A Multidisciplinary Approach to Human Movement

UNIVERSIDADE DE COIMBRA

Faculdade de Ciências do Desporto e Educação Física

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SPORT AND IMMUNE SYSTEM: DOES PHYSICAL ACTIVITY DECREASE SUSCEPTIBILTY TO DISEASE?

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Sport immunology is a relatively recent area in exercise science. The interest in health promotion, and the "exercise is good for you" message has increased the attention of researchers to exercise and immunity.

In contrast to the large numbers of studies on the immune response to acute exercise, only a small number have been done concerning the effect of physical conditioning or training on immune function. There are a few studies (reviewed by Pedersen et al, 1996) that provide data in support of the idea that moderate physical activity may decrease susceptibility to disease, especially upper respiratory tract infections (URTI). One by Nieman et al. (Nieman et al, 1990a) studied a group of 36 women who did a program of 45min walking, 5 days per week during 15 weeks compared to a sedentary control group. The active women group had significantly fewer days with URTI symptoms than the sedentary group (5,1 *versus* 10,8). In another study (Nieman et al, 1993) with elderly women (67 to 85 years), the incidence of colds during a 12 week period during the fall was the lowest in the group of subjects that exercised moderately each day for 1.5 hours, only 8%, raised to 21% in the group that did a 40 min walk, 5 times a week, and peaked to 50% for the sedentary control group.

Our own studies also support the viewpoint that moderate physical activity may reduce susceptibility to URTI. In a group of 53 elderly subjects, aged between 63 and 101 years old, the 23 that performed regular physical activity (at least 1hour a day, 3 times a week) reported significantly less episodes of flu (mean 0.59 *versus* 1.2 with p=0.003) and of

the common cold (a mean of 1,1 *versus* 1,6 with p= 0.014) during that current year when compared to the sedentary group. They also took significantly less regular medication (40,9% *versus* 80%) and reported less cases of high blood pressure (23,8% *versus* 31,1%) (results not published).

Another studied the incidence of URTI in a group of 40 young boys, aged between 11 and 14 years old. 20 belonged to a football (soccer) club and did regular physical activity during the whole week, the other 20 had no regular physical activity apart from the ones included in the school program. Significantly less episodes of the common cold (1.15 versus 1.8 with p=0.024) and the flu (0.85 versus 1.8 with p=0.001) were reported by the young football players in that last year compared to their sedentary school colleagues (results not published).

At the same time there is the belief among elite athletes and coaches that athletes are more susceptible to UTRI during intense training and major competition. One of the first reports that correlates intense exercise with susceptibility to disease dates from 1918 (Cowles, 1918). It reported that most of the cases of pneumonia at a boys school occurred in athletes. More, the respiratory infections seemed to progress to pneumonia after intense exercise and competition.

More recently, several studies that surveyed marathon runners (Peters and Bateman, 1983; Nieman et al, 1990b; Heath et al, 1991) have also found increased susceptibility to UTRI in the immediate weeks after a marathon race. One of the largest epidemiological studies was done by Nieman et al (Nieman et al, 1990b), who studied the incidence of URTI in a group of 2311 marathon runners that participated in the 1987 Los Angeles Marathon race. Their results showed that those participants who trained more than 97Km a week had more episodes of URTI (2:1) in the two months before the race than the athletes who trained less than 32Km per week. They also showed that during the week following the race 12.9% of the participants reported an infectious episode compared to only 2,2% of similarly experienced runners who had enrolled in the race but did not participate (for reasons other than illness). It was determined that the odds in favour of illness for the marathon race participants *versus* the nonparticipating runners were 6 to 1. These studies (Peters and Bateman, 1983; Nieman et al, 1990b; Heath et al, 1991) suggest that, in runners the incidence of infectious disease increases with training volume and after a major competition. URTI appear to be the most common illness among endurance athletes (e.g. marathon runners, cross-country skiers, swimmers) (Berglund and Hemmingsson, 1990).

