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REVIEW ARTICLE

Importance of exercise immunology in health promotion

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Abstract Chronic physical exercise with adequate intensity and volume associated with sufficient recovery promotes adaptations in several physiological systems. While intense and exhaustive exercise is considered an important immunosuppressor agent and increases the incidence of upper respiratory tract infections (URTI), moderate regular exercise has been associated with significant disease protection and is a complementary treatment of many chronic diseases. The effects of chronic exercise occur because physical training can induce several physiological, biochemical and psychological adaptations. More recently, the effect of acute exercise and training on the immunological system has been discussed, and many studies suggest the importance of the immune system in prevention and partial recovery in pathophysiological situations. Currently, there are two important hypotheses that may explain the effects of exercise and training on the immune system. These hypotheses including (1) the effect of exercise upon hormones and cytokines (2) because exercise can modulate glutamine concentration. In this review, we discuss the hypothesis that exercise may modulate immune functions and the importance of exercise immunology in respect to chronic illnesses, chronic heart failure, malnutrition and inflammation.

Keywords Acute physical exercise · Chronic physical exercise · Moderate training · Glutamine · Inflammation · Immunosuppression

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Introduction

In the last 30 years, interest in the practical aspects of physical exercise has grown. This increase in interest may be the result of great scientific advancements in the last decades demonstrating that chronic exercise plays an important role in the prevention of countless chronic, degenerative illnesses (Costa Rosa 2004; Woods et al. 2006) and consequently that it may be a therapeutic aid in the treatment of numerous pathophysiological conditions (Costa Rosa 2004). The traditional exercise term or alternative form as yoga practice can improve status and quality of life in healthy people as well as people suffering from chronic disease because it puts the individual in control as opposed to conventional treatments such as drugs that place the doctor in control (Ullman 2009).

Acute exercise, as well as others stressful agents, promotes a homeostatic break, which stimulates psychological, metabolic, hormonal, biochemical, and physiological changes. In this way, development of training programs may promote several adaptations in some physiological systems, such as the cardiac, muscular, immunological and other systems, because alterations prompted by the exercise reinforce the communication between the diverse physiological systems (Costa Rosa 2004).

Costa Rosa (2004) discussed the possible effects of exercise on the immune system and how this interaction may contribute to the prevention and handling of illnesses, especially chronic illnesses. Despite the premature death of Dr. Costa Rosa in May 2005, work has continued in his group through studies on his ideas about the importance exercise immunology in the promotion of health and prevention of illnesses. In this review, we will discuss the effect of physical exercise on the immune system, inflammation and the importance of exercise in glutamine metabolism, essential substrate by immune cells.

Exercise and the immune system

Classically, the immune system is considered a defence system; however, recent studies have shown a strong interaction between the immune system and several other physiological systems. This multidirectional interaction is possible because there are cytokine receptors in many cells, and immune cells have hormone receptors and metabolise substances, such as amino acids and glucose, that may act upon the immune system. In this way, the immune system can also modulate hormone production and release as well as corporal homeostasis (Turnbull and Rivier 1995; Nieman 2007).

The first studies about the effects of exercise on the immune system were reported in 1900 and demonstrated the occurrence of accentuated leucocytosis in rodents and humans after exercise. However, the last 30 years have had a significant impact in exercise immunology because approximately 75% of the papers have been published since 1990 (Nieman 2007).

The immune system has various cellular and humoral components in different compartments of the body (Nagatomi 2006), and it may be divided into innate and adaptive branches. The innate response consists of macrophages, neutrophils, NK cells, and complements factors such as defensins. Additionally, the innate response constitutes the first line of defence against foreign agents (Woods et al. 2006). Several studies suggest that the innate immune system exhibits more changes in response to exercise. The adaptive system, composed of lymphocytes and secreted factors, such as antibodies, seems to be largely unaffected by athletic endeavors (Nieman 2007), despite the fact that some papers have reported changes in lymphocyte proliferation and IgA salivary concentration.

Several studies present evidence that moderate chronic exercise (i.e., training) decreases the incidence of infections such as the common cold, while intense training, in contrast, is associated with increased upper respiratory tract infections (URTI) (Ortega 2003; Nagatomi 2006; Nieman 2007). The positive effect of exercise on other diseases has also been acknowledged, and there is increasing evidence that a lifestyle that includes physical activity offers protection against many diseases (Haskell et al. 2007) (Fig. 1).

Exercise acts upon the immune system by promoting several alterations. The cells most affected include lymphocytes, macrophages, and neutrophils, while less is known about the effects on eosinophils and basophils. The most common changes in immune cell function after strenuous exercise include decreases in neutrophil function, decreases in lymphocyte function such as immunoglobulin production by B cells, decreases in lymphocyte proliferation when the cells are challenged by a mitogen, and decreases in macrophage function such as phagocytosis and hydrogen peroxide production (Costa Rosa 2004; Woods et al. 2006; Nagatomi 2006; Nieman 2007). Additional profound changes after exercise include changes in soluble proteins, including decreases in IgA concentration in the plasma and saliva; extensive changes to cytokine profiles, including a 100-fold increase in interleukin-6 production; and an augmented production of anti-inflammatory mediators (Woods et al. 2006; Nieman 2007).

