Special Feature

Exercise effects on systemic immunity

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Summary   Heavy exertion has acute and chronic influences on systemic immunity. In the resting state, the immune systems of athletes and non-athletes are more similar than disparate with the exception of NK cell activity, which tends to be elevated in athletes. Many components of the immune system exhibit adverse change after prolonged, heavy exertion. These immune changes occur in several compartments of the immune system and body (e.g. the skin, upper respiratory tract mucosal tissue, lung, blood and muscle). Although still open to interpretation, most exercise immunologists believe that during this 'open window' of impaired immunity (which may last between 3 and 72 h, depending on the immune measure) viruses and bacteria may gain a foothold, increasing the risk of subclinical and clinical infection. The infection risk may be amplified when other factors related to immune function are present, including exposure to novel pathogens during travel, lack of sleep, severe mental stress, malnutrition or weight loss.

Key words: adaptive immunity, athlete, immune function, infection, natural killer cell.

Introduction

Publications on the topic of exercise immunology date from late in the 19th century. It was not until the mid-1980s, however, that a significant number of investigators worldwide devoted their resources to this area of research endeavour. From 1900 to 1999, just under 1200 papers on exercise immunology were published, with 78% of these appearing in the 1990s. In the present article, emphasis will be placed on reviewing literature published since 1990 on the acute and chronic effects of prolonged and intensive exercise on systemic immunity.

Immune function in endurance athletes and non-athletes

Among elite athletes and their coaches, a common perception is that stressful endurance race events and overtraining lower resistance to upper respiratory tract infection (URTI).[1] Several studies using epidemiological designs have verified that URTI risk is elevated during periods of heavy training and in the 1–2-week period following participation in competitive endurance races.[2–4] A high percentage of illnesses occur when elite athletes exceed individually identifiable training thresholds, mostly related to the strain of training.[4] Animal studies have generally supported the finding that one or two periods of exhaustive exercise following inoculation leads to a more frequent appearance of infection and a higher fatality rate (although results vary depending on the pathogen).[5,6]

In contrast, a common belief among endurance athletes is that normal training sessions confer resistance against infection. A survey of 750 Masters athletes (ranging in age from 40 to 81 years) has shown that 76% perceive themselves as less vulnerable to viral illnesses than their sedentary peers.[7] Three randomized exercise training studies have demonstrated that near daily exercise is associated with a significant reduction in URTI.[8–10]

Do the immune systems of endurance athletes and non-athletes function differently in the resting state? Although the URTI epidemiological data suggest that disparities should exist, comparisons indicate that athletic endeavour is linked to few clinically important alterations in immunity.

Adaptive immunity

In the resting state, the adaptive immune system is largely unaffected by intensive and prolonged exercise training, although results may vary according to training status, the assay method and age.

Baj *et al.*[11] have compared mitogen-induced lymphocyte proliferative responses in 16 untrained males and 15 elite male cyclists during periods of both low- and high-volume training. No significant difference between groups was measured while the cyclists engaged in low-volume training. However, during a period of high-volume training, two of four mitogen assays were elevated 35–50% in the endurance athletes. One other comparison, however, has reported no difference in mitogen-induced lymphocyte proliferative responses between controls and elite cyclists during periods of either low- or high-volume training.[12]

A study of elite female rowers and non-athletes 3 months prior to the world championships found a slight elevation in mitogen-induced lymphocyte proliferation when using a whole blood culture, but not with separated mononuclear cells (Fig. 1).[13]

Highly conditioned females have been reported to have a significantly greater proliferative response compared with their sedentary elderly peers, a finding also confirmed in comparisons of trained and untrained elderly males.[8,14]

