Original Article

New trends in biological aids to recovery after exercise: Immunomodulators

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ABSTRACT

The professional sport increases the physical and biochemical demands of muscle that is accompanied by important metabolic changes, such as the accumulation of toxic compounds, increased consumption of nutrients, and alterations in the physical, thermal and mechanical conditions of the cells. Neuroendocrine adaptations to the demands of elite athletic activity also modify local and systemic immune function, which contributes to the development and continuation of the inflammatory response. During intensive training and competition days, the recovery needs are also impressive. In such circumstances, athletes need to ingest often supplements as protein, micronutrients, minerals or substances to improve the muscular recovery In our experience, many specific products as the immunomodulators are directly linked to benefits, such as improved performance and concentration, reduced fatigue, better recovery and improved health or resistance against minor infections, which seem to occur more often when athletes are undergoing very intensive training. The purpose of this review is to provide an update on published research focusing primarily on the efficacy of immunomodulation substances in the recovery of athletes with respect to physical performance.
Key words: BIOLOGICAL AIDS, EXERCISE, RECOVERY, IMMUNOMODULATORS, GLUTAMINE, POLIPODIUM LEUCOTOMOS.

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INTRODUCTION

Many specific athletic events may be characterized by extremely high exercise intensities. The metabolic stress provoked during physical activity, is generally determined by the type and intensity of exercise, state of physical fitness, nutritional status and environmental factors. Depending on these factors, specific nutritional measures and dietary interventions can be undertaken, particularly in the phases of intense preparation and training or competition (Córdova & Álvarez-Mon, 2001).

A series of metabolic, hormonal, neurophysical and immunological changes that occur as a result of local muscular and systemic inflammatory responses to strenuous exercise are involved in the pathogenesis of decreased athletic performance, fatigue and overtraining (Nieman & Pedersen, 1999; Northoff, Enkel & Weinstock, 1995; Nieman, 1999).

Also, multiple factors influence the athlete's resistance to illness, and the immune system can become functionally depressed. Examples of such factors include genetically predisposed immune competency, inadequate nutrition, physical, psychological and environmental stresses and alterations in normal sleep schedule (Jeukendrup, 2010). Heavy training schedules or endurance competitions, such as marathons or long-distance cycling, are forms of extreme physical stress and lead to immunodepression in athletes, which is associated with increased susceptibility to infection, especially upper respiratory tract infections (URTI) (Gleeson, Nieman & Pedersen, 2004; Maughan & Gleseson, 2010).

The professional activity of an elite athlete increases the physical and biochemical demands of muscle and hepatocytes (Northoff et al., 1995; Nieman, 1999; Gleeson et al., 2004). Tissue requirements in these athletes is accompanied by important metabolic changes, such as increased consumption of nutrients, and alterations in the physical, thermal and mechanical conditions of the cells and accumulation of intermediate metabolic molecules (Córdova & Álvarez-Mon, 2001; Nieman, 2007). In this setting of cellular demand and stress, free radicals and stress proteins are produced, which promote the activation and attraction of inflammatory cells to the muscle tissue (Koning, Wagner, Elmadla & Berg, 2001). Due to the global nature of the immune system, these local changes have significant repercussions on lymphocytes and accessory cells outside the muscle tissue (Bousquet, Chanez, Mercier & Prefaut, 1996).

It is well recognized that the excessive training stress, associated with insufficient rest and recovery, may induce acute local inflammatory responses in working skeletal muscle that may evolve into chronic inflammation and produce systemic inflammation (Pedersen & Febbraio, 2008; Jurimae, Maestu, Jurimae, Mangus & von Duvillard, 2011).

During intensive training and competition days, the recovery needs are also impressive. In such circumstances, athletes need to ingest often supplements as protein, micronutrients, minerals or substances to improve the muscular recovery (Burke & Mujika, 2014; Burke, Millet & Tarnopolsky, 2007). Indeed, many products have been formulated with the specific aim of influencing performance-limiting physiological functions (Maughan, 1999).

