Adaptative mechanisms of the immune system in response to physical training

Carol Góis Leandro[1], Raul Manhães de Castro[2], Elizabeth Nascimento[2], Tânia Cristina Pithon-Curi[3] and Rui Curi[3]

ABSTRACT

Moderate physical training enhances the defense mechanisms, while intense physical training induces to immune suppression. The underlying mechanisms are associated with the link between nervous, endocrine, and immune systems. It suggests autonomic patterns and modulation of immune response. Immune cells, when exposed to regular bouts of stress, develop a mechanism of tolerance. In many tissues, it has been demonstrated that the response to aggressive conditions is attenuated by moderate physical training. Thus, training can induce tolerance to aggressive/stressful situations. In this review, studies suggesting the adaptation mechanisms of the immune system in response to physical training will be reported.

INTRODUCTION

The relationship between physical exercise and health has been consolidating over the last years. In clinical studies of wide epidemiological approach, it was demonstrated that the regular practice of physical exercise is associated with health promotion as well as prevention of chronic-degenerative diseases[1-2]. Recently, the effects of the physical exercise over the function of the immunological system have been approached in many studies[3-8].

Different types of physical exercise cause distinct alterations in the immune function. Regular exercise, or physical training of moderate intensity, improve the defense systems, while intense training causes immune suppression[9-10]. The subjacent mechanisms are associated with the communication between the nervous, endocrine and immunological systems, suggesting autonomic ways and immune response modulation[11]. Immune system cells, when exposed to small stress loads, develop tolerance mechanism. It has been shown in many tissues that the response to aggressive situations seems to be attenuated by physical training previously applied, that is, the training induces to tolerance to aggressive/stressing situations[12-13].

This review has the aim to approach some relevant aspects of the physical training influence over the function of immunological system components. In order to have a broader view, studies showing evidence on the probable mechanisms of organic adaptation associated with physical training will be also reported.

1. Departamento de Nutrição, CAV – Universidade Federal de Pernambuco – UFPE.
2. Departamento de Nutrição, Universidade Federal de Pernambuco – UFPE.
3. Instituto de Ciências Biomédicas ICB-1, Universidade de São Paulo – USP.

Approved in 14/6/07.

Correspondence to: Carol Góis Leandro, Av. Prof. Moraes Rego, 1.235, Cidade Universitária – 50670-901 – Recife, PE, Brazil. Phone: (81) 2126-8463, fax: (81) 2126-8470. E-mail: carolleandro22@yahoo.com.br

Keywords: Physical exercise. Cross-tolerance. Leukocytes.

THE IMMUNE SYSTEM: GENERAL CONSIDERATIONS

The immunological system is determinant in the combat to invading microorganisms, in the removal of dead cells and cellular detritus as well as in the establishment of the immunological memory[14]. The cells which constitute the immunological system are originated from pluripotent hematopoietic cells, placed in the bone marrow, and the posterior differentiations derived not only from it, but also from other specific sites on the organism. The leucocitary populations comprise the polymorphonuclear granulocytes (neutrophils, eosinophils and basophils), the monocytes/macrophages and the lymphocytes (T, B lymphocytes and 'natural killer' cells [NK]).

The neutrophils are important blood fagocytes and participate in the inflammatory reaction, being sensitive to chemiotaxic agents released by the mastocytes and basophils as well as by the activation of the complement system[15]. The leucocytosis by neutrophilia may indicate the presence of a bacteria infection or of an inflammation in response to a tissue injury[14].

Another group of phagocyte cells includes the mononucleotide monocytes and macrophages. Monocytes are cells present in peripheral blood which continuously differentiate in macrophages after migrating to the tissues[14]. The macrophages are involved in the microbicide and antitumoral activity and show accessory cellular function as antigens presenters[16]. Macrophages characteristic aspects include adherence capacity, chemiotaxis, production of oxygen reactive species and cytotoxity[14,17]. They are also a source of cytokines mediator of the physiopathologic reactions which usually follow the cellular injury[16].

Macrophages are cells of high fagocyte power and their functions are regulated by other cells (T and B lymphocytes)[18] and by chemical mediators produced by the sympathetic nervous system (SNS) and by the hypothalamus-pituitary-adrenal axis (HPA)[11,18]. The presence of glucocorticoids in cultures of macrophages results in the inhibition of some microbicide functions, for instance, the production of oxygen (ORS) and nitrogen reactive species (NRS)[17]. The macrophages also have pro and antiinflammatory effects and promote the development of immunity mediated by lymphocytes[14].

Lymphocytes are heterogeneous in size and morphology. The differences between these cells are observed concerning the nucleus/cytoplasm ratio and the presence or not of cytoplasmatic granules[18]. Cells of similar morphology are found in the spleen, bone marrow, lymph nodes, thymus, and other areas as the Peyer patches[18]. The lymphocytes may be classified according to their membrane markers, reactions to stimuli, migration patterns and mean-life[14]. In the thymus, when acquiring some characteristics, they change into T lymphocytes, with antigenic markers of CD4+ (helper) or CD8+ surface (suppressor and cytotoxic)[14,18]. These cells are part of the cellular immunological response and actively proliferate when stimulated by interleukine-2 (IL-2) or concanavalin A (ConA)[14,18].

Although they do not synthesize immune globulins (Ig), T lymphocytes act as modulators of the immunologic response[19]. This fact occurs through interactions between the many types of T lymphocytes with the macrophages and the dendritic cells during the immunological response mediated by cells[19]. The B lymphocytes reach maturity probably in the bone marrow and are precursors of the cells producers of antibodies, the plasmocytes[19]. When stimulated by lipopolysaccharides in culture, these cells proliferate[20-21].