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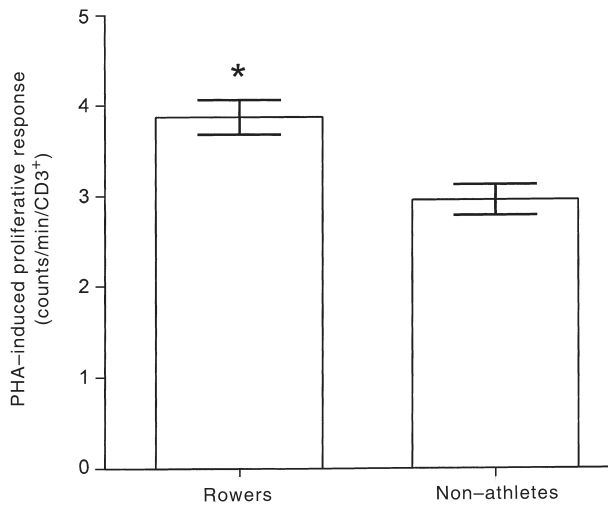
Figure 1 The PHA-induced proliferative response (whole blood data adjusted as counts/min for each CD3^{+} or T cell) was significantly greater in the elite female rowers compared with non-athletic controls at an optimal (25 μg/mL) concentration. No difference was measured when peripheral blood mononuclear cells were separated and then stimulated with PHA (data not shown). Data are from Nieman *et al.*[13] *P < 0.05.

Together, these data suggest that T- and B-cell function is not consistently altered by athletic endeavour, except in older adults. This interpretation is bolstered by the finding that the antibody response to vaccination is normal in endurance athletes.[15]

Innate immunity

The innate immune system appears to respond differentially to the chronic stress of intensive exercise, with natural killer cell activity (NKCA) tending to be enhanced while neutrophil function is suppressed (especially during periods of high-volume training).

Most, but not all, cross-sectional studies have shown an enhanced NKCA in endurance athletes when compared with non-athletes.[8,12,13,16] Trained rodents also demonstrate a greater NKCA.[17,18] Figure 2 summarizes the data from two studies comparing 22 male marathoners and 18 non-athletes, and 20 female elite rowers and 19 non-athletes.[13,16]

A study of elite cyclists in Denmark has indicated a higher NKCA during the summer (intensive training period) compared with the winter (their low training period).[12] Several prospective studies using moderate endurance training regimens of 8–15 weeks duration have reported no significant elevation in NKCA relative to sedentary controls (both young and older adults).[8–10] These data imply that endurance exercise may have to be at athletic workloads before NKCA is chronically elevated.

Neutrophil function (both phagocytic capacity and oxidative burst) has been reported as normal in endurance athletes except during periods of high intensity training, when it is suppressed.[11,13,19–21] This is especially apparent in the studies by Hack *et al.*[19] and Baj *et al.*,[11] with neutrophil function in athletes similar to controls during periods of low-volume
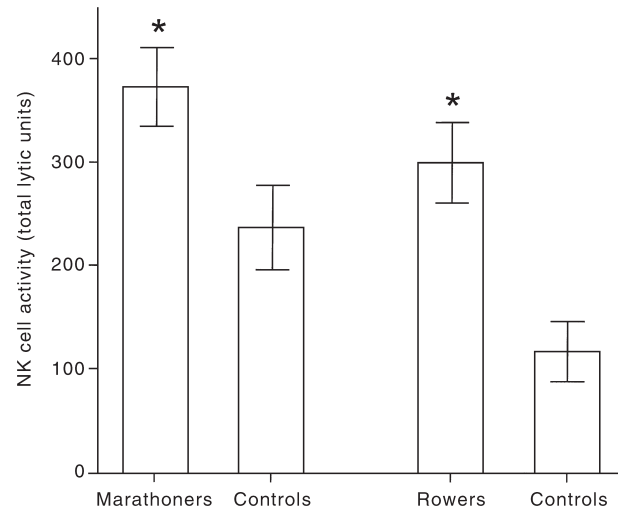
Figure 2 Natural killer cell activity was significantly higher in 22 male marathoners compared with 18 controls, and in 20 elite female rowers compared with 19 controls. Data are from Nieman *et al.*[13,16] *P < 0.05.

training but significantly suppressed during the summer months of intensive training. In contrast, no difference in neutrophil/monocyte phagocytosis or oxidative burst activity was measured in elite female rowers and controls 3 months prior to the world championships.[13]