In our experience, many specific products as the immunomodulators are directly linked to benefits, such as improved performance and concentration, reduced fatigue, better recovery and improved health or resistance against minor infections, which seem to occur more often when athletes are undergoing very intensive training. The purpose of this review is to provide an update on published research focusing primarily on the efficacy of immunomodulation substances in the recovery of athletes with respect to physical performance.

BIOLOGICAL AIDS

Ergogenic sports aids enhance performance by preventing the injurious responses to strenuous exercise and by modulating homeostatic processes of adaptation which lead to recovery and remodeling (Schubert & Astornino, 2013). Pharmacologic and nutritional ergogenic substances reduce the harmful effects of fatigue and accelerate the recovery process through rapid replacement of spent energy therefore avoiding the intense, prolonged metabolic and hormone imbalance that accompanies strenuous exercise (Kent & Hart, 1993; Fuentes & Córdova, 1999; Juhn, 2002; Thein, Thein & Landry, 1995). While many of these aids are simple nutritional supplements, some of the ergogenic aids used by athletes are considered to be doping agents. Unfortunately, there is very little adequate data on the number of biological sports aids now being employed by competitive sports players.

Some biological aids are designed to decrease the inflammatory process produced by exercise-induced muscular damage. This is accomplished via many different mechanisms. Immunomodulators help to recover immunological stability lost to the immunoaltering effects of intense physical activity. Antioxidants are used for eliminating free radicals whose rise in elite sport activity are implicated in causing muscular damage and inducing inflammation.

Immunomodulators

As a consequence of the muscular damage and inflammation caused by exercise, alterations of the immune system are accompanied by systemic modifications such as hyperthermia, asthenia, predisposition to infection, fatigue, and muscle and hepatic tissue alterations, all of which lead to decreased athletic performance (Córdova & Álvarez-Mon, 2001; Nieman & Pedersen, 1999; Fuentes & Córdova, 1999; Córdova & Álvarez-Mon, 1995; Canonico, 1981). Damage of tissue stimulates a wide range of defensive reactions known as the acute-phase response (Sorichter, Puschendorf & Mair, 1999).

The cytokine response is suggested to play a role in muscle reconstruction after strenuous exercise and in the development of tolerance to ROS-induced muscle damage (Powers, Duarte, Kavazis & Talbert, 2010). The functional complexity of the cytokine network is expanded by the involvement of soluble receptors of cytokines (Pedersen & Febbraio, 2008; Córdova, Monserrat, Villa, Reyes & Soto, 2006). In this way, it has also been reported little increases in TNF-α and IL1 after highly strenuous, prolonged exercise such as a marathon race (Nieman, 2007; Wallberg, Mikael Mattsson, Enquvist & Ekblom, 2011). It was hypothesized that the ultra-structural damage of muscle tissue is a potential stimulus for the production and release of proinflammatory cytokines (Wallberg et al., 2011; Pedersen, Steensberg, Fischer, Keller, Ostrowski & Schjerling, 2001).

During and after intensive exercise increase of cytokines, as IL-1 and tumour necrosis factor (TNF), are provoked consequently to the muscular injury. These and other cytokines mediate a wide range of metabolic events that affect every organ system in the body (Córdova, Álvarez-Mon, 2001; Córdova et al., 2006; Pedeser et al., 2001).

Moreover, as several authors reported high concentrations of pro-inflammatory cytokines to be correlated with over-training and reduced physical performance (Jurimae et al., 2011). The balanced modulation of cytokine-producing and cytokine- responding active immune cells is a promising medical field (Moreira, Delgado, Morerina & Haantela, 2009).

During the period of immunosuppression, there is an added risk of contracting infections caused by viruses and bacteria (Moreira et al., 2009; Nieman, 2003) with the onset of symptoms characteristic of the upper respiratory tract (Gleeson et al., 2004; Maughan & Gleeson, 2010; Nieman, 2003; Nieman 2008) which increase relative to the intensity and duration of the exercise undertaken (Nieman, 2007, Akerstrom & Pedersen, 2007; Nielsen & Lyberg, 2004).