Lymphocytes usually present in the circulation and lymphoid tissues are in quiescent state, a situation in which they are metabolic little active[19]. An invasive or neoplasia stimulus is able to promote the activation of these cells, leading them to proliferate and to secrete cytokines involved in the immune response[19]. The change to the activated state is also followed by metabolic alterations in these cells, where the biosynthetic and energetic ways are stimulated[22-24].

There are also the NK cells, a kind of lymphocyte found in the blood. These cells are known for triggering the early defense against certain intracellular infections and eliminating tumoral cells[19].

Local response to an infection or injured tissue involves the production of cytokines[19]. Cytokines are small soluble proteins secreted by leukocytes and other cells, and which have the purpose to modulate the immune response[25-26]. The local response for one infection or injured tissue involves the production of these mediators which will facilitate the inflow of the several types of leukocytes for the reached region[25]. Besides its mediator function in the immune system, the cytokines may also act in other systems, modifying their functions[25,27].

The immune system seems to be sensitive both to infection agents and alterations in the organic homeostasis, as occurs in stress[11,28]. These alterations suggest an interrelationship of the immune system with other systems, such as the nervous and endocrine ones[29]. The hormonal response is apparently standardized, and regardless the type of stressor agent. Initially, there is activation of the SNS resulting in increase in the catecholamines concentration in the circulation and also the activation of the HPA axis which induces increase in the glucocorticoids concentration and other hormones[30]. The cells of the immunological system have receptors for such hormones[28,31-33]. Likewise, they can secrete cytokines which will act in neuro-endocrin organs[32]. Actually, the bidirectional relationship between these systems seems to be the milestone of the current understanding of the immunological activity, demonstrating the multi-connected way in which the immune system acts[31-33]. Within this context, many studies have focused on the response of the immunological system to different stress inducer agents, such as physical exercise.

PHYSICAL EXERCISE, PHYSICAL TRAINING AND IMMUNOLOGICAL SYSTEM

Physical exercise may be classified according to the effort intensity as: mild, moderate and intense. This classification is based on the performance of some maximal effort tests for evaluation of the blood lactate concentration, the oxygen maximal uptake ($\dot{V}O_{2max}$), and/or the maximal heart rate (HR_{max}). In exercises of mild or moderate intensity, the blood lactate concentration remains steady (varying between 2 and 4 mmol/L), that is to say, the lactate is produced at lower rates[34]. The $\dot{V}O_{2max}$ and the HR_{max} are the physiological parameters more commonly used in studies in order to make reference to the effort intensity. Thus, a mild exercise usually refers from 20 to 50% of the $\dot{V}O_{2max}$ and the HR_{max}, a moderate exercise from 50-70% of the $\dot{V}O_{2max}$ and the HR_{max}, and intense exercise above 80% of the $\dot{V}O_{2max}$ and HR_{max}[13,35-36]. When the physical exercise is regularly performed, then it is called physical training.

The effect of an acute physical exercise (sudden load of physical effort) over the cells of the immunological system is already very well established[6,9,37-39]. Different kinds and effort loads may have distinct reflections on the immunological system. Moderate physical exercise seems to improve the defense mechanisms of the body, while intense exercise seems to weaken them[9-10,37]. Neutrophilia, lymphopenia and monocytosis occur in response to intense physical exercise[7]. The redistribution of these cells in the vascular compartment in response to exercise seems to be mediated by adrenaline and in lower extent by noradrenaline[29,33,40-41]. The expression of b-receptors in the different immune cells may provide the molecular grounding for action of catecholamines[11]. Nevertheless, the density of adrenergic receptors as well as the efficiency of the AMPc transduction system differ in the different types of immune competent cells[42-43]. The neutrophils and the NK cells seem to present greater number of receptors, being followed by decreasing order, by the TCD8+ lymphocytes, the B lymphocytes and finally by the TCD4+ lymphocytes[22,42,44].

Intense physical exercise may induce to many defense aspects of the body, including the activity of the NK cells, proliferative response of lymphocytes and the production of antibodies by the plasmocytes[3,7,18,45]. These alterations compromise the body's defense against infection and oncogenic agents, as well as in the allergic processes and auto-immunity[10,31]. Gillis *et al.*[46] have observed inhibition in the production of the growth factor of T lymphocytes induced by the increase of glucocorticoids. Woods *et al.*[47] verified decrease in the production of superoxide by peritoneal macrophages of rats in response to an intense load of physical exercise. These studies support the immune suppression induced by stress concept, since according to what was referred above, the lymphocytes and the macrophages act in a determinant way, against the carcinogenesis and autoimmunity.

On the other hand, moderate physical exercise seems to be associated with the increase of the leukocytes function. Many researchers verified that moderate physical exercise helps the chemotaxis, degranulation, fagocitosis and oxidative activity of the neutrophils one hour after physical exercise at 60% $\dot{V}O_{2max}$[6,48-50]. Woods *et al.*[47] verified increase of adherence, production of sueroxide anion, nitrogen metabolism rate, cytotoxic activity and the fagocitic capacity of macrophages. Tvede *et al.*[51] have studied the response of the lymphocytes populations in Dannish cyclists during 1 hour of physical exercise and verified increase in the cytolytic activity of NK cells and lymphokine activator of NK cells (LAK). Recent studies report that there was no alteration in the salivary concentration of IgA and IgE in the serum during a moderate exercise[42,53,56-57]. Actually, it has been well established that moderate physical exercise is associated with the immunological function and the decrease of susceptibility to diseases[52]. Therefore, it is plausible to establish a link between physical training of moderate intensity and the alterations occurred in the immunological system.