These changes are transient, and most of them return to the basal level few hours after exercise; however, there are some long-term changes in the immune response of athletes (Nieman 2007). Numerous factors modulate the magnitude of the effects of exercise on the immune system, such as type, duration, and intensity of exercise as well as the fitness, age of the subject, and nutritional status (Woods et al. 2006).

Exercise can be considered a potent immunodepressor when conducted at an elevated intensity, resulting in

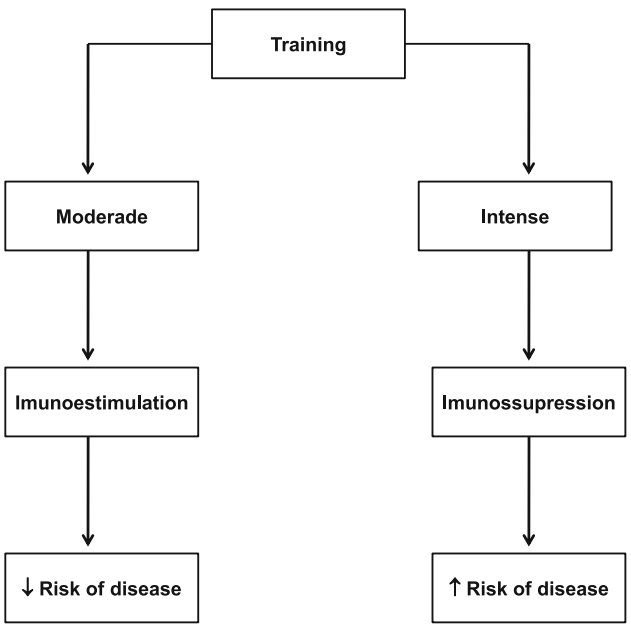

Fig. 1 Effect of training on immune system and health promotion

immunosuppression and increase in incidence of infections. However, if exercise is conducted with moderate intensity and sufficient recovery, its action may result in improvement of the immune response (Costa Rosa 2004; Woods et al. 2006).

Several mechanisms may be involved in modulating the effect of exercise on the immune system, including exercise-induced changes in stress hormones (Ortega 2003; Nieman 2007), exercise-induced changes in cellular glutamine metabolism (Parry-Billings et al. 1992, Parry-Billings et al. 1990), body temperature changes, increases in blood flow, lymphocyte apoptosis, and dehydration (Nieman 2007).

Over the last few years, two independent lines of research have emerged that have attempted to establish a link between exercise and immune system. One of these lines of research involves alterations in plasma glutamine concentration and metabolism (Parry-Billings et al. 1992, Parry-Billings et al. 1990), and the other research considers changes in the neuroendocrine hormones, especially catecholamines, cortisol, and other hormones, induced by exercise as the mechanism for partial impairment of the immune system (Nieman 2007; Newsholme et al. 1985a, b).

Glutamine and the immune response in exercise

Glutamine is a conditionally essential amino acid that comprises 20% of the total plasma amino acids and is actively produced in organs such as the liver, kidneys, lungs, and skeletal muscle (Parry-Billings et al. 1990). Skeletal muscle is the major tissue involved in glutamine synthesis and storage; it is known to release glutamine into the blood and to influence plasma glutamine concentration as well as the metabolism of glutamine in other tissues (Parry-Billings and Newsholme 1991).

Lymphocytes, macrophages and neutrophils are rapidly dividing cells and consume glutamine at high rates, even when quiescent (Newsholme et al. 1985b; Akerstrom and Pedersen 2007). Thus, appropriate glutamine concentrations allow efficient cellular functions such as lymphocyte proliferation as well as high secretory activity and phagocyte function (Nieman 1997; Castell 2003). In addition, it was shown that the glutamine pathway in these cells is under external regulation by supply of glutamine itself (Bruunsgaard et al. 1997; Nieman 1997; Robson et al. 1999; Castell 2003; Costa Rosa 2004). A decrease in glutamine concentration presents an elevated correlation with increase in diseases, especially URTI (Pedersen and Hoffman-Goetz 2000; Castell and Newsholme 2001; Castell 2003). During pathophysiological catabolic conditions, such as cancer, sepsis, AIDS, and politraumas, the change in glutamine concentration is associated with impairment of immune system functions, as lymphocyte proliferation, phagocytosis in macrophages, and cytokine production in both cells leads to immunosuppression (Castell 2003).

In vivo studies in humans have shown that physical exercise is initially accompanied by increased muscle glutamine release and hence an increase in plasma glutamine concentration. However, with increased duration of exercise (e.g., >1 h) this situation changes and plasma glutamine is reduced after prolonged exhaustive exercise in humans and rodents (Koyama et al. 1998; Bassit et al. 2000; Santos et al. 2007a; Agostini and Biolo 2010). However, the period during which glutamine concentration in the serum remains reduced is not well established. After marathon running, this decrease was found to be relatively transient, returning to control values after 6–9 h. However, athletes or rats with overtraining syndrome, and ultramarathon racers had low plasma glutamine that remained low for several weeks (Decombaz et al. 1979; Parry-Billings et al. 1992; Koyama et al. 1998; Castell and Newsholme 1998; Bassit et al. 2000).