The mechanisms responsible for the reported high incidence of URTI among elite athletes are not currently known. Several models have been proposed to explain the relationship between exercise and URTI risk. The first one proposed by Nieman (Nieman, 1994) suggest that the susceptibility to URTI follows a J-shaped curve (Fig.1). He postulates that while a moderate intensity and quantity of exercise over a prolonged period reduces the risk of infection below that of a sedentary person, when a critical level is reached, the more strenuous the exercise, the greater the risk of infection.

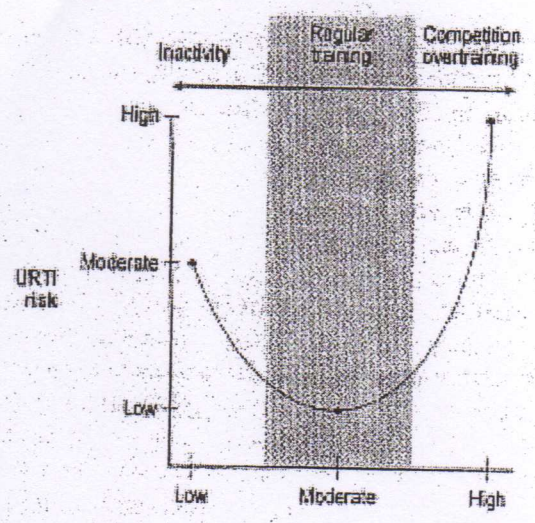

Fig. 1 - The J shaped model of relationship between intensity and volume of exercise and risk of URTI. (Adapted from Peters, 1997).

The open window hypothesis (Pederson and Ullum, 1994) postulates that in essence the immune system is enhanced during moderate exercise, and only intense long duration exercise is followed by immuno-supression. While the immunosupression lasts (i.e. hours), and this is the time period referred to as "the open window", microorganisms may invade the host and cause infections. It is during this "open window " of immune suppression that the athletes are at increased risk of contracting infections. One of the reasons for the overtraining effect seen in elite athletes could be that this window of opportunity for pathogens is longer and the degree of immunosupression higher. Severe immunosupression

may occur if athletes do not allow the immune system to recover after exercise and initiate a new training section while still immunosupressed.

The neuroendocrine model proposed by Smith and Weidemann (Smith et al, 1990a) proposes that during exercise, the release of immunomodulatory hormones, depending on exercise intensity, combine to either enhance or decrease immune function. Moderate exercise causes release of immunostimulatory hormones like prolactin, growth hormone, endorphins and stimulatory cytokines. With augmented exercise intensity, above a certain threshold, immunosuppressive hormones such as catecholamines, cortisol and ACTH are secreted thus rendering the athlete more susceptible to infections.

In order to better understand the why the exercise induced changes in the immune system parameters may be important to explain the relationship between exercise and susceptibility to disease, a brief overview of the immune system, follows.

The immune system probably developed as a mean to distinguish self from non-self and to maintain homeostasis. It is usually seen as the body defensive system against foreign microorganisms, like bacteria, viruses, fungi and parasites. It also deals with tumour cells and allergens. It is a complex system that requires complex communication and coordination between tissues, cells and messenger molecules throughout the body.

Cells of the immune system

All cells involved in the immune response arise from a common ancestor, the stem cell found in the bone marrow (Fig.2). This cell has the ability to proliferate and differenciate into several lineages that give rise to the immune cells.

The myeloid cells lineage gives rise to the monocytes/macrophages and granulocytes, the lymphoid cell lineage gives rise to the T and B lymphocytes and possibly to the NK cells. A third lineage gives rise to the erythrocytes. Immune cells are found in the blood and lymph circulation and throughout the body in several lymphoid organs like the thymus, the spleen and the lymph nodes.