Contrary to the massive amount of studies conducted with acute physical exercise, the reports on the relationship between physical training and immune system are scarce. Intervenient variables, such as the athletes' diet, the competition season, trips and psychological stress, are difficult to be controlled and can independently influence in the immune system function. Peters *et al.*[53] have reported lower incidence of the upper respiratory tract infections (URTI) in runners supplemented with 600 mg of vitamin C three days before the run, comparatively to their pairs. Robinson *et al.*[54] have also verified that the addition of the omega 3 fatty acid in the diet, regardless the moderate physical training, may provide positive effects in the immune function (increase of the NK cells activity). Nieman *et al.*[55], in a study with marathoners reported that 12% of the participants had 20% more URTI occurrence one week after the event when it was performed in the winter months. In this same study, higher incidence of URTI was observed in the period which preceded the event when compared with their non-participant pairs[55].

There is a general perception that high level athletes have higher risks to acquire infections, such as the URTI, during intense training periods (> 75% of $\dot{V}O_{2max}$) and after exhaustive competitions[6,56]. Bury *et al.*[57] have verified decrease in the proliferative response of T lymphocytes as well as in the fagocitic function of neutrophils in football players in the competition season. A more simplified explanation for the immune suppression in response to an intense physical exercise load would be that there is an increased use of the functions of the organism with exaggerated production of ORS and increase of oxidative stress in the tissues[9,12]. Lin *et al.*[5] have verified that the increase in the apoptosis occurrence in thymocytes is associated with increase in ORS production in rats submitted to two days of intense physical exercise, with these effects having been attenuated by the previous administration of the antioxidant hydroxyanisole butylated.

On the other hand, moderate physical training seems to improve many immune functions[58]. Pedersen *et al.*[51] evaluated trained cyclists for 4 consecutive years and detected decrease in the incidence of infections with a consequent increase of the immunological function. Non-competitive athletes or individuals who engage in a regular practice of mild or moderate exercise, comparing to the sedentary population, present higher protection from infections[8,59-61]. Pastva *et al.*[62] demonstrated that moderate intensity training decreases the infiltration of leukocytes, cytokines production, expression of adherence molecules and structural modulation in the lungs of asthmatic mice. The neutrophils function and the index of proliferation of B lymphocytes did not alter in studies performed with trained humans[63]. Moreover, Nieman *et al.*[55] demonstrated the effects of the moderate exercise in the increase of the resistance to infections, verifying that women who performed 45 minutes of walk five times per week, in the period of 15 weeks, had lower incidence of days reported with URTI.

The cytotoxic activity of NK cells also seems to increase in non-competitive athletes after a training period of 8 months[64]. In trained runners, Baum *et al.*[65] did not find alteration in the differential counting of leukocytes in the circulation 22 hours after the last moderate training session.

In animals, it has been observed an increase in the function of macrophages after a moderate training program. Woods *et al.*[66] have verified increase in the phagocyte function of peritoneal macrophages of rats after 12 weeks of swimming. Bacurau *et al.*[48] verified that macrophages of trained and with Walker-256 tumor animals present increase in the phagocyte activity. It has also been verified increase in the index of proliferation of lymphocytes and in the life time of the trained animals with tumor when compared with their sedentary pairs with tumor[48]. Our group observed increase in the phagocyte function of alveolar macrophages of rats submitted to 6 weeks of swimming (5 days/week, 60 minutes/day)[67]. Such studies evidenced that the cells of the immune system seem to present adaptative mechanisms which allow improvement if their function in response to regular and of moderate intensity physical exercise[64,68]. Thus, the hypothesis that the beneficial effects of moderate physical training may attenuate the effects of stressor agent inducers of immune suppression seem probable.

MODERATE PHYSICAL TRAINING PREVIOUS TO AN INTENSE PHYSICAL EXERCISE

The effect of the moderate training in the response of the immune system to an acute exercise has been studied[4-5,56,64,69-70]. The animals are submitted to moderate training and later to sudden loads of intense physical exercise, associating chronic stress models with the acute one. Lin *et al.*[5] verified that the decrease in the percentage of the T lymphocytes subpopulations, the mitogenic response of B lymphocytes from the spleen and the blood IL-2 concentrations after an acute load of intense physical exercise was attenuated in animals previously submitted to 10 weeks of moderate run (70% of $\dot{V}O_{2max}$). Fu *et al.*[60] verified that moderate training (during 4 weeks) prevents the decrease of TCD4+ lymphocytes in the plasma evaluated 24 hours after an extenuate acute physical exercise. The results are indicative that the immune suppression caused by intense physical exercise seems to decrease in trained animals with moderate intensity. The subjacent mechanisms to these responses still remain unknown; however, they can be associated to neuroendocrine factors inducing increase of leukocytes tolerance to a stressor agent[71].

The neuroendocrine and immunologic systems are particularly sensitive to acute loads of physical exercise, being verified increase of neurotransmissors, hormones and cytokines in the plasma[32]. It is interesting to observe that in response to moderate training, the plasmatic increase of the released hormones in response to an acute load of physical exercise seems to be attenuated[72]. Our group has verified that in trained rats (8 weeks at 70% of $\dot{V}O_{2max}$) the plasmatic concentrations of corticosterone did not alter 24 hours after the last physical exercise bout[13]. Kizaki *et al.*[73] did not verify increase in the plasmatic values of corticosterone of trained animals (swimming during 6 weeks, 5 days/week, 90 min/day) and later exposed to thermal stress (5°C during 3 hours) when compared with their only stressed pairs. Chennaoui *et al.*[74] verified in rats submitted to moderate training during 6 weeks, that the ACTH and cortisone plasmatic concentrations were not affected 24 hours after the last exercise bout. Additionally, Duclos *et al.*[72] verified that immediately after an acute exercise and 24 hours later, the cortisol concentrations did not increase in trained men compared with their sedentary pairs. This and other evidence points to the fact that repeated activation of the HPAS axis, such as in regular exercise, may lead to an adaptation in its response to situations of acute organic situations. More specifically, there is apparently less adrenal sensitivity to the ACTH[75-77]. Such hypothesis has been reinforced by the results by Inder *et al.*[78] and Duclos *et al.*[79], where the increase of the ACTH basal concentrations in the plasma was not followed by cortisol increase in trained men, comparatively with their sedentary pairs.