The mechanism by which this decrease in plasma glutamine concentration occurs during prolonged physical exercise and recovery is not well understood. During prolonged exercise, it has been suggested that lower glutamine plasma concentration is promoted by increases in glutamine uptake in several tissues, mainly the liver, kidneys and some immune cells, while other hypotheses suggest that glutamine release changes in skeletal muscle because of a partial impairment in glutamine syntheses. (Newsholme and Calder 1997; Negro et al. 2008). In according, we found a 50% reduction of glutamine synthetase activity in the soleus muscle 24 h after the last bout of training in rats submitted to moderate exercise training, suggesting that the exercise decreases the glutamine synthesis in skeletal muscle during recovery (dos Santos et al. 2009).

This decrease in plasma glutamine (Parry-Billings et al. 1992; Bassit et al. 2000, 2002; Costa Rosa 2004) due to impairment in cellular functions of the immune system (Newsholme et al. 1985a; Newsholme et al. 1996; Bacurau et al. 2002; Castell 2003; Santos et al. 2007a; dos Santos et al. 2009; Santos et al. 2009). Parry-Billings et al. (1990) suggested that small decreases (about 10%) in plasma glutamine concentration are sufficient to promote impairment of immune cells because the glutamine consumption by immune system cells may be decreased. In contrast, recent reviews suggest that the magnitude of the observed decrease in plasma glutamine concentration after exercise is not large enough to compromise immune cell function (Hiscock and Pedersen 2002; Moreira et al. 2007), or it is not the only mechanism (Hiscock and Pedersen 2002; Costa Rosa 2004). However, studies conducted with macrophages and lymphocytes from trained rats demonstrated

that exercise promotes an increase in glutamine utilization after exercise, as well as the importance of maintenance of glutamine concentration in the modulation of cellular proliferation in lymphocytes during and after exercise (Haskell et al. 2007; Santos et al. 2007a). These results from our laboratory and from others studies suggest that the maintenance of glutamine concentration during and after exercise is important for preservation of immune function and decrease of the "open window" period (Koyama et al. 1998; Bassit et al. 2000, 2002; Bacurau et al. 2002; Castell 2002; Gleeson 2008).

Exercise and chronic illnesses

Physical exercise is a non-pharmacological treatment modality for several diseases (Pedersen and Saltin 2006). In addition, moderate exercise a pleasurable, inexpensive intervention without side effects. Investigations from the 1950s showed the benefits of physical exercise in the treatment of several diseases, including heart disease (Eckstein 1957; Heller 1967; McGavock et al. 2004; Warburton et al. 2007), type 2 diabetes (McGavock et al. 2004), malnutrition (Dos Santos Cunha et al. 2004), kidney transplants (Riess et al. 2006), hypertension (Choquette and Ferguson 1973; Cornelissen and Fagard 2002; Fagard and Cornelissen 2007), obesity (Bradfield et al. 1971; Dachs 2007; Strohacker and McFarlin 2010), psychological disorders (Pedersen and Saltin 2006), sleep disorders (Driver and Taylor 1996; Santos et al. 2007b), and other inflammatory diseases (Rohde et al. 1995; Mathur and Pedersen 2008; Nicklas et al. 2008) (Fig. 2).

Studies show that even low-level physical activity combined with daily mental training and adequate diet have a very good preventive effect too, which is enhanced when it is accompanied by mental activity and psychological well-being (Jennen and Uhlenbruck 2004) since that can induce health behavior modification (Willison et al. 2007). However, despite the encouraging results, the greatest problem with physical exercise programs is that the training programs are not well defined, including the appropriate exercise overload (intensity and volume of exercise) (Costa Rosa 2004). In the following section, we will discuss the effect of chronic exercise on the immune system in some catabolic conditions such as chronic heart failure [CHF], cancer, and malnutrition from evidence derived from studies in the Costa Rosa group.

Chronic heart failure

The development of CHF includes several changes and homeostasis imbalance in tissues and cells which influences many extra-cardiac manifestations, including the immune system (Warburton et al. 2006) and metabolic system in several tissues. In this context, a decrease in plasma glutamine concentration and elevated plasma pro-inflammatory cytokine concentration, especially TNF-α and IL-6, is found in patients with CHF when compared with healthy people. TNF-α has been shown to be involved in generating the oxidative stress, sympathetic activation and elevated blood pressure (Guggilam et al. 2007; Zera et al. 2008).

