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MEDIADORES DE ESTRÉS EN LA MODULACIÓN DE LA RESPUESTA INFLAMATORIA DURANTE EL EJERCICIO Y EL ENTRENAMIENTO. APLICACIONES PRÁCTICAS EN ENFERMEDADES INFLAMATORIAS: FIBROMIALGIA

STRESS MEDIATORS IN THE MODULATION OF INFLAMMATORY RESPONSE DURING ACUTE EXERCISE AND TRAINING. PRACTICAL APPLICATIONS IN INFLAMMATORY DISEASES: FIBROMYALGIA

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INTRODUCTION

It is well known that, together with the muscle skeletal and cardiovascular systems, physical activity also strongly modulates the immune system. Thus, the evaluation of the effects of different types and intensities of exercise and training on the immune system appears to be very important in order to know the beneficial (or harmful) effects of exercise on health. The immune system is a system for self-recognition and maintaining homeostasis. It is an extremely complex network that extends throughout the body, and it can recognize and defend the organism against a theoretically infinity array of challenges. The participants in innate immune mechanisms are macrophages and neutrophils, along with natural killer (NK) cells, complement and defensins, and they constitute the first line of host defence. All its constituents need a basic capacity to distinguish between self and non-self (foreign material), and danger or non-danger signals with the involvement of pattern recognition receptors (PRRs) such as the Toll-like (TLR) family of receptors. By engulfing, processing and presenting antigens, macrophages form the critical link to the specific (acquired) branch of the immune system that mainly comprises the various subpopulations of lymphocytes and their products. The cellular innate immune response together cytokines (pro- and anti-inflammatory ones) and other proteins are crucial in the inflammatory response mechanisms[1].

While regular moderate exercise is very likely to be associated with decreased susceptibility to infection, excessive exhaustive exercise has been associated with symptoms of transient immunodepression, leading to increased susceptibility to infection. However, the last decades have seen a perhaps excessive generalization of the idea that, while moderate exercise is beneficial, intense exercise is harmful for the immune system. The latest studies, however, have revealed that this general finding cannot be extended to the innate immune response, and particularly to phagocytes. Some stages of the phagocytic process - chemotaxis and phagocytosis in particular - are stimulated by both moderate and intense exercise. In 1992[2], we postulated that the stimulation of macrophages during strenuous physical activity might counterbalance the decreased lymphoid activity, and that this may be regarded as an adaptation of the phago-

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cytic cells to exercise-stress situations, in which stress hormones are involved. The behaviour of the phagocytic cells may also counteract the "open window" situation, in which stress hormones are also involved, sometimes stimulating phagocytic cells and decreasing lymphocyte function. Thus, we suggested that phagocytes, and the innate defences in general, play a major role in the defence against infection during exercise-induced stress, probably preventing the entry and maintenance of microorganisms in situations where the specific response seems to be depressed[3]. However, while inflammation is necessary in host defence, uncontrolled inflammatory reactions are responsible for the initiation and progression of autoimmune and inflammatory diseases, especially in women, who are more susceptible to these kinds of pathologies[4] probably because they have a "higher basal inflammatory status"[5]. The balance between pro-and anti-inflammatory cytokines is also critical in these pathologies[6].

Exercise as a model of stress response: norepinephrine (NE) and 72 kDa heat shock protein (Hsp72) as "stress messengers" or "danger signals" in exercise-induced immunomodulation

Years ago it was thought that the immune system was a self-regulating physiological system. Nonetheless, today it is accepted as one of the three major regulatory systems together with the nervous and endocrine systems, communicating via neurotransmitters, neurohormones, hormones, and cytokines. Also, its functioning should be understood both in normal homeostatic conditions and when homeostasis is altered, as in sickness or in situations of stress.