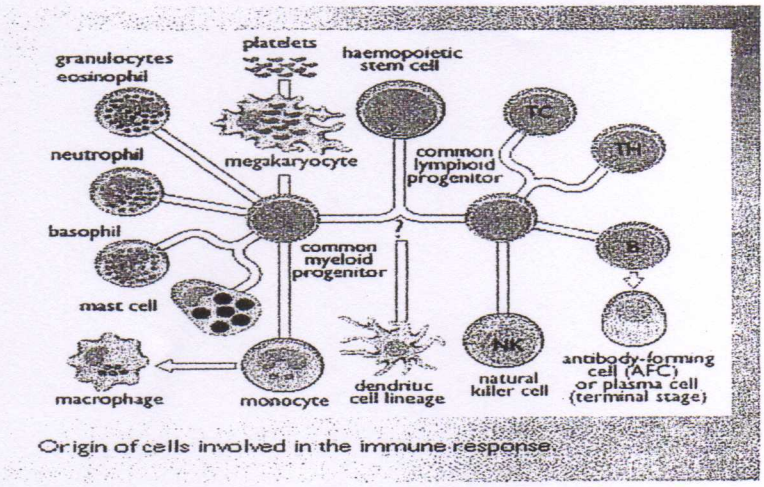

Fig. 2 - The origin of cells involved in the immune response. *(Adapted from Immunology Interactive 2.0, Male, Brostoff, Gray and Roitt, 1998 Mosby).*

Functions of the immune cells

Granulocytes are large cells containing granules in their cytoplasm. There are three types of granulocytes: neutrophils, which make up the biggest population of circulating leukocytes, eosinophils, basophils and mast cells.

Neutrophils are phagocytic cells that ingest and kill microorganisms by releasing the proteases contained in their cytoplasmic granules. They also generate toxic molecules such as hydrogen peroxide and oxygen radicals. They participate in the inflamatory process: they are attracted to the sites of infection by chemotactic molecules produced by other leukocytes and move through the capillary walls to reach the site of infection.

Eosinophils comprise a small percentage of circulating leukocytes and are also involved in the phagocytic process. They are specially involved in the resistance to parasytes.

Basophils and **mast cells** also represent a very small percentage of circulating leukocytes and are mainly involved in allergic and inflammatory reactions.

Monocytes and macrophages are phagocytic and antigen presenting cells. Monocytes can localise to tissues during infection, inflammation and

injury. Once there they differenciate into macrophages. They kill ingested microorganisms by releasing proteases from lysosomes and by generating oxygen radicals. They also produce several soluble factors that activate lymphocytes. They are also able to kill tumour and virus infected cells.

Lymphocytes can be divided into three main types of cells: The T, B and Natural Killer (NK) cells.

The T cells are characterised by the presence of the T-cell receptor (a cluster of specific proteins) on the cell surface. T cells are involved in initiating and regulating the immune responses by modulating the activity of several immune cells. The T cells are further subdivided into T helper (Th CD4+ T cells) and T cytotoxic/suppressor cells (Tc/s CD8+ cells). Th cells regulate the immune response by secreting soluble factors (lymphokines) that stimulate B and T cell proliferation and differentiation. Antigen recognition by Th cells is an essential first step for most immune responses. Tc/Ts are cytotoxic and regulatory cells. Tc cells can kill tumour cells, virus infected cells and parasites. Ts cells are involved in suppressing the immune response once completed.

B cells are the antibody producing cells. Upon activation by T cells, the B cells proliferate and differenciate into plasma cells producing large amounts of antibody. They are responsible for the immune system "memory" of previous encounters with antigen.

NK cells can recognise and kill tumour and virus infected cells. They also exhibit antibody dependent, cell mediated cytotoxicity.

Innate and acquired immunity

The immune response can be subdivided into two types: the innate or also referred to as natural immunity and the acquired or adaptive immunity (Table 1). The innate immunity represents the non-specific defences of the immune system. They include the physical barriers such as the skin and mucus, the chemical barriers, complement, lysozyme, pH of body fluids and acute phase proteins. The cells involved in the innate immunity, monocytes, macrophages, granulocytes and natural killer cells, can recognise and deal with an invading microorganism without prior exposure. Natural immunity does not improve with repeated exposure.

Acquired immunity, on the other hand, involves the recognition of a specific infectious agent and mounts an immune response directed to that agent only. It improves with repeated exposure, by memorising the invading agent.