Therefore, would exercise have the same effect on the immune system during CHF? The following questions

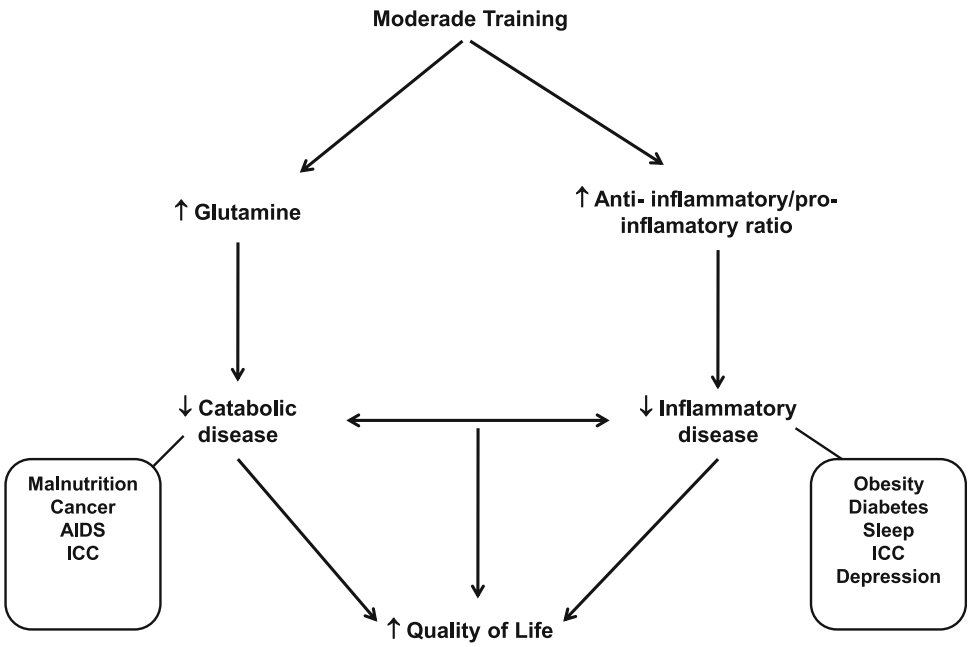

Fig. 2 Effect of training on immune system and improve in quality of life

were addressed in three recent CHF studies in our laboratory (Batista et al. 2006, 2007, 2008): (1) What is the role of macrophages in the progression of CHF? (2) Would exercise affect the Th1/Th2 lymphocyte imbalance and immunosuppression observed in CHF? The first study (Batista et al. 2006) was on pro-inflammatory cytokine pro-inflammatory cytokine production and other macrophage functions in rats with CHF induced by myocardial infarction. In the study, the CHF group presented with higher macrophages ($p < 0.001$) and total cell count ($p < 0.001$) in the peritoneal cavity in comparison to the control group. In addition, the macrophages from CHF rats showed increases in macrophage functions, such as the chemotaxis index ($p < 0.001$), phagocytosis ($p < 0.001$), and H_2O_2 production ($p < 0.05$). This increase in macrophage function in CHF animals was followed by significantly elevated IL-6 and TNF-α production, demonstrating that there is a modification in macrophage function during CHF and that macrophages are important in the inflammatory-induced conditions of CHF.

Additionally, some papers have indicated that leucocytes may play important functions in the course of CHF and that the CD4+ helper cell population is increased in CHF patients. The increase in CD4 number is associated with an increase in T Ly responsiveness to polyclonal mitogens, inducing higher IL-4. Therefore, Th2 cells might function as physiological regulators of the immune response by inhibiting potentially injurious Th1 responses during CHF.

After a moderate aerobic training program (55–65% VO_{2max}, 5 days/week, 60 min/day) for 8 weeks, there was an improvement in macrophage and lymphocyte functions. In fact, the moderate endurance training was efficient, at least partially, in reducing the CHF effect on macrophage hyper activation, characterized by increased in chemotaxis and elevation on TNF-α and IL-6 production restored these values by baselines (Batista et al. 2006). The moderate training was also efficient in promoting changes in lymphocytes from CHF subjects. After training, there was an increase in IL-2 production and restoration in IL-4 production, suggesting a trend toward normalisation of lymphocyte function. These results suggest a possible diversion of the immune response back toward a Th1-type response (Batista et al. 2008). Several mechanisms may explain this improvement promoted by exercise, including the change in cytokine profile production in other tissues such as skeletal muscle and adipose tissue; however, these parameters were not studied in our papers. Other hypotheses are associated with glutamine concentration. In fact, CHF induces a catabolic situation with consequently decrease in glutamine concentration, while the training increased the glutamine concentration**,** restoring it to normal levels (Batista et al. 2008).

Some studies had showed increased glutamine availability may contribute to decreased inflammation and health benefits associated with optimal training (Agostini and Biolo 2010), however, the importance of glutamine during systemic inflammation are unknown (Garrett-Cox et al. 2009). Kretzmann et al. (2008) suggest that glutamine effects may be brought about by inhibition of oxidative stress and reduced expression of proinflammatory cytokines. In fact the inflammation is controlled by increase in protein level of NF-kappaB p50 and p65 subunits in the nucleus and significant phosphorylation/degradation of the inhibitor IkappaBalpha (Kretzmann et al. 2008). It is possible that glutamine increases induced by training can inhibit NF-kBeta activation and cytokine expression during CHF in a process mediated by neddylation of Cullin-1 (Cul-1) to proceed as proposed by (Singleton and Wischmeyer 2008).

