Adaptive mechanisms of the immune system in response to physical training

Carol Góis Leandro¹, Raul Manhães de Castro², Elizabeth Nascimento², Tânia Cristina Pithon-Curi³ and Rui Curi³

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 diseases¹-². Recently, the effects of the physical exercise over the function of the immunological system have been approached in many studies³-⁴. 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 suppression⁵-⁹. The subjacent mechanisms are associated with the communication between the nervous, endocrine and immunological systems, suggesting autonomic ways and immune response modulation¹¹. 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 situations¹²-¹³.

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.

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 memory¹⁴. 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 chemiotactic agents released by the mastocytes and basophils as well as by the activation of the complement system¹⁵. The leukocytosis by neutrophilia may indicate the presence of a bacteria infection or of an inflammation in response to a tissue injury¹⁴.

Another group of phagocyte cells includes the mononucleotide monocytes and macrophages. Monocytes are cells present in the peripheral blood which continuously differentiate in macrophages after migrating to the tissues¹⁴. The macrophages are involved in the microbicde and antitumoral activity and show accessory cellular function as antigens presenters¹⁶. Macrophage characteristic aspects include adherence capacity, chemiotaxis, production of oxygen reactive species and cytotoxicity¹⁴,¹⁷. They are also a source of cytokines mediator of the physiopathologic reactions which usually follow the cellular injury¹⁸.

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 microbicde functions, for instance, the production of oxygen (ORS) and nitrogen reactive species (NRS)¹⁹. The macrophages also have pro and antiinflammatory effects and promote the development of immunity mediated by lymphocytes¹⁴.

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 granules¹⁸. Cells of similar morphology are found in the spleen, bone marrow, lymph nodes, thymus, and other areas as the Peyer patches¹⁸. The lymphocytes may be classified according to their membrane markers, reactions to stimuli, migration patterns and mean-life¹⁴. 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 concanaavalin A (ConA)¹⁴,¹⁸.
Although they do not synthesize immune globulins (Ig), T lymphocytes act as modulators of the immunologic response\textsuperscript{[19]}. This fact occurs through interactions between the many types of T lymphocytes with the macrophages and the dendritic cells during the immunologic response mediated by cells\textsuperscript{[18]}. The B lymphocytes reach maturity probably in the bone marrow and are precursors of the cells producers of antibodies, the plasmocytes\textsuperscript{[18]}. When stimulated by lipopolysaccharides in culture, these cells proliferate\textsuperscript{[22-24]}.

Lymphocytes usually present in the circulation and lymphoid tissues are in a quiescent state, a situation in which they are metabolic little active\textsuperscript{[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\textsuperscript{[19]}. The change to the activated state is also followed by metabolic alterations in these cells, where the biosynthetic and energetic ways are stimulated\textsuperscript{[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\textsuperscript{[19]}.

Local response to an infection or injured tissue involves the production of cytokines\textsuperscript{[19]}. Cytokines are small soluble proteins secreted by leukocytes and other cells, and which have the purpose to modulate the immune response\textsuperscript{[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\textsuperscript{256}. Besides its mediator function in the immune system, the cytokines may also act in other systems, modifying their functions\textsuperscript{25,27}.

The immune system seems to be sensitive both to infection agents and alterations in the organic homeostasis, as occurs in stress\textsuperscript{[11,28]}. These alterations suggest an interrelationship of the immune system with other systems, such as the nervous and endocrine ones\textsuperscript{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\textsuperscript{300}. The cells of the immunological system have receptors for such hormones\textsuperscript{28,31-33}. Likewise, they can secrete cytokines which will act in neuro-endocrin organs\textsuperscript{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 immunee system acts\textsuperscript{[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 (\(VO_2\max\)), and/or the maximal heart rate (HR\textsubscript{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\textsuperscript{34}. The \(VO_2\max\) and the HR\textsubscript{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 \(VO_2\max\) and the HR\textsubscript{max}, a moderate exercise from 50-70% of the \(VO_2\max\) and the HR\textsubscript{max} and intense exercise above 80% of the \(VO_2\max\) and HR\textsubscript{max}\textsuperscript{[35-39]}. 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\textsuperscript{[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\textsuperscript{[19,10,37]}. Neutrophilia, lymphopenia and monocytosis occur in response to intense physical exercise\textsuperscript{40}. 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\textsuperscript{[29,33,40,41]}. The expression of b-receptors in the different immune cells may provide the molecular grounding for action of catecholamines\textsuperscript{[71]}

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\textsuperscript{[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\textsuperscript{[10,31]}. Gillis et al\textsuperscript{[46]} have observed inhibition in the production of the growth factor of T lymphocytes induced by the increase of glucocorticoids. Woods et al\textsuperscript{[47]} verified decrease in the production of superoxide by pteronuclear 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% \(VO_2\max\)\textsuperscript{,48-50}. Woods et al\textsuperscript{[47]} verified increase of adherence, production of superoxide anion, nitrogen metabolism rate, cytotoxic activity and the fagocitic capacity of macrophages. Tvede et al\textsuperscript{[51]} have studied the response of the lymphocytes populations in Danish 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\textsuperscript{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\textsuperscript{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\textsuperscript{[53]} have reported lower incidence of the upper respiratory tract infections (URTIs) in runners supplemented with 600 mg of vitamin C three days before the run, comparatively to their pairs. Robinson et al\textsuperscript{[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\textsuperscript{[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\textsuperscript{[56]}.
There is a general perception that high level athletes have higher risks to acquire infections, such as the URI, during intense training periods (> 75% of VO$_{2\text{max}}$) and after exhaustive competitions$^{6,56,64}$. 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$^{8,12}$. Lin et al.$^{55}$ 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$^{56,60}$. Pedersen et al.$^{53,57}$ 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$^{8,53,61}$. 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.$^{56,61}$ 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 URI.

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 adaptive 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$^{8,5,56,64,69-73}$. 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.$^{19}$ verified that the decrease in the percentage of 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 VO$_{2\text{max}}$). Fu et al.$^{62}$ 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 neurotransmitters, 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 VO$_{2\text{max}}$) 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$^{75,76,77}$. 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 guidance 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$^{80}$. Hoffman-Goetz et al.$^{81}$ 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)$^{82}$. 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$^{83}$. 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 exposure 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 H2O2, 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(88). 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(86). As expected, moderate physical training (70% of VO2 max) or intense (> 80% VO2 max) increases the expression of the HSP70 and HSP90 proteins in leukocytes(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 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.

Besides the way mediated by the Fas, the cellular death may also be induced via mitochondrial oxidative stress(90). Alterations in the mitochondrial transmembrane potential (MTP) are followed by overflow of proteins from the intermembrane space, as the cytochrome 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(93). The genomic instability after stress is less pronounced in trained rats(86).

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 adaptive 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(93,96). 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, ionizing radiation, hypoxic and other stressors which lead to a massive apoptosis in the leukocytes(96). 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(83). 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(96,99).

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(98).

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 adaptive 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


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.


93. 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.