Some hours after the application of an acute load of physical exercise, a guidence of the hormonal profile with the aim to stimulate the tissue anabolic processes is expected[77]. Due to the antagonist action of the glucocorticoids in this process in the skeletal muscles, the hypothesis that physical training may develop tolerance mechanisms, such as decreased sensitivity to cortisol in order to protect the muscles from this hormone action, it seems reasonable once the increase of the plasma concentration is associated with the tissue catabolism and, consequently, failure in the repairing process of post-exercise injuries[72,78-79].

In humans, physical training may be associated with important alterations in the immune regulation induced by the glucocorticoids[74]. Particularly, there seems to be reduced sensitivity of the peripheral blood lymphocytes for the effect of these *in vitro* hormones[74]. Hoffman-Goetz *et al.*[61] observed lower apoptosis rate in timocytes of trained men when exposed to *in vitro* glucocorticoids.

It is known that an acute load of physical exercise, even moderate, may induce apoptosis in lymphocytes[80]. The apoptosis plays an important role in the embryogenesis, morphogenesis and regulation of the number of tissue cells. However, inappropriate induction of cellular death may result in a variety of pathological effects such as Alzheimer disease, cancer and chronic auto-immune diseases (AIDS and systemic lupus erythematosus)[37]. The subjacent mechanisms seem to be related with hormonal alterations (increase of the plasma concentration of glucocorticoids and catecholamines), cytosolic calcium and cellular redox state[81-83].

Moderate physical training results in improvement in the antioxidant defense mechanisms and it seems to protect the immune cells from injuries which can lead to their death[70]. We observed decrease in the percentage of lymphocytes in apoptosis induced

by exposition to a model of psychological stress (contention during 60 minutes) in trained animals[13]. Avula *et al.*[84] found reduction in the apoptosis of lymphocytes induced by H_2O_2, with no alteration in the spontaneous apoptosis of lymphocytes of mice exercised during 10 months. It is important to highlight the possible contribution of the thermal shock proteins (*Heat Shock Protein,* HSP) especially in the repairing of the proteins damaged in response to intense exercise[85]. The HSP70 induction seems to protect the thymic cells from the apoptosis induced by stress through reduction of the expression of the p53 and Bax proteins[85]. The HSP70 induction may therefore represent an important mechanism through which the immune suppressor effects associated with acute exercise may be minimized[85]. As expected, moderate physical training (70% of $\dot{V}O_{2max}$) or intense (> 80% $\dot{V}O_{2max}$) increases the expression of the HSP70 and HSP90 proteins in leucocytes[86]. Besides the HSP, it is suggested that the Bcl-2 protein has some importance in this protecting effect[87]. Siu *et al.*[85] verified that physical training (5 days per week, during 8 weeks) attenuates the apoptosis extension in the cardiac ans skeletal muscle of rats. These authors have associated this result to the increase of the Bcl-2, HSP70 and Mn-SOD content in the myocardium and soleus muscle of the trained animals when compared with the control animals.

The cells death may be induced via receptors of the Fas cellular surface and Fas ligand (FasL) or by pro-inflammatory cytokines (TNF-α and IL-6)[88]. Ferenbarch and Northoff[86] have reported increase of the FasL expression after an acute physical stressor agent, indicating increased occurrence of apoptosis in leukocytes. On the other hand, in response to training, there is decrease of the soluble apoptosis inducers: the FasL, the Fas receptor and the sFasL, a cytokine which induces apoptosis when it links to the Fas receptor of membrane activating the caspases[88]. Adamopoulos *et al.*[89] verified decrease in the Fas and FasL expression after mild (> 50% of $\dot{V}O_{2max}$) and moderate exercise (60-70% of $\dot{V}O_{2max}$). The authors concluded that physical training reduces the Fas/FasL system and, therefore, tends to attenuate the apoptosis. Physical training also seems to cause significant decrease in the production of pro-inflammatory cytokines and their soluble receptors (TNF-RI, TNF-RII and IL-6R) which are products of the interaction of endothelial cells with monocytes and simultaneously biological modulators of the circulating cytokines action[89].

Besides the way mediated by the Fas, the cellular death may also be induced via mitochondrial oxidative stress[70]. Alterations in the mitochondrial trasnsmembrane potential (MTP) are followed by overflow of proteins from the intermembrane space, as the cytocrome and the apoptosis 1 activation factor (Apaf-1)[90]. These molecules trigger the apoptosis by activation of the caspases or by direct condensation of the independent chromatin of caspases[90]. The initial signs involve increase in the intracellular calcium concentration and/or the formation of ORS and NRS[91]. In order to prevent injuries resulting from this oxidative or nitrosilative stress, the cell is equipped with different defense mechanisms. Antioxidant substances such as glutathione or enzymes as superoxide dismutase, glutathione peroxidase and glutathione redutase, seem to play an important role in this protection[92]. There is massive evidence that regular training is associated with the increase of the cellular protection mechanisms against the ORS and NRS[92-93].

When there is DNA injury and no repair is possible, apoptosis occurs as a cellular defense mechanism[91]. Tsai *et al.*[94] demonstrated that a stressor agent, depending on its magnitude, is usually followed by increase of DNA fragmentation. We observed that in trained and exposed to acute stress animals, there is no alteration in the percentage of cells with fragmented DNA[13]. Likewise, in trained and submitted to marathon men, there is also decrease of the percentage of the blood apoptotic lymphocytes when compared with non-trained and submitted to the same intense effort subjects[95]. The genomic instability after stress is less pronounced in trained rats[90].