Malnutrition

Malnutrition can induce a partial impairment of the immune response and an increase in the susceptibility to infections in normal and hospitalised patients (Huang 2001a, b). Malnutrition depresses many aspects of the immune system, including both cell-mediated and humoral immunity, resulting in thymus, spleen, and lymph node atrophy as well as poor macrophage and lymphocyte function (Pallaro et al. 2001). It also seems that the changes depend on the severity and time of exposure to caloric restriction as well as on the type of dietary protein consumed (Pallaro et al. 2001). A previous study showed that during malnutrition, decreases in glutamine concentration may lead to the impairment of lymphocyte function as well as alterations in proliferation and cytokine production when lymphocytes from the lymph node and spleen are stimulated with phytohemagglutinin (PHA) (Pallaro et al. 2001). However, in vitro, the restoration of physiological glutamine concentration partially recovers the changes found in lymphocyte function especially in cytokine production by cells obtained from the spleen, indicating a balance towards a Th1 response (Pallaro et al. 2001).

Additionally, what is the effect of exercise on the immune system in rats suffering from malnutrition? Dos Santos and colleagues (2004) suggested that if the moderate regular exercise contributes to improvement in immune response, then exercise could also be important in treating malnutrition; although this strategy has not been well studied.

To respond to this question, Dos Santos and colleagues (2004) randomly assigned rodents into four groups: sedentary rats fed ad libitum, sedentary-energy-restricted rats that received 50% of the mean amount of chow consumed

by eutrophic rats, eutrophic rats submitted to endurance training (treadmill, 60–65% $VO_{2\ max}$), and rats trained 30 days after the beginning of the energy restriction.

After 10 weeks of moderate aerobic training (treadmill, 60–65% $VO_{2\ max}$), immune cell (from spleen and mesenteric lymph nodes) functions were re-established. In addition, the moderate training effect induced to a decrease in corticosterone levels and glutamine plasma concentration. These results support the hypothesis that glutamine concentration has an important role also in immunomodulation during malnutrition (Cunha et al. 2003; Dos Santos Cunha et al. 2004).

Inflammation

Inflammation is a natural host response to acute infectious episode, whereas chronic inflammation has been considered a sign of chronic infection. Today, it is known that inflammation is associated with initiation of many chronic diseases such as some cancers, chronic respiratory conditions, type 2 diabetes, cardiovascular diseases, hypertension, cachexia, and others (Petersen and Pedersen 2005; Pedersen and Saltin 2006; Lira et al. 2009b). Inflammation affects people of all nationalities as well as classes and is reaching epidemic proportions worldwide (Petersen and Pedersen 2005; Lira et al. 2009b).

The pathophysiology of the inflammation has a strong link with physical condition since a sedentary lifestyle has a direct relationship with inflammation and accelerates the development of major chronic diseases, especially cardiovascular disease (Mathur and Pedersen 2008; Nicklas et al. 2008; Lira et al. 2010). Consequently, moderate chronic exercise and a low-fat, high-fiber diet have been suggested as a protection against chronic diseases and inflammation (Soliman et al. 2009).

However, the decrease in inflammation induced by exercise is dependent on the pro-inflammatory/anti-inflammatory ratio. This balance may be modulated by several factors, including volume and intensity of exercise, kind of exercise, fitness, and tissue analysed. Several tissues, including skeletal muscle, adipose tissue, and leukocytes, produce and release pro-inflammatory cytokines such as TNF-α and anti-inflammatory cytokines such as IL-10 (Petersen and Pedersen 2005; Lira et al. 2009b; Soliman et al. 2009; Lira et al. 2009c; Rosa Neto et al. 2009).

Most studies in humans indicate that during and following prolonged exercise, plasma cytokine concentrations (e.g., IL-6, IL-10, CSF, and TNF) peak at the end of exercise (Woods et al. 2006; Lira et al. 2009a) with the exception of IL-1ra, which peaks 1–2 h after exercise (Pedersen and Hoffman-Goetz 2000).

Our study showed that 8 weeks of moderate training in rats increased the IL-10/TNF-α ratio in mesenteric adipose tissue and retroperitoneal adipose tissue. However, the mesenteric depot seemed to be more responsive to moderate intensity exercise training than the retroperitoneal fat pad, similar to the case of humans (Lira et al. 2009a).

Additionally, we recently found decreased expression of IL-1β, TNF-α, and IL-10 in the extensor digital longus (EDL) in trained rats, when compared with sedentary rats. In the soleus, IL-1β, TNF-α, and IL-10 protein levels were similarly decreased in trained in relation to sedentary rats, while IL-6 expression was not affected by the training protocol (Lira et al. 2009c). These data show that in healthy rats, 8 weeks of moderate aerobic training down-regulates the skeletal muscle production of cytokines involved in the onset, maintenance, and regulation of inflammation. However, exhaustive acute exercise (moderate intensity to exhaustion) presents a different effect in different tissues: in the muscle, there was an anti-inflammatory effect, noted in type 2 fibers, while in adipose tissue; the exercise induced pro-inflammatory cytokine expression (Rosa Neto et al. 2009).