Stress or unsuitable diet during periods of competition is additional factors for the immunosuppressant effect in athletes (Hackey, 2013). Studies have shown that this immunosuppression normally lasts for 3–72 hours after intense physical activity (Newsholme, 1994) although the possibility of acquiring infection may extend to 1–2 weeks for athletes taking part in competitions (Moereira et al., 2009; Hackney, 2013; Newsholem, 1994; Pedersen & Hoffman-Goetz, 2000). The duration of the immunosuppressant effect depends on the intensity of the exercise and on the prevailing state of the athlete's immune system.

The immunomodulators that are considered to be, or are, potentially active in the prevention or recovery of immune system changes associated with competitive sport activity include immunoglobulins, glycophosphopeptical, levamisole, interleukins and their soluble receptors, and antibodies against several important molecules (Córodova, 2010). Immunomodulators, such as glychophosphopeptical, glutamine and Polypodium leucotomos Extract have been shown to influence the components of the immune system.

Glycophosphopeptical (AM3)

AM3 (Inmunoferón®) is an oral polysaccharide/protein immunomodulator purified from Candida, with a low toxicity profile, utilize with regulatory effects on the production of several cytokines (Brieva, Guerrero & Pivel, 2002; Martín-Vilchez et al., 2008). AM3 exerts its regulatory effect on TNF-α expression through a hypothalamo-pituitary-adrenal-dependent mechanism (Brieva, Guerrero & Pivel, 2003). AM3 stimulates monocyte derived dendritic cells to increase the proliferation of allogenic T suggesting that AM3 might be useful in regulating immune responses in pathophysiological situations requiring dendritic cell maturation (Martín-Vilchez et al., 2008) (Table 1). In this sense, the changes related to high performance sport were reported in terms of the effects of AM3 on the immune system, with a protective action against cellular stress (Córdova, Martín, Reyes & Álvarez-Mon, 2004).

Together these modulations result in a net anti-inflammatory effect. In our experience with the AM3 we have shown this immunomodulator is able to reduce and normalize the increased serum concentration of muscle enzymes found in intense and prolonged sport competition (Córdova et al., 2004). This biochemical effect is associates to a reduction of the proinflammatory cytokine levels found in these subjects. The potential use of this immnunomodulator in the prevention of the immunodisturbance and tissue damage associated to intense sport practice may be suggested (Córdova et al., 2006; Córdova, 2010; Córodva et al., 2004).

In cyclists in a prospective, randomized, double-blind trial involving the administration of AM3 (Inmunoferon), an oral booster immunomodulator, or placebo to 16 professional cyclists (n = 8 in each group) for 65 consecutive days, we have observed that the concentrations of serum TNFR-I and -II both 4 h after finishing the mountain stage and 18 h after the fifth and last day of competition were significantly higher than those recorded after training (Córdova et al., 2006).

More recently, also we have communicated that TNF-α serum levels increased after 180 days of training and the AM3 treatment avoided this response. This effect was accompanied by a rise in serum levels of TNF-α receptors I and II (TNFRI and II) after 90 and 180 days of treatment with the immunomodulator AM3 (Córdova, Sureda, Pons & Álvarez-Mon, 2015).

In our opinion the AM3 has important immunomodulatory effect (Table 1), in sportman after inflammation and pain muscle induced by prolonged, intense and strenuous physical exercise. We have observed that athletes participating in an intensive exercise such as marathon, ultramarathon, cyclist stage race and elite team in a regular season, experience acute physiological stress reflected by muscle microtrauma, oxidative stress, inflammation. The use of immunomodulators AM3 significantly reduces serum concentrations of proteins associated with muscle damage as such creatine kinase (CK), Myogloblin (Mb), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) (Córdova et al., 2004). Also, concomitant with these stressors are widespread, transient perturbations in innate and adaptive immunity. AM3 has a wide range of regulatory effects on innate and adaptive immunity. Some studies have determined an increase of number and activity of: NK cells, monocytes/macrophages and Lymphocytes T (CD3, CD4) (Córdova, 2010) C) exercise-induced inflammation involves the secretion of cytokines. The AM3, partially inhibits the production of tumor necrosis factor (TNF-α) and modulates the production of regulatory cytokines (IL-1, IL-2, IL-6, IL-12, IFN-δ) (Córdova et al., 2006; Córdova, 2010; Córdova et al., 2015).