The p53 seems to act as a transition factor induced by the stress condition and plays an important role in the activation and integration of a great quantity of adaptative cellular responses for a multitude of environmental stressor agents[96]. Depending on the kind and severity of the cellular stress, the p53 may be associated or not with the apoptosis induction[83,96]. For instance, specifically to apoptosis induced by radiation, seems to be dependent on p53[96]. The p53 content is dramatically increased after exposition to radiation x, ionic radiation, hypoxic and other stressors which lead to a massive apoptosis in the leucocytes[86]. Nevertheless, the apoptosis in response to the increase of the glucocorticoids concentration seems to be independent from the p53[97]. In human granulose cells, the glucocorticoids seem to protect them from the apoptosis, probably increasing the Bcl-2 content in these cells[87]. It is possible that a crossed response between the TNF-α action and the glucocorticoids occurs in the apoptosis modulation, via control of the Bcl-2 concentrations[98-99].

The Bcl-2 content in lymphocytes may alter the pro-apoptotic effect of the glucocorticoids for an anti-apoptotic effect when they are exposed to a stressor agent[100]. The glucocorticoids may also hamper the signaling of the p53 in the apoptosis induction, and consequently, prevent excessive cells injury after different types of stressor agents implied in the increase of the p53 expression[97]. In thymic cells, training seems to attenuate the percentage of apoptotic lymphocytes[101]. It is probable that the adaptations occurred derive from the increase of the IL-2, which then increases the content of mRNA of the Bcl-2[85].

Therefore, the homeostatic alterations in response to aggressive situations, such as intense physical exercise, seem to be attenuated by the application of a previous moderate physical training. The cells of the immune system seem to present adaptative tolerance mechanisms which allow improvement of their function in response to regular and of moderate intensity physical exercise.

All the authors declared there is not any potential conflict of interests regarding this article.

REFERENCES

1. Farrell SW, Kampert JB, Kohl HW, 3rd, Barlow CE, Macera CA, Paffenbarger RS, et al. Influences of cardiorespiratory fitness levels and other predictors on cardiovascular disease mortality in men. Med Sci Sports Exerc. 1998;30:899-905.
2. Bousquet-Santos K, Vaisman M, Barreto ND, Cruz-Filho RA, Salvador BA, Frontera WR, et al. Resistance training improves muscle function and body composition in patients with hyperthyroidism. Arch Phys Med Rehabil. 2006;87:1123-30.
3. Pedersen BK, Tvede N, Hansen FR, Andersen V, Bendix T, Bendixen G, et al. Modulation of natural killer cell activity in peripheral blood by physical exercise. Scand J Immunol. 1988;27:673-8.
4. Nehlsen-Cannarella SL, Nieman DC, Balk-Lamberton AJ, Markoff PA, Chritton DB, Gusewitch G, et al. The effects of moderate exercise training on immune response. Med Sci Sports Exerc. 1991;23:64-70.
5. Lin YS, Jan MS, Chen HI. The effect of chronic and acute exercise on immunity in rats. Int J Sports Med. 1993;14:86-92.
6. Nieman DC. Is infection risk linked to exercise workload? Med Sci Sports Exerc. 2000;32:S406-11.
7. Pedersen BK, Hoffman-Goetz L. Exercise and the immune system: regulation, integration, and adaptation. Physiol Rev. 2000;80:1055-81.
8. Davidson SR, Burnett M, Hoffman-Goetz L. Training effects in mice after long-term voluntary exercise. Med Sci Sports Exerc. 2006;38:250-5.
9. Angeli A, Minetto M, Dovio A, Paccotti P. The overtraining syndrome in athletes: a stress-related disorder. J Endocrinol Invest. 2004;27:603-12.
10. da Nobrega AC. The subacute effects of exercise: concept, characteristics, and clinical implications. Exerc Sport Sci Rev. 2005;33:84-7.
11. Besedovsky HO, del Rey AE, Sorkin E. Immune-neuroendocrine interactions. J Immunol. 1985;135:750s-4s.
12. Ascensao A, Magalhaes J, Soares J, Oliveira J, Duarte JA. Exercise and cardiac oxidative stress. Rev Port Cardiol. 2003;22:651-78.

