Stress-induced immunosuppression and physical performance

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Abstract Sports training and competition are significant sources of stress. Elite athletes may be subject to specific exercise-related physical and mental stressors that promote the development of mood, anxiety disorders and depression. Psychological stress has been shown to adversely impact the function of the immune system and compromise host defenses against various infections. Inflammation may also play a role in neuropsychiatric diseases, including major depression. These associations between stress and inflammation are relevant. The current short review discusses psychological stress and the immune system in athletes, providing a comprehensive overview of the effect of the stress response on physical performance.

Keywords : immunosuppression, pro-inflammatory cytokines, depression, elite performance

Introduction

Psychological stress in humans causes physiological, immunological and behavioral alterations that can be maladaptive and negatively affect the quality of life^{1,2}. The interaction between stress and the immune response has been studied using various experimental paradigms. It is well documented that exhausting physical activity and intense exercise training lead to inflammatory responses and immunosuppression, whereas regular physical exercise has a positive influence³. Furthermore, other factors associated with a high level of pressure to perform well, in addition to other stressors, contribute to the high prevalence of mental disorders among elite athletes, involving a physically debilitating condition that results in total compromise of their capacity to perform and compete⁴. Recent evidence indicates that inflammation and altered immune signaling significantly contribute to the etiology of many psychiatric symptoms and disorders⁵⁻⁷. Indeed, chronic psychological stress substantially enhances the pro-inflammatory profile⁸. These associations between stress and inflammation are relevant because immune activity potently regulates mood and behavior^{5,7,9}. This article reviews psychological stress and the immune system in athletes, with a comprehensive overview of the stress response, and discusses the effect on physical performance.

Psychological stress and immune response

It is increasingly being recognized that social, psycho-

logical and physical stressors, such as anxiety, insecurity, social isolation or academic examinations, affect health^{1,2,10}. Activation of the neuroendocrine and sympathetic systems stimulates physiological pathways linking stress and negative immune outcomes.

Psychological, emotional and physical stressors stimulate the autonomous nervous system, including efferent sympathetic and vagal pathways and the hypothalamic-pituitary-adrenal (HPA) axis, resulting in the release of pituitary and adrenal hormones¹¹, with consequent immune alterations (Fig. 1). Various stressors may either increase or decrease the immune response, depending on kind and duration of stress^{12,13}. Acute short-term low-intensity stressors or moderate stressors enhance the innate and adaptive immune system, which benefits the host¹⁴⁻¹⁶, while chronic stressors inhibit the immune function and increase susceptibility to infection, tumors, hypertension, heart attacks, stroke, autoimmunity and affective disorders¹⁷⁻²². Stress hormones, such as glucocorticoids and catecholamines, are known to regulate immune cell functions, particularly at the level of cytokine secretion^{23,24}. Patients with major depression have been found to exhibit increased peripheral blood inflammatory cytokines, such as interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)- α , which have been shown to access the brain and interact with virtually every pathophysiologic domain known to be involved in depression^{25,26}. Interestingly, animal and human studies suggest that inflammatory cytokines play a pivotal role in mediating sickness-related behaviors by communicating signals of peripheral inflammation to the brain^{5,27}. For example, normal volunteers challenged with lipopolysaccharide (LPS) exhibit acute increases in the symptoms of depression and anxiety²⁸,

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Fig. 1 Brain-immune interactions. Dotted lines represent negative regulatory pathways, and solid lines represent positive regulatory pathways. CRH, corticotrophin-releasing hormone; AVP, arginine vasopressin; TRH, thyrotropin-releasing hormone; GnRH, gonadotropin-releasing hormone; ACTH, adrenocorticotropin hormone; TSH, thyroid-stimulating hormone.

and the administration of typhoid vaccine to healthy individuals induces a depressed mood, fatigue, mental confusion and psychomotor slowing²⁹). These findings suggest that the activation of the immune system can cause marked behavioral alterations, such as depression.

Immune dysfunction and physical performance in athletes

Regular moderate exercise reduces the risk of infection compared with a sedentary lifestyle; however, prolonged bouts of exercise and periods of intensified training are associated with an increased risk of infection against pathogenic agents^{3,30-32}). Athletes with intensive training schedules or undergoing endurance competitions, such as marathons, experience chronic exposure to physical and/or psychological stress-induced hormones and cytokines. Hence, the accumulation of stress in elite athletes may lead to chronic immunosuppression and consequent increased susceptibility to opportunistic infections, resulting in the impairment of exercise performance^{30,32}). It has been established that high-intensity exercise promotes

a greater release of stress-associated hormones, such as catecholamines and cortisol, and modulates the immune system. Additionally, it is widely accepted that acute and chronic exercise alters the number and function of circulating immune cells^{3,32}). Moreover, acute short-term exercise experienced at the time of immune activation may enhance innate and adaptive immune responses. In contrast, chronic or long-term exercise can suppress immunity by decreasing immune cell functions and/or increasing active immunosuppressive mechanisms (e.g. regulatory T cell pathways)³³). Chronic or intensive training can also impair the balance of Th1/Th2 cytokines³⁴), thereby modulating susceptibility to various immune-related disorders. Intensive exercise, excessive repetition of training and sports injuries stimulate local inflammation and generate a systemic inflammatory response, similar to that induced by infection³⁵). Furthermore, higher serum levels of inflammatory cytokines, mainly IL-6 and TNF- α , have been observed after marathon races or long-distance cycling^{35,36}). Although inflammation is a critical response to acute infection or injury, chronic or excessive inflammation may be detrimental to health. LPS, a potent stimulant

of cytokine release, and inflammatory cytokines signal the brain to produce changes in cognitive, behavioral and emotional functioning characteristic of sickness behavior^{5,7}). Therefore, controlling immunological alterations is important during intensive training to avoid declines in exercise performance.