Table 1- Innate and acquired immunity *(Adapted from Exercise and Immunology, MacKinnon LT, Current Issues in Exercise Science Series, Human Kinetics Publishers, 1992)*

ACQUIRED IMMUNITY	INNATE IMMUNITY
Humoral Antibodies Memory Cell-mediated T cells	Physical Barriers Skin, epithelial cell barrier Mucus Chemical Barriers Complement Lysozyme pH of bodily fluids Acute phase proteins Other secretions Cells Monocytes/macrophages Granulocytes Natural killer Cells

Cooperation between cells involved in immune responses (Fig.3) occurs at many levels. Phagocytes and antigen presenting cells can take up antigen in the periphery and transport it to secondary lymphoid

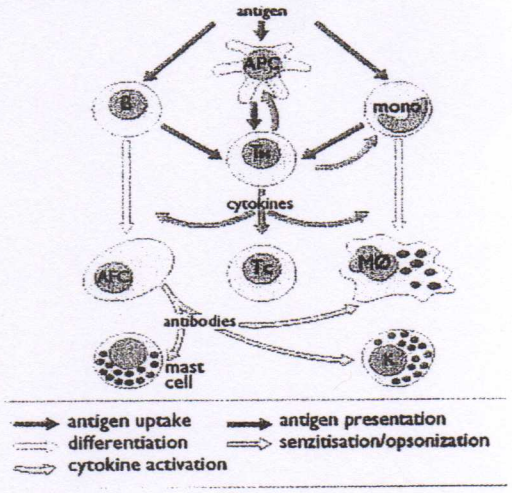

Fig. 3 - Cooperation between cells involved in the immune response. *(Adapted from Immunology Interactive 2.0, Male, Brostoff, Gray and Roitt, 1998 Mosby).*

tissues, like lymph nodes or the spleen. Antigen presenting cells and B cells are able to internalise antigen, process it and present it to CD4+ Th cells. The cytokines produced by the activated T cells can stimulate B cells to grow and differentiate into plasma cells. Other cytokines can also activate Tc cells, antigen presenting cells and mononuclear phagocytes. Antibodies released by the B cell can bind to receptors on phagocytes facilitating the up take of antigen. IgG antibodies allow killer cells to recognise target cells coated with antibody. IgE antibodies can sensitise mast cells and basophils to release their inflammatory mediators when they bind specific antigen.

Immunological parameters affected by regular moderate (chronic) exercise.

Several cross sectional studies comparing resting levels of the immune system in athletes and in untrained controls have shed some light on the effect of chronic exercise in the immune system. Two studies on male cyclists (Pederson et al, 1989; Tvede et al, 1991) have shown an increase in NK cell activity in trained compared to untrained subjects, 38.1% versus 30.3 with p=0.008 in the first study. In the second study the values were 39.2% versus 30.9% during low a low training period and 55.2% versus 33.6% during a high training period. No differences were found in these two studies on other lymphocyte subpopulations and on the lymphocyte proliferative responses. Another study (Nieman et al, 1995) done with marathon athletes and sedentary controls also found increased NK cell activity in the athletes. They found no significant differences between groups in the concentrations of leucocytes and lymphocytes subsets nor in the mitogen stimulated proliferative responses. However a study by the same author (Nieman et al, 1993) comparing 12 highly conditioned and 30 sedentary elderly women reported significantly increase in the mitogen stimulated proliferative responses as well as in the NK cell activity in the highly conditioned group when compared to the sedentary group. In a recent study (Nieman et al, 2000) comparing a group of 20 female elite rowers and 19 non-athletes female controls they also found significantly higher mitogen induced lymphocyte proliferative response and NK cell activity in rowers when compared to the controls. No differences in granulocyte and monocyte phagocytosis, oxidative burst activity and plasma concentrations of IL-6, tumour necrosis factor-α and IL-1 receptor

antagonist, were seen between the groups. In another study with elite rowers (Nehlsen-Cannarella, 2000) resting saliva immunoglobulin A (sIgA) concentration was 77% higher in the rowers compared to nonathletes. No differences were found for the IgM and IgG levels between the rowers and the control group. Serum IgG concentration was also reported to be higher in elite distance runners early in the training season when compared to non-athlete control subjects (Wit, 1984). Resting IL-1 levels have also been found to be higher in endurance runners when compared to non-athletes (Evans et al, 1986). It was however suggested that high resting levels of IL-1 in runners may reflect muscle proteolysis and repair as a result of intense regular exercise (Evans et al, 1986).