Clinical implications

Even when significant changes in the concentration and functional activity of blood immune parameters have been observed in athletes, investigators have had little success in linking these to a higher incidence of infection and illness.[13,20,22] Elite swimmers undertaking intensive training have significantly lower neutrophil oxidative activity at rest than age- and sex-matched sedentary individuals, but URTI rates do not differ between the swimmers and sedentary controls.[20] The URTI rates were similar in female elite rowers and non-athletes during a 2 month winter/spring period, despite higher NKCA and T-cell function (whole blood assay) in the rowers.[13]

The acute immune response: The 'open window' theory

Comparing resting immune function in athletes and non-athletes may not be as meaningful from a clinical perspective as measuring the magnitude of change in immunity that occurs after each bout of prolonged exercise. During this 'open window' of altered immunity (which may last between 3 and 72 h, depending on the immune measure) viruses and bacteria may gain a foothold, increasing the risk of subclinical and clinical infection.

Although this is an attractive hypothesis, no serious attempt has been made by investigators to demonstrate that the athletes showing the most extreme immunosuppression following heavy exertion are those that contract an infection during the following 1–2 weeks. This link must be established before the 'open window' theory can be wholly accepted.
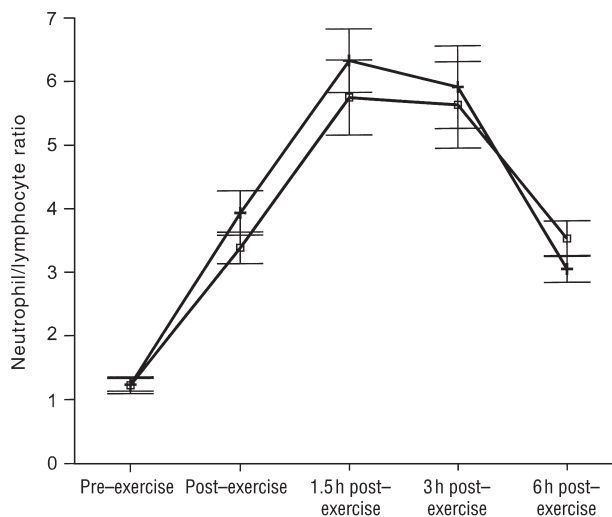
Figure 3 The neutrophil/lymphocyte ratio increased in 10 triathletes following two separate sessions of 2.5 h of running (□) and cycling (+) at approximately 75% maximal aerobic power (VO$_{2max}$). Data are from Nieman *et al*.[26]

Figure 4 Natural killer cell activity response to 2.5 h of intensive running in 62 marathoners. Data are from Nieman[23] and Nieman *et al*.[38] *$P < 0.05$.

Many components of the immune system exhibit change after prolonged, heavy exertion.[23] Some examples follow.

High neutrophil and low lymphocyte blood counts induced by high plasma cortisol

Exercise is associated with an extensive perturbation of blood white blood cell counts, with prolonged, high intensity endurance exercise leading to the greatest degree of cell trafficking (an increase in granulocyte and monocyte counts, a decrease in lymphocytes and an increase in the neutrophil/lymphocyte ratio; see Fig. 3).[24–31] Several mechanisms appear to be involved, including exercise-induced changes in stress hormone and cytokine concentrations, body temperature changes, increases in blood flow, lymphocyte apoptosis and dehydration. Following prolonged running at high intensity, the concentration of serum cortisol is significantly elevated above control levels for several hours and this has been related to many of the cell trafficking changes experienced during recovery.[23]

Increase in blood granulocyte and monocyte phagocytosis, but a decrease in nasal neutrophil phagocytosis