We have concluded (Córdova et al., 2006; Córdova, 2010; Córdova et al., 2015) that the changes produced by regular training and competition can be modulated by AM3 treatment reducing the instauration of an inflammatory state and immunological disorders. In addition, to being beneficial for its competitive performance, is also an important element to consider as mechanisms to preserve the athlete's health by an effective therapeutic use of an immunomodulator such as AM3.

Polypodium leucotomos

Polypodium leucotomos (PL) is a plant extract that acts on different biological systems; therefore, it has a broad therapeutic spectrum and no adverse effects were reported in laboratory studies. It is used as an antioxidant and an anti-inflammatory agent (Vargas, Muñoz, Osoro & García-Olivares, 1983). As an antioxidant it inhibits lipid peroxidation by decreasing production of free radicals caused by oxidative stress (González & Pathak, 1996). As an immunomodulator it inhibits the inflammatory activity of TNF-α and IL-6. It increases NK cell activity, and in rats its capacity to inhibit the production of some cytokines has been observed (Vargas et al., 1983; (González & Pathak, 1996; Rayward et al., 1997).

On the other hand, orally administered PL extract decreases UV-mediated oxidative damage to DNA by enhancing the activity of endogenous antioxidant systems responsible for blocking the formation of reactive oxygen species (El-Haj & Goldstein, 2014).

Some authors have suggested that the PL can be an option for further development of oral supplementation that may evolve into a true immunomodulator (Horvarth, Alvarado, Szöes, de Alvardo & Padilla, 1967; Sempere, Rodrigo, Campos, Villalba & Diaz, 1997; Bern et al., 1995; Nestor, Berman & Swenson, 2015).

In vitro studies carried out on humans show that PL extract stimulates the proliferation of peripheral blood mononuclear cells in vitro and increases interleukin- 2 (IL-2) and interferon-γ secretion. It also enhances the stimulant effect of other mitogens on cytokines such as IL-10 (Bern et al., 1995). Therefore,

it is capable of significantly reducing and delaying IL-1β secretion in the same way it tends to reduce tumor necrosis factor-α levels. Several of the correlations obtained in the reference studies for different cytokines lead to the conclusion that PL extract actually produces an opposing and independent effect on IL-1β and IL-2 and IL-1β and IL-10 (Sempere et al., 1997; Bernd et al., 1995). These results indicate a pleiotropic effect of PL extract for different cytokines, probably due to a different way of acting on distinct areas of the immune system. In this sense, Bernd et al (1995) have observed that the PL increases the percentage of T lymphocytes in their helper population (CD4+). They result indicate an ability of Anapsos to up-regulate the percentage of these cytotoxic cells.

Recently, Solivellas and Martín (2012) have observed that athletes treated with PL extract demonstrated a lower incidence of infectious diseases – related to the degree of physical activity. Their symptomatic processes – when infected – were shorter than those athletes do not treated, and they were much less prone to relapses.

The duration of the immunosuppressant effect depends on the intensity of the exercise and on the prevailing state of the athlete's immune system (Solivellas & Martín, 2012). The same happens in the athletes when they suffer inflammation processes and muscle damage associated with exercise (Córdova, 2010). In previous studies Sempere et al., (1997) have demonstrated that Polyphodium Leucotomos Extract possess anti-inflammatory and immunomodulatory activity, producing differentes effects on cell immunity – both natural and specific. Polyphodium Leucotomos Extract offers an optimum security profile alone or when used with other medications, thus offering a suitable alternative for the prevention of the open window effect in athletes who might be vulnerable to immunological stress due to intense physical exercise (Solivellas & Martín, 2012).