13. Leandro CG, Martins de Lima T, Folador A, Alba-Loreiro T, do Nascimento E, Manhaes de Castro R, et al. Physical training attenuates the stress-induced changes in rat t-lymphocyte function. Neuroimmunomodulation. 2006;13:105-13.
14. Schulenburg H, Kurz CL, Ewbank JJ. Evolution of the innate immune system: the worm perspective. Immunol Rev. 2004;198:36-58.
15. Mabbott NA. The complement system in prion diseases. Curr Opin Immunol. 2004;16:587-93.
16. Boscolo P, Di Gioacchino M, Qiao N, Sabbioni E. Work, environment, immune system and human health. Int J Immunopathol Pharmacol. 2004;17:1-2.
17. Di Rosa M, Radomski M, Carnuccio R, Moncada S. Glucocorticoids inhibit the induction of nitric oxide synthase in macrophages. Biochem Biophys Res Commun. 1990;172:1246-52.
18. Peres CM, Otton R, Curi R. Modulation of lymphocyte proliferation by macrophages and macrophages loaded with arachidonic acid. Cell Biochem Funct. 2005; 23:373-81.
19. Hames B, Glover D. Molecular Immunology, in frontiers in molecular biology. 2nd ed. Oxford; 1996.
20. Verlengia R, Gorjao R, Kanunfre CC, Bordin S, de Lima TM, Curi R. Effect of arachidonic acid on proliferation, cytokines production and pleiotropic genes expression in Jurkat cells – a comparison with oleic acid. Life Sci. 2003;73:2939-51.
21. Verlengia R, Gorjao R, Kanunfre CC, Bordin S, Martins De Lima T, Martins EF, et al. Comparative effects of eicosapentaenoic acid and docosahexaenoic acid on proliferation, cytokine production, and pleiotropic gene expression in Jurkat cells. J Nutr Biochem. 2004;15:657-65.
22. Lagranha CJ, de Lima TM, Senna SM, Doi SQ, Curi R, Pithon-Curi TC. The effect of glutamine supplementation on the function of neutrophils from exercised rats. Cell Biochem Funct. 2005;23:101-7.
23. Nascimento E, Manhães-de-Castro R, Castro CM, Leandro CG. Pode a glutamina modular a imunidade? Anais Fac Med UFPE. 2001;46(2):67-70.
24. Pithon-Curi TC, De Melo MP, Curi R. Glucose and glutamine utilization by rat lymphocytes, monocytes and neutrophils in culture: a comparative study. Cell Biochem Funct. 2004;22:321-6.
25. Vizi ES. Receptor-mediated local fine-tuning by noradrenergic innervation of neuroendocrine and immune systems. Ann N Y Acad Sci. 1998;851:388-96.
26. Gleeson M. Interleukins and exercise. J Physiol. 2000;529 Pt 1:1.
27. Besedovsky HO, del Rey A. Regulating inflammation by glucocorticoids. Nat Immunol. 2006;7:537.
28. Besedovsky HO, del Rey A. Immune-neuro-endocrine interactions: facts and hypotheses. Endocr Rev. 1996;17:64-102.
29. Blalock JE. The syntax of immune-neuroendocrine communication. Immunol Today. 1994;15:504-11.
30. Seltzer JG. Stress and the general adaptation syndrome or the theories and concepts of Hans Selye. J Fla Med Assoc. 1952;38:481-5.
31. Atanackovic D, Kroger H, Serke S, Deter HC. Immune parameters in patients with anxiety or depression during psychotherapy. J Affect Disord. 2004;81:201-9.
32. Faure M, Gapin L, Viret C. Stressing the virtues of the immune system. Microbes Infect. 2004;6:960-4.
33. Garcia C, de Oliveira MC, Verlengia R, Curi R, Pithon-Curi TC. Effect of dexamethasone on neutrophil metabolism. Cell Biochem Funct. 2003;21:105-11.
34. Silveira L, Denadai B. Efeito modulatório de diferentes intensidades de esforço sobre a via glicolítica durante o exercício contínuo e intermitente. Rev Paulista Educ Fis. 2003;16(2):186-97.
35. Hoffman-Goetz L. Influence of physical activity and exercise on innate immunity. Nutr Rev. 1998;56:S126-30.
36. Pyne DB, Gleeson M, McDonald WA, Clancy RL, Perry C Jr, Fricker PA. Training strategies to maintain immunocompetence in athletes. Int J Sports Med. 2000; 21(Suppl 1):S51-60.
37. Lagranha CJ, Senna SM, de Lima TM, Silva EP, Doi SQ, Curi R, et al. Beneficial effect of glutamine on exercise-induced apoptosis of rat neutrophils. Med Sci Sports Exerc. 2004;36:210-7.
38. Niess AM, Baumann M, Roecker K, Horstmann T, Mayer F, Dickhuth HH. Effects of intensive endurance exercise on DNA damage in leucocytes. J Sports Med Phys Fitness. 1998;38:111-5.
39. Leandro CG, Nascimento E, Manhães-de-Castro R, Duarte JA, de-Castro CM. Exercício físico e sistema imunológico: mecanismos e integrações. Rev Port Cien Desp. 2002;2(5):80-90.
40. Besedovsky HO, del Rey A. Introduction: immune-neuroendocrine network. Front Horm Res. 2002;29:1-14.
41. Besedovsky HO, del Rey A. Immune-neuroendocrine circuits: integrative role of cytokines. Front Neuroendocrinol. 1992;13:61-94.
42. Miller AH. Neuroendocrine and immune system interactions in stress and depression. Psychiatr Clin North Am. 1998;21:443-63.
43. Kohut ML, Thompson JR, Lee W, Cunnick JE. Exercise training-induced adaptations of immune response are mediated by beta-adrenergic receptors in aged but not young mice. J Appl Physiol. 2004;96:1312-22.