Exercise is a form of stress, and the effects that exercise induces in the immune response are mediated by "stress mediators or messengers" that are released when the activity is being performed. Indeed, the interactions between the immune system and physical exercise are today regarded as a model of the response to stress[7], including the cellular non-specific immune response carried out by the phagocytes[1,3]. This is essential in order to recognize the beneficial (or harmful) effects of physical exercise on health.

The effects of exercise on the immune system are mainly mediated by alterations in the sympathetic nervous system (SNS) and/or the hypothalamus-pituitary-adrenal axis (HPA). Depending on their plasma concentration and time of exposure, although stress hormones (mainly glucocorticoids and catecholamines) can impair some specific and adaptive immune functions, they may also significantly stimulate some other aspects of the innate immune and/or inflammatory response[3]. For example, we found that corticosterone is at least partly responsible for the exercise-induced enhancement of murine macrophage phagocytosis[8] and chemotaxis[9]. In addition, there appears to be an "optimal" physiological range in which glucocorticoids may stimulate phagocytic cells, in agreement with the idea that low levels of glucocorticoids may enhance immunity rather than suppress it.

In general, while cortisol may be responsible for maintaining elevated circulating numbers of neutrophils after exercise of long duration, catecholamines mediate the acute effects on neutrophils[10], including their functional capacity. Thus, epinephrine (E) is involved as "stress mediator" or "danger signal" in the stimulation of chemotaxis and phagocytosis of neutrophils induced by single bouts of intense exercise in sedentary women[11]. The effects of training on phagocyte function may also involve E, since we found a correlation between the phagocytosis and peaks in E observed during the training season of a team of cyclists[12]. Although both E and norepinephrine (NE) can mediate the immune response during intense exercise, NE appears to be responsible during acute bouts of moderate exercise[11]. The participation of NE in the modulation of the functional capacity of neutrophils during single bouts of moderate exercise has been confirmed in studies with untrained men, showing that the increase in the circulating concentration of NE following the exercise stimulates chemotaxis[13], phagocytosis[14] and, indirectly, the microbicidal capacity[15] of neutrophils.

Recently, several laboratories have reported that exercise-induced stress also results in the release

of the 72 kDa heat shock protein (Hsp72), which also has marked effects on innate immunity, suggesting that this protein acts as a "danger signal" during physical exercise stress[16]. The 70 kDa heat shock protein (Hsp70) family constitutes the most conserved and best-studied intracellular class of Hsp, which have an important role in cell protection following exercise and exercise training[17]. In addition, exogenously added Hsp72 possesses potent chaperone and cytokine activity, a term that has been referred to as the "chaperokine" capacity of Hsp72[18], suggesting an important role of extracellular Hsp72 (eHsp72) during stress situations. Walsh and co-workers[19] were the first to demonstrate that Hsp72 is released into the blood during intense exercise, and recent studies have shown that both intensity and duration of exercise influence the circulating concentration of Hsp72 in both sedentary and trained people[20,21]. Furthermore, we have recently found that eHsp72 also participates in the stimulation of neutophil chemotaxis induced by a single bout of intense exercise (1h on a cycle ergometer at 70% VO_{2max}) performed by sedentary women[22].

While traditionally only intense exercise has been regarded as stressful, there is growing acceptance that moderate exercise can also be viewed as stress situation since it can also substantially alter homeostasis. Recent studies conducted in our laboratory have shown how both NE and Hsp72 also participate in modulating the immune response during exercise of moderate intensity – exercise which is more suitable for the quality of life and well-being of the healthy population and for complementary therapies in various pathologies. As has been already reported for NE, the elevated concentration of eHsp72 in blood following moderate exercise (45 min at 55% VO2 max) also stimulates chemotaxis, phagocytosis and microbicidal capacity of neutrophils[13,15]. It may be speculated that during exercise, the induction of a rapid release of NE into the circulation would constitute the first "danger signal" for the organism, and subsequently NE could be the signal for the release of eHsp72. This has given rise to a new wave of functional interpretations of the activation processes of the immune system by factors released in situations of exercise-induced stress ("stress mediators", "messengers of stress", and/or "danger signals"), even in the absence of any prior antigenic stimulus.