Conclusion

In this review, we have discussed the improvements in quality of life stimulated by aerobic training, how exercise modulates immune function in some pathological conditions, and the importance of the plasma glutamine concentration in those conditions. From our studies conducted with animal models, we conclude that physical exercise, when performed chronically, can reverse the immunosuppression and inflammation caused by catabolic conditions. These results demonstrate the importance of the exercise-immune system relationship with regards to addressing potential treatments for some illnesses. Therefore, new studies are necessary to deepen the available knowledge and to evaluate the possibility of transference of these results to humans.

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References

Agostini F, Biolo G (2010) Effect of physical activity on glutamine metabolism. Curr Opin Clin Nutr Metab Care 13:58–64

Akerstrom TC, Pedersen BK (2007) Strategies to enhance immune function for marathon runners: what can be done? Sports Med 37:416–419

Bacurau RF, Bassit RA, Sawada L, Navarro F, Martins E Jr, Costa Rosa LF (2002) Carbohydrate supplementation during intense

exercise and the immune response of cyclists. Clin Nutr 21:423–429
Bassit RA, Sawada LA, Bacurau RF, Navarro F, Costa Rosa LF (2000) The effect of BCAA supplementation upon the immune response of triathletes. Med Sci Sports Exerc 32:1214–1219
Bassit RA, Sawada LA, Bacurau RF, Navarro F, Martins E Jr, Santos RV, Caperuto E, Costa Rosa LF (2002) Branched-chain amino acid supplementation and the immune response of long-distance athletes. Nutrition 18:376–379
Batista ML Jr, Santos RV, Cunha LM, Mattos K, Oliveira EM, Seelaender MC, Costa Rosa LF (2006) Changes in the pro-inflammatory cytokine production and peritoneal macrophage function in rats with chronic heart failure. Cytokine 34:284–290
Batista ML Jr, Santos RV, Oliveira EM, Seelaender MC, Costa Rosa LF (2007) Endurance training restores peritoneal macrophage function in post-MI congestive heart failure rats. J Appl Physiol 102:2033–2039
Batista ML Jr, Santos RV, Lopes RD, Lopes AC, Costa Rosa LF, Seelaender MC (2008) Endurance training modulates lymphocyte function in rats with post-MI CHF. Med Sci Sports Exerc 40:549–556
Bradfield RB, Paulos J, Grossman L (1971) Energy expenditure and heart rate of obese high school girls. Am J Clin Nutr 24:1482–1488
Bruunsgaard H, Hartkopp A, Mohr T, Konradsen H, Heron I, Mordhorst CH (1997) In vivo cell-mediated immunity and vaccination response following prolonged, intense exercise. Med Sci Sports Exerc 29:1176–1181
Castell LM (2002) Can glutamine modify the apparent immunodepression observed after prolonged, exhaustive exercise? Nutrition 18:371–375
Castell L (2003) Glutamine supplementation in vitro and in vivo, in exercise and in immunodepression. Sports Med 33:323–345
Castell LM, Newsholme EA (1998) Glutamine and the effects of exhaustive exercise upon the immune response. Can J Physiol Pharmacol 76:524–532
Castell LM, Newsholme EA (2001) The relation between glutamine and the immunodepression observed in exercise. Amino Acids 20:49–61
Choquette G, Ferguson RJ (1973) Blood pressure reduction in "borderline" hypertensives following physical training. Can Med Assoc J 108:699–703
Cornelissen VA, Fagard RH (2002) Effects of endurance training on blood pressure, blood pressure-regulating mechanisms, and cardiovascular risk factors. Hypertension 46:667–675
Costa Rosa LF (2004) Exercise as a time-conditioning effector in chronic disease: a complementary treatment strategy. Evid Based Complement Alternat Med 1:63–70
Cunha WD, Friedler G, Vaisberg M, Egami MI, Costa Rosa LF (2003) Immunosuppression in undernourished rats: the effect of glutamine supplementation. Clin Nutr 22:453–457
Dachs R (2007) Exercise is an effective intervention in overweight and obese patients. Am Fam Physician 75:1333–1335
Decombaz J, Reinhardt P, Anantharaman K, von Glutz G, Poortmans JR (1979) Biochemical changes in a 100 km run: free amino acids, urea, and creatinine. Eur J Appl Physiol Occup Physiol 41:61–72
dos Santos Cunha WD, Giampietro MV, De Souza DF, Vaisberg M, Seelaender MC, Rosa LF (2004) Exercise restores immune cell function in energy-restricted rats. Med Sci Sports Exerc 36:2059–2064
dos Santos RV, Caperuto EC, de Mello MT, Batista ML Jr, Rosa LF (2009) Effect of exercise on glutamine synthesis and transport in skeletal muscle from rats. Clin Exp Pharmacol Physiol 36:770–775
Driver S, Taylor SR (1996) Sleep disturbances and exercise. Sports Med 21:1–6
Eckstein RW (1957) Effect of exercise and coronary artery narrowing on coronary collateral circulation. Circ Res 5:230–235
Fagard RH, Cornelissen VA (2007) Effect of exercise on blood pressure control in hypertensive patients. Eur J Cardiovasc Prev Rehabil 14:12–17
Garrett-Cox RG, Stefanutti G, Booth C, Klein NJ, Pierro A, Eaton S (2009) Glutamine decreases inflammation in infant rat endotoxemia. J Pediatr Surg 44:523–529
Gleeson M (2008) Dosing and efficacy of glutamine supplementation in human exercise and sport training. J Nutr 138:2045S–2049S
Guggilam A, Haque M, Kerut EK, McIlwain E, Lucchesi P, Seghal I, Francis J (2007) TNF-a blockade decreases oxidative stress in the paraventricular nucleus and attenuates sympathoexcitation in heart failure rats. Am J Physiol 293:H599–H609
Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, Bauman A (2007) Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Circulation 116:1081–1093
Heller EM (1967) Rehabilitation after myocardial infarction: practical experience with a graded exercise program. Can Med Assoc J 97:22–27
Hiscock N, Pedersen BK (2002) Exercise-induced immunodepression-plasma glutamine is not the link. J Appl Physiol 93:813–822
Huang YC (2001a) Malnutrition in the critically ill. Nutrition 17:263–264
Huang YC (2001b) Malnutrition in the critically ill. Nutrition 17:745–746
Jennen C, Uhlenbruck G (2004) Exercise and life-satisfactory-fitness: complementary strategies in the prevention and rehabilitation of illnesses. Evid Based Complement Alternat Med 1:157–165
Koyama K, Kaya M, Tsujita J, Hori S (1998) Effects of decreased plasma glutamine concentrations on peripheral lymphocyte proliferation in rats. Eur J Appl Physiol Occup Physiol 77:25–31
Kretzmann NA, Fillmann H, Mauriz JL, Marroni CA, Marroni N, González-Gallego J, Tuñón MJ (2008) Effects of glutamine on proinflammatory gene expression and activation of nuclear factor kappa B and signal transducers and activators of transcription in TNBS-induced colitis. Inflamm Bowel Dis 14:1504–1513
Lira FS, Koyama CH, Yamashita AS, Rosa JC, Zanchi NE, Batista ML, Seelaender MC Jr (2009a) Chronic exercise decreases cytokine production in healthy rat skeletal muscle. Cell Biochem Funct 27:458–461
Lira FS, Rosa JC, Yamashita AS, Koyama CH, Batista ML Jr, Seelaender M (2009b) Endurance training induces depot-specific changes in IL-10/TNF-alpha ratio in rat adipose tissue. Cytokine 45:80–85
Lira FS, Rosa JC, Zanchi NE, Yamashita AS, Lopes RD, Lopes AC, Batista ML Jr, Seelaender M (2009c) Regulation of inflammation in the adipose tissue in cancer cachexia: effect of exercise. Cell Biochem Funct 27:71–75
Lira FS, Rosa JC, Pimentel GD, Tarini VA, Arida RM, Faloppa F, Alves ES, do Nascimento CO, Oyama LM, Seelaender M, de Mello MT, Santos RV (2010) Inflammation and adipose tissue: effects of progressive load training in rats. Lipids Health Dis 9:109
Mathur N, Pedersen BK (2008) Exercise as a mean to control low-grade systemic inflammation. Mediators Inflamm 2008:109502
McGavock JM, Eves ND, Mandic S, Glenn NM, Quinney HA, Haykowsky MJ (2004) The role of exercise in the treatment of cardiovascular disease associated with type 2 diabetes mellitus. Sports Med 34:27–48

