolated from muscle samples, and the transcription rates for IL-6 mRNA determined by the nuclear run-on technique. This study showed an early activation of the gene encoding IL-6 (after 30 minutes of exercise). In the low glycogen-content trial, the transcription of IL-6 mRNA was elevated >100-fold after 180 minutes of exercise. In the control leg (normal glycogen content), a reduced increase in the transcription rate of IL-6 mRNA and the total level of IL-6 mRNA was measured. Given that IL-6 has been shown to stimulate the hepatic synthesis of glucose, muscle-derived IL-6 might be a link between working muscles and the liver, acting to maintain glucose levels during prolonged exercise (Fig. 1).

Exercise stress and immune function

A major theme of the conference revolved around identifying doses of stress or exercise that lead to improvements in immune function. Currently, F. Dhabhar (Columbus, OH, USA) is working on a hypothesis that under acute conditions, just as the stress response prepares the cardiovascular system and the musculoskeletal system for fight or flight, it might also prepare the immune system for challenge. He demonstrated that acute stress induces the trafficking of immune cells to the skin, which enhances the delayed-type hypersensitivity (DTH) response. By contrast, chronic or long-term stress suppressed the skin response significantly. These studies using restraint stress in mice fit nicely with the hypothesis that moderate exercise improves immune function, whereas intense exercise of long duration suppresses the immune response[3,4]. This idea was substantiated by M. Davis (Columbia, SC, USA), who studied the influence of long-term exhaustive and moderate exercise on morbidity and mortality rates, following the inoculation of rodents with herpes simplex virus (HSV). Moderate exercise decreased morbidity and mortality by 46% and 38%, respectively, whereas exhaustive exercise increased morbidity and mortality by 35% and 17%, respectively. The ingestion of oat β-glucan, a soluble fiber with immunostimulatory effects, did not enhance the beneficial effect of moderate exercise, but did prevent the increase in morbidity and mortality induced by intense exercise.

'…the level of salivary IgA is decreased in over-trained subjects, and might be linked to increased levels of infection of the upper respiratory tract.'

Lymphopenia and a decrease in lymphocyte proliferation are common findings following heavy exertion. Using carboxyfluorescein diacetate succinamidyl ester labeling of lymphocyte populations, D.G. Rowbottom (Brisbane, Australia) and K.J. Green (Brisbane, Australia) demonstrated that exercise decreases the expansion of cell populations by an increase in the rate of apoptosis of both $CD4^+$ and $CD8^+$ T lymphocytes, rather than a decrease in the rate of proliferation. Also, a study by F.C. Mooren (Munster, Germany) indicated that apoptosis contributes to lymphopenia owing to exercise. Other research showed that strenuous exercise induces a relative suppression of type-1-cytokine-producing cells in the blood, both in animals (M. Okutsu, Tohoku, Japan) and humans (A. Steensberg, Copenhagen, Denmark). The influence of a second bout of exercise compared with the first bout was studied in a model that controlled for diurnal variations. The second bout of exercise increased inflammatory responses and the responsiveness of lymphocytes, indicating a 'carry-over' effect (O. Ronssen, Oslo, Norway). Additional reports during the conference indicated that the level of salivary IgA is decreased in over-trained subjects, and might be linked to increased levels of

Key outcomes of the meeting

- HSP72 is released into the circulation during strenuous exercise.
- Exercise-induced changes to the immune system might be mediated by danger signals, such as HSPs.
- The transcription of the gene encoding IL-6 takes place locally in working skeletal muscles.
- Large quantities of IL-6 are released from working skeletal muscles into the circulation.
- Apoptosis contributes to post-exercise lymphopenia.
- In infected animals, moderate exercise decreases morbidity and mortality, whereas exhaustive exercise increases morbidity and mortality.

infection of the upper respiratory tract (M. Gleeson, Callaghan, Australia; M. Gleeson, Birmingham, UK; D. Pyne, Canberra, Australia; and D. Nieman, Boone, NC, USA).

In a cross-sectional study of 73 children, D. Nieman showed that body-mass index and the width of two skinfolds were positively correlated with counts of blood leukocyte subsets, phagocytosis by monocytes and granulocytes, and the concentration of salivary IgA, and negatively correlated with the phytohemaglutinin (PHA)-stimulated proliferation of lymphocytes. These findings are remarkably similar to those from an earlier study of obese and nonobese women, supporting the contention that both childhood and adult obesity are associated with alterations in immune function.

The effect of nutrition

Given the multiple metabolic changes that occur during physical activity, nutritional intervention might, in principle, alter the exercise-induced immune changes or protect against damage to the muscle. Alternatively, nutritional intervention might be used as a tool to study the mechanisms underlying exercise-induced changes in immunity.

A number of studies showed that the intake of carbohydrate (CHO) attenuates exercise-induced increases in neutrophil degranulation and the synthesis of IL-6, IL-10 and IL-1 receptor antagonist (G. Lancaster, Birmingham, UK and D. Nieman). D. Henson (Boone, NC, USA) demonstrated that the ingestion of CHO during a competitive marathon was linked to lower neutrophilia and monocytosis compared with ingestion of a placebo, but had no effect on the rate of T-cell proliferation or salivary IgA secretion.

Anti-oxidant vitamins appear to modulate the immune system in elderly people (P. Calder, Southampton, UK). The formation of free radicals and the suppression of natural killer (NK)-cell functions are parallel phenomena during chronic physical training in rats, indicating a relationship between them (I. Jonsdottir, Goteborg, Sweden). Although it was reported that vitamin C supplements influence the response to IL-6 during exercise (T.L. Hurst, Leicestershire, UK) and that vitamin E influences the response to HSPs (E. Fehrenbach, Tuebingen, Germany), it would be premature to draw strong conclusions about the effects of anti-oxidants in exercise immunology, owing to the lack of support for this data from other studies[5,6].

Conclusion

Exercise induces numerous changes in various components of the immune system. The recent demonstration that working skeletal muscles produce large quantities of IL-6, particularly during glycogen-depleted states, suggests that this cytokine might operate in a hormone-like manner, optimizing the metabolic response during exercise, and in addition, be linked with some of the beneficial effects to health of being physically active. Some of the exercise-induced changes to the immune system appear to be mediated by danger signals, such as HSPs, which might result in either immunopotentiation or immunosuppression. However, although animal models suggest strongly that a link exists between exercise-induced immune changes and susceptibility to infections, the clinical significance of these changes has yet to be determined in a human model.

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