In many cases, the results and conclusions drawn from immunophysiological studies on exercise, stress, and immunity seem paradoxical. Is exercise good or bad for health? Is stress good or bad for health? And is the release of stress hormones and heat shock proteins good or bad for heath? When one accepts that physical exercise, even that of moderate intensity, is a stress situation, and that it is not necessarily either good or bad for the organism but will simply cause it to produce an appropriate response (adaptation) to the homeostatic changes naturally caused by the exercise, the mist begins to clear from the concepts. (Also, when we accept exercise as a model of stress, it becomes clear that no general statement that stress induces immunosuppression can be maintained for all levels the immune system, especially for the innate and/or inflammatory response).

Exercise, stress and inflammatory diseases: Fibromyalgia

It is well known that physically active people are at a lower risk of illnesses, and the accumulated evidence shows that habitual exercise is an effective means of preventing or delaying chronic diseases in healthy people. However, the optimal level of exercise that improves, but does not impair or over-stimulate, an optimal immune function is not yet well known, especially in women, who have higher innate or "inflammatory markers" than men (including higher levels of NE and Hsp72) in their basal state[5]. Based on the hypothesis of the anti-inflammatory effects of exercise[23,24], habitual training is especially considered as a good therapeutic help for inflammatory pathologies. Nevertheless, more investigation are needed to confirm or reject the anti-inflammatory hypothesis of exercise that allow better applications of exercise therapy in the treatment of inflammation-associated diseases,[24], moreover taking into account that most of the studies on the anti-inflammatory effects of exercise have been performed in healthy sports-

men. Even if we think it is highly likely, it is not formally proven whether an induced anti-inflammatory effect of exercise in healthy people, with an optimal neuroendocrine and inflammatory feedback, is good or not for an optimal regulation homeostasis. It is at least possible that the anti-inflammatory effects of exercise are mainly or only positive for people with an unhealthy high inflammatory status, such as individuals suffering diseases associated with chronic inflammation[25]. A well controlled and regulated stimulation of the innate immune mechanisms during moderate exercise can help prevent infections, but over-stimulation of the innate and/or inflammatory response (sometimes during single or repetitive bouts of high intensity exercise) could also be harmful for people with inflammatory and/or autoimmune diseases, mainly in women, who are more susceptible to these types of pathologies. The modulation of the systemic or local pro-/anti-inflammatory cytokine balance during stress, including exercise, may suppress or potentiate autoimmune disease activity and/or progression, and catecholamines[6] and eHsp72[18,26] are involved in this regulation[13]. In this context, the regular performance of moderate exercise or good levels of training leading to the release of Hsp72 could contribute to a good "training of the immune system", with particular importance in people who are increasingly sedentary and frequently subjected to psychological stress as a result of their "modern lifestyle". On the contrary, exercise, performed at inappropriate intensities (irregular and high intensity) and/or in states of poor health may result in dysregulation in the immunophysiological mechanisms of these "danger signals", potentiating or exacerbating the disease. Thus, the roles of NE and eHsp72 in vivo may be different depending on the health status of the organism.