Moreira A, Kekkonen RA, Delgado L, Fonseca J, Korpela R, Haahtela T (2007) Nutritional modulation of exercise-induced immunodepression in athletes: asystematic review and meta-analysis. Eur J Clin Nutr 61:443–460

Nagatomi R (2006) The implication of alterations in leukocyte subset counts on immune function. Exerc Immunol Rev 12:54–71

Negro M, Giardina S, Marzani B, Marzatico F (2008) Branched-chain amino acid supplementation does not enhance athletic performance but affects muscle recovery and the immune system. J Sports Med Phys Fitness 48:347–351

Newsholme EA, Calder PC (1997) The proposed role of glutamine in some cells of the immune system and speculative consequences for the whole animal. Nutrition 13:728–730

Newsholme EA, Crabtree B, Ardawi MS (1985a) Glutamine metabolism in lymphocytes: its biochemical, physiological and clinical importance. Q J Exp Physiol 70:473–489

Newsholme EA, Crabtree B, Ardawi MS (1985b) The role of high rates of glycolysis and glutamine utilization in rapidly dividing cells. Biosci Rep 5:393–400

Newsholme P, Costa Rosa LF, Newsholme EA, Curi R (1996) The importance of fuel metabolism to macrophage function. Cell Biochem Funct 14:1–10

Nicklas BJ, Hsu FC, Brinkley TJ, Church T, Goodpaster BH, Kritchevsky SB, Pahor M (2008) Exercise training and plasma C-reactive protein and interleukin-6 in elderly people. J Am Geriatr Soc 56:2045–2052