Following prolonged, high-intensity running, substances released from injured muscle cells initiate an inflammatory response.[32,33] Monocytes and neutrophils invade the inflamed area and phagocytose debris. The increase in blood granulocyte and monocyte phagocytosis may therefore represent a part of the inflammatory response to acute muscle injury. Phagocyte specimens collected from the peripheral blood react differently than those taken from the respiratory tract. Using nasal lavage samples, Müns *et al*. have shown that the capacity of phagocytes to ingest *Escherichia coli* is significantly suppressed in athletes compared with controls for more than 3 days after running a 20 km road race.[34]
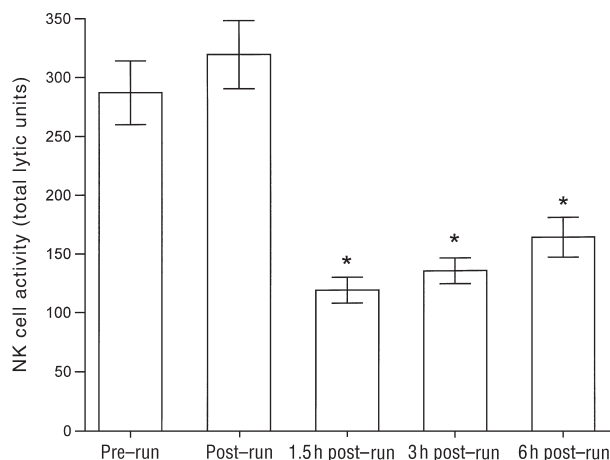
Decrease in nasal and salivary IgA concentration

Immunoglobulin A concentration in nasal secretions is decreased by nearly 70% for at least 18 h after racing 31 km.[35] Following strenuous prolonged exercise, salivary secretion rates fall, decreasing the level of IgA-mediated immune protection at the mucosal surface.[36]

Decrease in nasal mucociliary clearance

Nasal mucociliary transit time is significantly prolonged after a marathon race for several days and is caused in part by abnormally functioning ciliated cells.[37] These data, combined with the impairment in nasal neutrophil function and nasal/salivary IgA secretion rates, suggest that host protection in the upper airway passages is suppressed for a prolonged time after endurance running races.

Decrease in granulocyte and macrophage oxidative burst activity (killing activity)

Following sustained, heavy exertion, granulocytes have a reduced oxidative burst capacity.[24] The decrease in granulocyte oxidative burst may represent a reduced killing capacity by blood neutrophils (on a per cell basis) due to stress and overloading.

Decrease in NK cell cytotoxic activity

Following intensive and prolonged endurance exercise, NKCA is decreased 40–60% for at least 6 h (Fig. 4).[23,38,39] This decrease is greater and longer lasting than following exercise of less than 1 h duration and is related to the cortisol-induced redistribution of blood NK lymphocytes from the blood compartment to other tissues.[23] The decrease in NKCA closely parallels the drop in blood NK cell concentration, implying that each NK cell retains normal function. It has not yet been determined where the blood NK cells go to and whether the decreased NKCA in the blood compartment

represents what is occurring in other lymphoid tissues or is linked with URTI risk.

Decrease in mitogen-induced lymphocyte proliferation

Whole blood Con A-induced lymphocyte proliferation falls 30–40% (unadjusted for changes in T cell number) for more than 3 h following 2.5 h of intensive running.[27] Others have reported an even greater decrease after endurance race events.[39] The decrease in T-cell function is more prolonged than has been described after exercise of less than 1 h duration. Except for the immediate post-run time point, the decrease in T-cell function parallels the drop in blood T-cell concentration.[23,27]

Decrease in the delayed-type hypersensitivity skin response

The delayed-type hypersensitivity (DTH) reaction was suppressed 60% in triathletes 2 days after competing in a half-iron man triathlon (mean time 6.5 h).[15] These results indicate an impairment in this complex immunological process that involves several different cell types (including T cells) and chemical mediators.

Increase in plasma concentrations of pro- and anti-inflammatory cytokines

Exercise bouts that induce muscle cell injury cause a sequential release of the pro-inflammatory cytokines TNF-α, IL-1β and IL-6, followed very closely by anti-inflammatory cytokines, such as IL-10 and IL-1 receptor antagonist (IL-1ra).[29,40–44] Tumour necrosis factor-α and IL-1β stimulate the production of IL-6, which induces the acute phase response and the production of IL-1ra. Recent work using muscle biopsies and urine samples has shown more clearly the intimate link between all of these cytokines.[32,40,43] The inflammatory cytokines help regulate a rapid migration of neutrophils, and then later monocytes, into areas of injured muscle cells and other metabolically active tissues to initiate repair.[45] Endurance exercise associated with muscle soreness (e.g. marathon running) induces a greater inflammatory cytokine response than modes, such as cycling or rowing, that are more concentric in nature.[25,40,42]