Fibromyalgia (FM) is a form of non-articular rheumatism characterized by widespread musculo-skeletal pain and allodynia to pressure in more than 11 of 18 specified sites or tender points[27]. However, its biophysiology remains elusive and its treatment is empirical. The aim of non-pharmacological treatments of FM patients, such as exercise training programs (particularly pool-aquatic physical activity), is to improve overall health, fitness, muscle strength and to decrease the pain. Exercise training program also appear to raise the pain threshold and change the perception of pain. Recent hypothesis of the etiology of FM include the involvement of inflammatory and neuroendocrine disorders; and today special attention has been paid to the inflammatory hypothesis of FM[25]. Cytokines, such as IL-6 and IL-8 may play a major role because the former has been associated with hypersensitivity to pain and the latter promotes sympathetic pain. Besides the generation of pain and hyperalgesia in inflammatory conditions, pro-inflammatory cytokines, such as IL-1beta, TNFalpha, IL-8, or inflammation-associated cytokines such as IL-6, may also induce other characteristic symptoms of FM syndrome, such as stress, fatigue, sleep disorders and depression symptoms, while the anti-inflammatory cytokine IL-10 may block pain[25,28-30]. Neuroendocrine disorders, including circulating levels of NE and cortisol[25] and also eHsp72 are also involved in this pathology. In addition, we have found that 4 and/or 8 months of an aquatic training protocol improved (i.e. decreased) the very high circulating levels of inflammatory cytokines, such as IL-8 and interferon (IFN)-γ, and C-reactive protein (CRP, a systemic inflammatory marker) in these patients[25]; as well as the balance of pro-/anti-inflammatory cytokines (IL-1beta, TNFalpha, IL-6, and IL-10) released by circulating monocytes[31], all of them in parallel with an improvement in the health-related quality of life. Nevertheless, in our opinion further studies are necessary to define the duration and intensities of exercise programs in order to get anti-inflammatory responses that restore an optimal cytokine-HPA axis feedback circuit, and to avoid unhealthy pro-inflammatory responses, since alteration in the cytokine-glucocorticoid feedback circuit can itself provoke FM[25,32].

Finally, it is necessary to bear in mind that the immune system is a homeostatic regulatory system that operates in situations of high energy costs such as exercise-induced stress, and, moreover, is involved in disease situations that also need high energy contributions.

ABSTRACT

It is well known that physical activity strongly modulates the immune system, including the innate and/or inflammatory response. The effects of exercise and training on the inflammatory response are mainly mediated by alterations in the sympathetic nervous system (SNS) and/or the hypothalamus-pituitary-adrenal axis (HPA), but also by other "danger signals" such as extracellular 72 kDa heat shock protein (Hsp72). This review is focused on the role of "stress mediators" or "danger signals", such as norepinephrine (NE) and Hsp72, on the exercise-induced activation of the innate and/or inflammatory response. Based on the hypothesis of the anti-inflammatory effects of exercise, habitual physical activity or training is especially considered as a good non-pharmacological intervention in inflammatory diseases. Particular attention is focused on the effect of habitual exercise on Fibromyalgia Syndrome, in which neuroendocrine and inflammatory disorders are involved.

Key words: Exercise. Stress. Immunity. Inflammation. Noradrenaline. Hsp72. Fibromyalgia.

RESUMEN

Es bien conocido que la actividad física modula fuertemente el sistema inmunitario, incluyendo la respuesta innata y/o inflamatoria. Los efectos del ejercicio y el entrenamiento sobre la respuesta inflamatoria están principalmente mediados por alteraciones en el sistema nervioso simpático (SNS) y/o el eje hipotálamo-hipófisis-adrenal (HHA), aunque también por otras "señales de peligro" como las proteínas del choque térmico de 72 kDa (Hsp72). La presente revisión se centra en el papel que los "mediadores de estrés" o "señales de peligro", como la norepinefrina (NE) y la Hsp72, tienen en la activación inducida por el ejercicio en la respuesta inmunitaria innata y/o inflamatoria. Además, y basándose en la hipótesis de los efectos anti-inflamatorios del ejercicio, la actividad física habitual o entrenamiento es considerada en la actualidad como una buena estrategia no farmacológica en enfermedades inflamatorias. Prestamos especial atención a los efectos del ejercicio habitual sobre la Fibromialgia, una patología en la que parecen estar involucrados diferentes desórdenes neuroendocrinos e inflamatorios.

Palabras clave: Ejercicio. Estrés. Inmunidad. Inflamación. Noradrenalina. Hsp72. Fibromialgia.

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