Nieman DC (1997) Immune response to heavy exertion. J Appl Physiol 82:1385–1394

Nieman DC (2007) Marathon training and immune function. Sports Med 37:412–415

Ortega E (2003) Neuroendocrine mediators in the modulation of phagocytosis by exercise: physiological implications. Exerc Immunol Rev 9:70–93

Pallaro AN, Roux ME, Slobodianik NH (2001) Nutrition disorders and immunologic parameters: study of the thymus in growing rats. Nutrition 17:724–728

Parry-Billings M, Newsholme EA (1991) The possible role of glutamine substrate cycles in skeletal muscle. Biochem J 279:327–328

Parry-Billings M, Leighton B, Dimitriadis GD, Bond J, Newsholme EA (1990) Effects of physiological and pathological levels of glucocorticoids on skeletal muscle glutamine metabolism in the rat. Biochem Pharmacol 40:1145–1148

Parry-Billings M, Budgett R, Koutedakis Y, Blomstrand E, Brooks S, Williams C, Calder PC, Pilling S, Baigrie R, Newsholme EA (1992) Plasma amino acid concentrations in the overtraining syndrome: possible effects on the immune system. Med Sci Sports Exerc 24:1353–1358

Pedersen BK, Hoffman-Goetz L (2000) Exercise and the immune system: regulation, integration, and adaptation. Physiol Rev 80:1055–1081

Pedersen BK, Saltin B (2006) Evidence for prescribing exercise as therapy in chronic disease. Scand J Med Sci Sports 16(Suppl 1):3–63

Petersen AM, Pedersen BK (2005) The anti-inflammatory effect of exercise. J Appl Physiol 98:1154–1162

Riess KJ, Gourishankar S, Oreopoulos A, Jones LW, McGavock JM, Lewanczuk RZ, Haykowsky MJ (2006) Impaired arterial compliance and aerobic endurance in kidney transplant recipients. Transplantation 82:920–923

Robson PJ, Blannin AK, Walsh NP, Castell LM, Gleeson M (1999) Effects of exercise intensity, duration and recovery on in vitro neutrophil function in male athletes. Int J Sports Med 20:128–135

Rohde T, Ullum H, Rasmussen JP, Kristensen JH, Newsholme E, Pedersen BK (1995) Effects of glutamine on the immune system: influence of muscular exercise and HIV infection. J Appl Physiol 79:146–150

Rosa Neto JC, Lira FS, Oyama LM, Zanchi NE, Yamashita AS, Batista ML Jr, Oller do Nascimento CM, Seelaender M (2009) Exhaustive exercise causes an anti-inflammatory effect in skeletal muscle and a pro-inflammatory effect in adipose tissue in rats. Eur J Appl Physiol 106:697–704

Santos RV, Caperuto EC, Costa Rosa LF (2007a) Effects of acute exhaustive physical exercise upon glutamine metabolism of lymphocytes from trained rats. Life Sci 80:573–578

Santos RV, Tufik S, De Mello MT (2007b) Exercise, sleep and cytokines: is there a relation? Sleep Med Rev 11:231–239

Santos RV, Caperuto EC, de Mello MT, Costa Rosa LF (2009) Effect of exercise on glutamine metabolism in macrophages of trained rats. Eur J Appl Physiol 107:309–315

Singleton KD, Wischmeyer PE (2008) Glutamine attenuates inflammation and NF-kappaB activation via Cullin-1 deneddylation. Biochem Biophys Res Commun 373:445–449

Soliman S, Aronson WJ, Barnard RJ (2009) analyzing serum-stimulated prostate cancer cell lines after low-fat, high-fiber diet and exercise intervention. Evid Based Complement Alternat Med 6:1–7

Strohacker K, McFarlin BK (2010) Influence of obesity, physical inactivity, and weight cycling on chronic inflammation. Front Biosci (Elite Ed) 1:98–104

Turnbull AV, Rivier C (1995) Regulation of the HPA axis by cytokines. Brain Behav Immun 9:253–275

Ullman D (2009) A review of a historical summit on integrative medicine. Evid Based Complement Alternat Med 7:1–4

Warburton DE, Nicol CW, Bredin SS (2006) Health benefits of physical activity: the evidence. CMAJ 174:801–809

Warburton DE, Taylor A, Bredin SS, Esch BT, Scott JM, Haykowsky MJ (2007) Central haemodynamics and peripheral muscle function during exercise in patients with chronic heart failure. Appl Physiol Nutr Metab 32:318–331

Willison KD, Williams P, Andrews GJ (2007) Enhancing chronic disease management: a review of key issues and strategies. Complement Ther Clin Pract 13:232–239

Woods JA, Vieira VJ, Keylock KT (2006) Exercise, inflammation, and innate immunity. Neurol Clin 24:585–599

Zera T, Ufnal M, Szczepanska-Sadowska EJ (2008) Central TNF-alpha elevates blood pressure and sensitizes to central pressor action of angiotensin II in the infarcted rats. Physiol Pharmacol 59:117–121