Immunological parameters affected by long intense exercise.

The appearance of overtraining among athletes during intense training and major sport events has raised awareness to the importance of further research in the exercise immunology field. Some laboratory studies have revealed a number of potentially negative changes in immunological parameters following prolonged exercise. These include a decrease in lymphocyte numbers during the recovery period, that fall below pre-exercise levels and remain low for up to 6 hours (MacCarthy and Dale, 1988; Berk et al, 1990 ; Nieman et al, 1994; Nieman et al, 1989; Boucchard et al, 1993). Proliferative response to mitogens may also be suppressed after prolonged exercise. Two studies with marathon runners (Gmunder et al, 1988; Eskola et al, 1978) have shown a 50% and 40% decrease respectively after a marathon run.

A marked decrease in circulating NK cells 1 to 2 hours into recovery and cytotoxic capacity has also been shown (Berk et al, 1990;MacKinonn, 1989; Nieman et 1990a; Pederson et al, 1989; Pederson et al, 1990).

Decreased salivary IgA levels have also been reported after intense endurance exercise in elite skiers (Tomasi et al, 1982), swimmers (Gleeson et al, 1999; Tharp and Barnes, 1990), distance runners (Cameron and Priddle, 1990) and cyclists (MacKinonn et al, 1987 and 1989). The degree of salivary IgA supression is associated with the intensity of the exercise and the duration or volume of the training. Low levels of salivary IgA, especially the IgA1 subclass are associated with increased risk of respiratory illness (Gleeson et al, 1999). Thus monitoring mucosal IgA levels during intense training periods and establishing personal profiles for individual athletes may predict the risk of the athlete for UTRI. Until

now this is the only immunological parameter that has been associated with an increased risk of URTI.

Serum Ig levels do not appear to change after intense exercise. However, a paper reported on an in vitro reduction of production of Ig (IgG, IgA and IgM) after cycling exercise (Hedfors et al, 1983) but this reduction could be accounted for by a transitory change in lymphocyte subsets at the time of sampling.

In general extreme exercise suppresses neutrophil phagocytosis and the oxidative burst. Chemotaxis and degranulation do not seem to be affected (Smith et al, 1990b). A study that done after a 20 Km race found that the neutrophils from the runners were less able to ingest bacteria, an effect that lasted for 3 days (Nieman, 1994).

After intense prolonged exercise, increased urinary excretion of several cytokines has been reported (reviewed by Northoff et al, 1994). Increased IL-6 plasma concentration and urinary excretion of IL-1β, soluble IL-2 receptor, IL-6, TNFα and IFNγ after a 20Km run was reported by Sprenger et al. (Sprenger at al, 1992). In contrast to moderate exercise, which causes little change in plasma or urinary excretion of cytokines, intense exercise (e.g. >60min at 75% VO_2max) generally causes large increases in urinary excretion of cytokines and decreases *in vitro* production of cytokines in cells isolated after exercise. The exception seems to be IFNγ that appears to increase (Northoff et al, 1994). However, no direct correlation between changes in cytokines and alterations of immune function in athletes has been reported until now. It has been suggested that the increase in pro-inflammatory cytokines such as IL-1, IL-6 and TNFα reflects an acute inflammatory response to intense exercise.

Summary and conclusions

Today there is enough epidemiological evidence to support the fact that the immune system responds to increased physical activity and may be given some of the credit for exercise related reduction in disease. While regular exercise seems to be important in the prevention of a variety of diseases including heart disease, hypertension, obesity and diabetes, reports of increased infections among highly trained athletes have cast a shadow over the "exercise is good for you message". However most exercise effects on immune function are relatively small and elite athletes are not immunodepressed in the clinical sense. It is possible that increased

susceptibility to infection among athletes results in part from additive effects of small changes in immunological parameters important for host defence. It is also likely that psychological stress associated with major competitions, which is known to have immunosuppessive effects, will have a cumulative effect on the immunological changes induced by vigorous training.

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