Decrease in ex vivo production of cytokines in response to mitogens and endotoxin

The mitogen-induced release of various cytokines (in particular, TNF-α, IL-1, IL-2, IL-6, IL-10 and IFN-γ) is suppressed after prolonged and strenuous exercise.[44,46,47]

Blunted major histocompatibility complex II expression and antigen presentation in macrophages

Exhaustive exercise (2–4 h/day for 7 days) significantly suppresses the expression of MHC II and antigen presentation in mice macrophages, an effect due in part to elevated cortisol levels.[48,49] These data imply that heavy exertion can blunt macrophage expression of MHC II, negatively affecting the process of antigen presentation to T lymphocytes and thus their ability to respond to an antigenic challenge (e.g. DTH).

Summary and clinical implications

Taken together, these data suggest that the immune system is suppressed and stressed, albeit transiently, following prolonged endurance exercise. Infection risk may be increased when the endurance athlete goes through repeated cycles of heavy exertion, has been exposed to novel pathogens and experiences other stressors to the immune system, including lack of sleep, severe mental stress, malnutrition or weight loss.

The ability of the immune system to mount an antibody response to vaccination over the 2–4 week post-exercise period, however, is not affected. For example, male triathletes when compared to sedentary controls had normal antibody production to pneumococcal, tetanus and diphtheria vaccines following a half-iron man triathlon competitive event.[15]

The immune changes after heavy exertion differ markedly from those following moderate exercise. For example, after brisk walking or sports play and drills, blood cortisol and cytokine levels remain close to pre-exercise levels, perturbation of immune cell counts and function is mild and overall immunosurveillance is enhanced.[25,50,51]

To counter exercise-induced alterations in immunosurveillance and host protection against pathogens, the endurance athlete should consider these guidelines:[1]

1. Keep other life stresses to a minimum (mental stress in and of itself has been linked to increased URTI risk).
2. Eat a well-balanced diet to keep vitamin and mineral pools in the body at optimal levels.
3. Avoid overtraining and chronic fatigue.
4. Obtain adequate sleep on a regular schedule (disruption is linked to suppressed immunity).
5. Avoid rapid weight loss (linked to adverse immune changes).
6. Avoid putting the hands to the eyes and nose (a major route of viral self-inoculation).
7. Before important race events, avoid sick people and large crowds when possible.
8. For athletes competing during the winter months, influenza vaccination is recommended.

There are some preliminary data suggesting that various immunomodulator drugs may afford athletes some protection against infection during competitive cycles, but much more research is needed before any of these can be recommended.[52,53]

The influence of a growing list of nutritional supplements on the immune and infection response to intense and prolonged exercise has been measured.[54] Supplements studied thus far include zinc, dietary fat, plant sterols, antioxidants (e.g. vitamins C and E, β-carotene, *N*-acetylcysteine and butylated hydroxyanisole), glutamine and carbohydrate. Vitamin and glutamine supplements have received much attention, but the data thus far do not support their use as countermeasures to exercise-induced alterations in immunity. At this point, athletes should eat a varied and balanced diet in accordance with the food guide pyramid and energy needs and should be assured that vitamin and mineral intake is adequate for both health and immune function.

Carbohydrate supplementation before, during and after intensive endurance exercise lasting longer than 90 min is recommended, however.[55] Carbohydrate beverage ingestion has been associated with higher plasma glucose levels, an attenuated cortisol and growth hormone response, fewer perturbations in blood immune cell counts and a diminished pro- and anti-inflammatory cytokine response. Overall, these data indicate that the physiological stress to the immune system is reduced when endurance athletes use carbohydrate beverages (about 1 L/h of a 6% carbohydrate beverage). Although it is logical to assume that these favourable carbohydrate-induced effects on the endocrine and immune systems should reduce the risk of infection, well-designed studies of large groups of athletes are necessary before this link can be established.

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