44. Pithon-Curi TC, Trezena AG, Tavares-Lima W, Curi R. Evidence that glutamine is involved in neutrophil function. Cell Biochem Funct. 2002;20:81-6.
45. Jonsdottir IH. Exercise immunology: neuroendocrine regulation of NK-cells. Int J Sports Med. 2000;21(Suppl 1):S20-3.
46. Gillis S, Crabtree GR, Smith KA. Glucocorticoid-induced inhibition of T cell growth factor production. I. The effect on mitogen-induced lymphocyte proliferation. J Immunol. 1979;123:1624-31.
47. Woods JA, Davis JM, Mayer EP, Ghaffar A, Pate RR. Effects of exercise on macrophage activation for antitumor cytotoxicity. J Appl Physiol. 1994;76:2177-85.
48. Bacurau RF, Belmonte MA, Seelaender MC, Costa Rosa LF. Effect of a moderate intensity exercise training protocol on the metabolism of macrophages and lymphocytes of tumour-bearing rats. Cell Biochem Funct. 2000;18:249-58.
49. Bruunsgaard H, Pedersen BK. Special feature for the Olympics: effects of exercise on the immune system: effects of exercise on the immune system in the elderly population. Immunol Cell Biol. 2000;78:523-31.
50. Gleeson M, Pyne DB. Special feature for the Olympics: effects of exercise on the immune system: exercise effects on mucosal immunity. Immunol Cell Biol. 2000; 78:536-44.
51. Pedersen BK, Tvede N. The immune system and physical training. Ugeskr Laeger. 1993;155:856-62.
52. Peters EM, Goetzsche JM, Grobbelaar B, Noakes TD. Vitamin C supplementation reduces the incidence of postrace symptoms of upper-respiratory-tract infection in ultramarathon runners. Am J Clin Nutr. 1993;57:170-4.
53. Lancaster GI, Halson SL, Khan Q, Drysdale P, Wallace F, Jeukendrup AE, et al. Effects of acute exhaustive exercise and chronic exercise training on type 1 and type 2 T lymphocytes. Exerc Immunol Rev. 2004;10:91-106.
54. Bury T, Marechal R, Mahieu P, Pirnay F. Immunological status of competitive football players during the training season. Int J Sports Med. 1998;19:364-8.
55. Dos Santos Cunha WD, Giampietro MV, De Souza DF, Vaisberg M, Seelaender MC, et al. Exercise restores immune cell function in energy-restricted rats. Med Sci Sports Exerc. 2004;36:2059-64.
56. Robinson LE, Field CJ. Dietary long-chain (n-3) fatty acids facilitate immune cell activation in sedentary, but not exercise-trained rats. J Nutr. 1998;128:498-504.
57. Nieman DC, Buckley KS, Henson DA, Warren BJ, Suttles J, Ahle JC, et al. Immune function in marathon runners versus sedentary controls. Med Sci Sports Exerc. 1995;27:986-92.
58. Makras P, Koukoulis GN, Bourikas G, Papatheodorou G, Bedevis K, Menounos P, et al. Effect of 4 weeks of basic military training on peripheral blood leucocytes and urinary excretion of catecholamine and cortisol. J Sports Sci. 2005;23:825-34.
59. Escribano BM, Aguera EI, Vivo R, Santisteban R, Castejon FM, Rubio MD. Benefits of moderate training to the nonspecific immune response of colts. Equine Vet J Suppl. 2002:182-5.
60. Fu SC, Qin L, Leung CK, Chan BP, Chan KM. Regular moderate exercise training prevents decrease of CD4+ T-lymphocytes induced by a single bout of strenuous exercise in mice. Can J Appl Physiol. 2003;28:370-81.
61. Hoffman-Goetz L, Duerrstein L. The effect of chronic and acute exercise on thymocyte apoptosis and necrosis in ovariectomized mice given dietary genistein. J Sports Med Phys Fitness. 2004;44:281-7.
62. Pastva A, Estell K, Schoeb TR, Atkinson TP, Schwiebert LM. Aerobic exercise attenuates airway inflammatory responses in a mouse model of atopic asthma. J Immunol. 2004;172:4520-6.
63. Nehlsen-Cannarella SL. Cellular responses to moderate and heavy exercise. Can J Physiol Pharmacol. 1998;76:485-9.
64. Mackinnon LT. Chronic exercise training effects on immune function. Med Sci Sports Exerc. 2000;32:S369-76.
65. Baum M, Liesen H, Enneper J. Leucocytes, lymphocytes, activation parameters and cell adhesion molecules in middle-distance runners under different training conditions. Int J Sports Med. 1994;15(Suppl 3):S122-6.
66. Woods J, Lu Q, Ceddia MA, Lowder T. Special feature for the Olympics: effects of exercise on the immune system: exercise-induced modulation of macrophage function. Immunol Cell Biol. 2000;78:545-53.
67. Nascimento E, Cavalcante T, Pereira S, Palmeira A, Rocha MC, Viana MT, et al. O exercício físico crónico altera o perfil leucocitário e a taxa de fagocitose de ratos estressados. Rev Port Cien Desp. 2004;4(3):26-33.
68. Friman G, Wesslen L. Special feature for the Olympics: effects of exercise on the immune system: infections and exercise in high-performance athletes. Immunol Cell Biol. 2000;78:510-22.
69. Liu J, Yeo HC, Overvik-Douki E, Hagen T, Doniger SJ, Chyu DW, et al. Chronically and acutely exercised rats: biomarkers of oxidative stress and endogenous antioxidants. J Appl Physiol. 2000;89:21-8.