When an appropriate dose is prescribed and compliance is adequate, we suggest the use of Polyphodium Leucotomos Extract, in elite athletes, by the pleiotropic effects it has on the different cell populations and cytokines of the immune system (Sempere et al., 1997; Bernd et al., 1995; Nestor et al., 2015; Solivellas & Martín, 2012). Considering that the competitive athletes, compared to less physically active people, are more prone to contracting infections. Polypodium leucotomos extract has been shown to be useful in the prevention of intercurrent infectious processes that would produce a decrease on athletic performance.

Glutamine

Glutamine is a conditionally essential amino acid, which comprises 20% of the total plasma amino acid. Glutamine it is important as a constituent of proteins and as a means of nitrogen transport between tissues. It is also important in acid-base regulation, gluconeogenesis, and as a precursor of nucleotide bases and the antioxidant glutathione. Glutamine is the most abundant free amino acid in human muscle and plasma. Glutamine is a highly abundant amino acid, largely synthesized by skeletal muscle and released in plasma. Also, the intramuscular concentration of glutamine is known to be related to the rate of net protein synthesis and there is also some evidence for a role for glutamine in promoting glycogen synthesis (Bowtell et al., 1999). Glutamine is endogenously synthesized from glutamate and ammonia by glutamine synthase. Activity of such an enzyme is affected by several hormones. Glucocorticoids promote glutamine synthesis, whereas growth hormone downregulates this process (Agostini & Biolo, 2010). It has traditionally been considered a non-essential amino acid but is now known to be conditionally essential after critical illness and injury (Wilmore, 2001).

The neuroendocrine and immune responses to exercise may modulate activity of the cells that participate in the immune response in alternative ways. One of these ways is exercise-induced muscle damage, which results in the secretion of inflammatory cytokines by innate immune cells (Pedersen et al., 1997). Another way is the effect of exercise upon plasma glutamine levels (Newsholeme & Parry-Billings, 1990). As communicate Castel (2003) in a review, several studies have shown a decrease in plasma glutamine concentration after exhaustive exercise in humans and animals as well as in the presence of overtraining syndrome. Other study had communicated that L-Glutamine levels increase after short-term exercise, but decrease after prolonged, strenuous exercise (Kargotich et al., 2007). In this situation of prolonged exercise and intense training is known to cause an elevation in plasma cortisol concentration, which stimulates not only catabolic process that results in the rupture and destruction of muscular tissue and therefore tissue growth (Fiel, Jonhson & Pratt, 2000). Also increases gluconeogenesis in the liver, gastrointestinal tract, and kidneys. This increased hepatic, gastrointestinal, and renal uptake of glutamine could place a significant drain on plasma glutamine availability after prolonged exercise (Gleeson, 2008). In this way, physical inactivity induces reduction of skeletal muscle glutamine synthesis, whereas moderate exercise enhances glutamine release from muscle. Exhaustive exercise causes a higher uptake of glutamine by activated immune cells as well as by the liver (gluconeogenesis) that is not balanced by an increased synthesis in Figure 1 (Agostini & Biolo, 2010). These alterations lead to glutamine depletion in overtrained individuals (Agostini & Biolo, 2010).

In particular, glutamine is utilized by rapidly dividing immune cells, especially lymphocytes, neutrophil and monocytes. For such reasons, glutamine was considered as conditionally essential and named as 'fuel of immune system'. The importance of its role in activation and regulation of the immune system was investigated in different models (Wasinski et al., 2014; Lagranha et al., 2008).

In metabolic stress situations, L-Glutamine is utilized at high rates by various immunologic tissues and cells during inflammatory states, muscle damage and endocrine stress which occur in conditions such as prolonged exercise and intense training, the glutamine consumption in immunologic tissues and cells increases above normal physiological ratios. This increase in glutamine consumption, coupled with enhanced utilization by other tissues abovementioned, results in a demand for glutamine that outstrips supply. As a result, blood, immunologic tissue and muscle glutamine levels fall. The low concentrations of glutamine limit the function of key tissues and cells, especially cells of the immune system (Moura et al., 2017; Newsholeme, 2001).