70. Mooren FC, Lechtermann A, Volker K. Exercise-induced apoptosis of lymphocytes depends on training status. Med Sci Sports Exerc. 2004;36:1476-83.
71. Forner MA, Barriga C, Rodriguez AB, Ortega E. A study of the role of corticosterone as a mediator in exercise-induced stimulation of murine macrophage phagocytosis. J Physiol. 1995;488(Pt 3):789-94.
72. Duclos M, Corcuff JB, Pehourcq F, Tabarin A. Decreased pituitary sensitivity to glucocorticoids in endurance-trained men. Eur J Endocrinol. 2001;144:363-8.
73. Kizaki T, Haga S, Sakata I, Ookawara T, Segawa M, Sakurai T, et al. Swimming training prevents generation of suppressor macrophages during acute cold stress. Med Sci Sports Exerc. 2000;32:143-8.
74. Chennaoui M, Gomez Merino D, Lesage J, Drogou C, Guezennec CY. Effects of moderate and intensive training on the hypothalamo-pituitary-adrenal axis in rats. Acta Physiol Scand. 2002;175:113-21.
75. Gomez-Merino D, Drogou C, Chennaoui M, Tiollier E, Mathieu J, Guezennec CY. Effects of combined stress during intense training on cellular immunity, hormones and respiratory infections. Neuroimmunomodulation. 2005;12:164-72.
76. Jacobson L. Hypothalamic-pituitary-adrenocortical axis regulation. Endocrinol Metab Clin North Am. 2005;34:271-92, vii.
77. Luger A, Deuster PA, Kyle SB, Gallucci WT, Montgomery LC, Gold PW, et al. Acute hypothalamic-pituitary-adrenal responses to the stress of treadmill exercise. Physiologic adaptations to physical training. N Engl J Med. 1987;316:1309-15.
78. Inder WJ, Hellemans J, Ellis MJ, Evans MJ, Livesey JH, Donald RA. Elevated basal adrenocorticotropin and evidence for increased central opioid tone in highly trained male athletes. J Clin Endocrinol Metab. 1995;80:244-8.
79. Duclos M, Gouarne C, Bonnemaison D. Acute and chronic effects of exercise on tissue sensitivity to glucocorticoids. J Appl Physiol. 2003;94:869-75.
80. Hsu TG, Hsu KM, Kong CW, Lu FJ, Cheng H, Tsai K. Leukocyte mitochondria alterations after aerobic exercise in trained human subjects. Med Sci Sports Exerc. 2002;34:438-42.
81. Curi TC, De Melo MP, Palanch AC, Miyasaka CK, Curi R. Percentage of phagocytosis, production of O2.-, H2O2 and NO, and antioxidant enzyme activities of rat neutrophils in culture. Cell Biochem Funct. 1998;16(1):43-9.
82. Otton R, Soriano FG, Verlengia R, Curi R. Diabetes induces apoptosis in lymphocytes. J Endocrinol. 2004;182:145-56.
83. Pithon-Curi TC, Schumacher RI, Freitas JJ, Lagranha C, Newsholme P, Palanch AC, et al. Glutamine delays spontaneous apoptosis in neutrophils. Am J Physiol Cell Physiol. 2003;284:C1355-61.
84. Avula CP, Muthukumar AR, Zaman K, McCarter R, Fernandes G. Inhibitory effects of voluntary wheel exercise on apoptosis in splenic lymphocyte subsets of C57BL/6 mice. J Appl Physiol. 2001;91:2546-52.
85. Siu PM, Bryner RW, Martyn JK, Alway SE. Apoptotic adaptations from exercise training in skeletal and cardiac muscles. Faseb J. 2004;18:1150-2.
86. Fehrenbach E, Northoff H. Free radicals, exercise, apoptosis, and heat shock proteins. Exerc Immunol Rev. 2001;7:66-89.
87. Sasson R, Tajima K, Amsterdam A. Glucocorticoids protect against apoptosis induced by serum deprivation, cyclic adenosine 3',5'-monophosphate and p53 activation in immortalized human granulosa cells: involvement of Bcl-2. Endocrinology. 2001;142:802-11.
88. Sata M, Walsh K. TNFalpha regulation of Fas ligand expression on the vascular endothelium modulates leukocyte extravasation. Nat Med. 1998;4:415-20.
89. Adamopoulos S, Parissis J, Karatzas D, Kroupis C, Georgiadis M, Karavolias G, et al. Physical training modulates proinflammatory cytokines and the soluble Fas/soluble Fas ligand system in patients with chronic heart failure. J Am Coll Cardiol. 2002;39:653-63.
90. Ueda S, Masutani H, Nakamura H, Tanaka T, Ueno M, Yodoi J. Redox control of cell death. Antioxid Redox Signal. 2002;4:405-14.
91. Baumann S, Krueger A, Kirchhoff S, Krammer PH. Regulation of T cell apoptosis during the immune response. Curr Mol Med. 2002;2:257-72.
92. Silveira LR, Pilegaard H, Kusuhara K, Curi R, Hellsten Y. The contraction induced increase in gene expression of peroxisome proliferator-activated receptor (PPAR)-gamma coactivator 1alpha (PGC-1alpha), mitochondrial uncoupling protein 3 (UCP3) and hexokinase II (HKII) in primary rat skeletal muscle cells is dependent on reactive oxygen species. Biochim Biophys Acta. 2006;1763:969-76.
93. Hirabara SM, Silveira LR, Alberici LC, Leandro CV, Lambertucci RH, Polimeno GC, et al. Acute effect of fatty acids on metabolism and mitochondrial coupling in skeletal muscle. Biochim Biophys Acta. 2006;1757:57-66.
94. Tsai K, Hsu TG, Hsu KM, Cheng H, Liu TY, Hsu CF, et al. Oxidative DNA damage in human peripheral leukocytes induced by massive aerobic exercise. Free Radic Biol Med. 2001;31:1465-72.
95. Miyazaki H, Oh-ishi S, Ookawara T, Kizaki T, Toshinai K, Ha S, et al. Strenuous endurance training in humans reduces oxidative stress following exhausting exercise. Eur J Appl Physiol. 2001;84:1-6.
96. Fridman JS, Lowe SW. Control of apoptosis by p53. Oncogene. 2003;22:9030-40.
97. Lee MC, Lee JS, Lee MJ, Lee JH, Kim HI. Fas mediates apoptosis in steroid-induced myopathy of rats. Neuropathol Appl Neurobiol. 2001;27:396-402.
98. Crochemore C, Michaelidis TM, Fischer D, Loeffler JP, Almeida OF. Enhancement of p53 activity and inhibition of neural cell proliferation by glucocorticoid receptor activation. Faseb J. 2002;16:761-70.
99. Huang ST, Cidlowski JA. Glucocorticoids inhibit serum depletion-induced apoptosis in T lymphocytes expressing Bcl-2. Faseb J. 1999;13:467-76.
100. Amsterdam A, Sasson R. The antiinflammatory action of glucocorticoids is mediated by cell type specific regulation of apoptosis. Mol Cell Endocrinol. 2002; 189:1-9.
101. Concordet JP, Ferry A. Physiological programmed cell death in thymocytes is induced by physical stress (exercise). Am J Physiol. 1993;265:C626-9.