It has been estimated that when plasma glutamine levels fall in a "glutamine-deficient" then the immune system is compromised (Wilmore & Shabert, 1998). Parry-Billings et al (1992) corroborated that small decreases in plasma glutamine concentration are sufficient to promote immunosuppression. This decrease in plasma glutamine correlates with increased symptoms of upper respiratory tract infections (URTI), due to partial impairment of immune cell function (Castell, 2003).

Likewise, previous studies demonstrated numerous benefits of Glutamine administration in experimental models of serious neuro-metabolic stress and attenuation of inflammatory reactions, in conclusion, glutamine contributes to preserve the function of the endocrine and immune system (Tsai, Yeh, Liu, Chiu & Yeh, 2012). Glutamine neutralizes the catabolic effect or the cellular tissue destruction caused by cortisol which segregates in large quantities during training, and whose aim is to create cell intoxication and finally cell destruction. L-Glutamine plays an important role in increasing muscle mass, strength and recovery (Table 2) (Fiel et al., 2000; Welbourne, 1995). The effects of acute exercise on plasma glutamine concentration appear to be largely dependent on the duration and intensity of exercise

(Kargotich et al., 2007; Walsh, Blannin, Robson & Gleeson, 1998). An increase in L-Alanine, L-Citruline, L-Histidine and L-Arginine has been observed after administration of L-Glutamine together with an increase in branched chain amino acid (BCAA) absorption by the muscles which also promotes the recovery and growth of new muscle fibres (Kreider, Miriel & Bertun, 1993; Lemon, 1995).

The supplementation with L-Glutamine, is known the utilization and the pathway of metabolism of glutamine by cells of the immune system (Newsholme, 2001). The macrophages utilize high rates of glutamine and satisfy their energy requirements through partial oxidation of glutamine (Hyeyoung, 2011). Dos Santos et al (2009) suggest that the increase in macrophage function induced by exercise is supported by enhanced glutamine consumption and metabolism, which highlights the importance of this amino acid in the modulation of macrophage function during and after exercise. The glutamine appears to regulate T-lymphocyte proliferation, the rate of interleukin (IL)-2 production and IL-2 receptor expression (Newsholme, 2001). The differentiation of B-lymphocytes into antibody synthesizing and secreting cells is glutamine dependent and increases significantly over a range of physiologic glutamine concentrations (Crawford & Cohen, 1995).

Currents studies by Wasinski et al (2014) show that L- Glutamine are important energetic and biosynthetic nutrients for T and B lymphocytes. Also, glutamine support the potential of Lymphokine-activated killer cells (LAK cells) to kill target cells (Juretic, Spagnoli & Horig, 1994). In neutrophils, L-Glutamine plays an important role by increasing both phagocytosis and reactive oxygen intermediate (ROI) production.This may suggest that careful consideration should be given to neutrophil functions in athletes particularly those using glutamine supplementation as part of their diet (Lagranhan et al., 2008; Saito, Furukawa & Matsuda, 1999). On the other hand, oral glutamine administration to exercising rats prevented immune cells apoptosis by reducing DNA fragmentation. Also, overtrained athletes were shown to display lower viable lymphocytes and neutrophils, as a consequence of apoptosis induction (Agostini & Biolo, 2010). Therefore, preventing the fall in plasma glutamine by supplementing glutamine orally should prevent the associated immune impairment due to prolonged and strenuous physical efforts of athletes (Smith & Norris, 2000).

CONCLUSION

Because muscle damage, inflammation, and acute phase response may normally occur during exercise training and competition, it is critical to contextualize the use of possible nutritional aids. The athletes in general shawn high levels of inflammatory markers related with the chronic stress, fatigue and performance decrements. Some ergogenic sports aids as immunomodulators (AM3, Polypodium leucotomos, and glutamine) can be used to reduce the harmful effects of stress inflammation and fatigue and accelerate the recovery process. The use of these immunomodulators have been shown to influence the components of the immune system and therefore in the muscular recovery of athletes. These biological aids may be important to enhance performance by preventing the injurious responses to strenuous exercise and by modulating homeostatic processes of adaptation which lead to recovery and remodelling.

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