In addition to exercise-induced immune responses, other factors associated with a high level of pressure to perform well and other stressors, contribute to the immune suppression and high prevalence of mental disorders observed among elite athletes. The central nervous system, endocrine system and immune system are complex systems that interact with each other. Mental disorders and physiological maladaptations have been reported to be associated with a state of chronic low-grade inflammation and immunological dysfunction. This is a physically debilitating condition that results in total compromise of the capacity to perform and compete⁴). Therefore, considering the importance of knowledge regarding the relationship between exercise and the wide range of issues in the field of neuroimmune science involved in mental health, it is essential to avoid declines in physical performance in order to improve the success of athletes.

Conclusion

Elite athletes may be subject to specific exercise-related physical and mental stressors that favor the emergence of mood, anxiety disorders and depression. It should thus be emphasized that an athlete's behavior and mental health may affect their performance. In conjunction with these considerations, athletes, coaches and medical support personnel should pay attention to the brain-to-immune and immune-to-brain communication that functions to regulate mental health and competitive performance.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this article.

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References

- 1) Glaser R and Kiecolt-Glaser JK. 2005. Stress-induced immune dysfunction: implications for health. *Nat Rev Immunol* 5: 243-251.
- 2) Segerstrom SC and Miller GE. 2004. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. *Psychol Bull* 130: 601-630.
- 3) Pedersen BK and Nieman DC. 1998. Exercise immunology: integration and regulation. *Immunol Today* 19: 204-206.
- 4) Schaal K, Tafflet M, Nassif H, Thibault V, Pichard C, Alcotte M, Guillet T, El Helou N, Berthelot G, Simon S and Tous-saint JF. 2011. Psychological balance in high level athletes: gender-based differences and sport-specific patterns. *PLoS One* 6: e19007.
- 5) Dantzer R, O'Connor JC, Freund GG, Johnson RW and Kelley KW. 2008. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci* 9: 46-56.
- 6) Evans DL, Charney DS, Lewis L, Golden RN, Gorman JM, Krishnan KR, Nemeroff CB, Bremner JD, Carney RM, Coyne JC, Delong MR, Frasure-Smith N, Glassman AH, Gold PW, Grant I, Gwyther L, Ironson G, Johnson RL, Kanner AM, Katon WJ, Kaufmann PG, Keefe FJ, Ketter T, Laughren TP, Leserman J, Lyketsos CG, McDonald WM, McEwen BS, Miller AH, Musselman D, O'Connor C, Petitto JM, Pollock BG, Robinson RG, Roose SP, Rowland J, Sheline Y, Sheps DS, Simon G, Spiegel D, Stunkard A, Sunderland T, Tibbits P Jr and Valvo WJ. 2005. Mood disorders in the medically ill: scientific review and recommendations. *Biol Psychiatry* 58: 175-189.
- 7) Krishnadas R and Cavanagh J. 2012. Depression: an inflammatory illness? *J Neurol Neurosurg Psychiatry* 83: 495-502.
- 8) Miller AH, Maletic V and Raison CL. 2009. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol Psychiatry* 65: 732-741.
- 9) Dantzer R, Capuron L, Irwin MR, Miller AH, Ollat H, Perry VH, Rousey S and Yirmiya R. 2008. Identification and treatment of symptoms associated with inflammation in medically ill patients. *Psychoneuroendocrinology* 33: 18-29.
- 10) Gibb J, Hayley S, Poulter MO and Anisman H. 2011. Effects of stressors and immune activating agents on peripheral and central cytokines in mouse strains that differ in stressor responsiveness. *Brain Behav Immun* 25: 468-482.
- 11) Charmandari E, Tsigos C and Chrousos G. 2005. Endocrinology of the stress response. *Annu Rev Physiol* 67: 259-284.
- 12) Dhabhar FS and McEwen BS. 1997. Acute stress enhances while chronic stress suppresses cell-mediated immunity in vivo: a potential role for leukocyte trafficking. *Brain Behav Immun* 11: 286-306.
- 13) Li H, Chen L, Zhang Y, Lesage G, Zhang Y, Wu Y, Hanley G, Sun S and Yin D. 2011. Chronic stress promotes lymphocyte reduction through TLR2 mediated PI3K signaling in a beta-arrestin 2 dependent manner. *J Neuroimmunol* 233: 73-79.
- 14) Anane LH, Edwards KM, Burns VE, Drayson MT, Riddell NE, van Zanten JJ, Wallace GR, Mills PJ and Bosch JA. 2009. Mobilization of gammadelta T lymphocytes in response to psychological stress, exercise, and beta-agonist infusion. *Brain Behav Immun* 23: 823-829.
- 15) Anane LH, Edwards KM, Burns VE, Zanten JJ, Drayson MT and Bosch JA. 2010. Phenotypic characterization of gammadelta T cells mobilized in response to acute psychological stress. *Brain Behav Immun* 24: 608-614.
- 16) Powell ND, Mays JW, Bailey MT, Hanke ML and Sheridan JF. 2011. Immunogenic dendritic cells primed by social defeat enhance adaptive immunity to influenza A virus. *Brain Behav Immun* 25: 46-52.
- 17) Mohr DC and Pelletier D. 2006. A temporal framework for understanding the effects of stressful life events on inflammation in patients with multiple sclerosis. *Brain Behav Immun* 20: 27-36.

- 18) Phillips AC, Carroll D, Ring C, Sweeting H and West P. 2005. Life events and acute cardiovascular reactions to mental stress: a cohort study. *Psychosom Med* 67: 384-392.
- 19) Sandberg S, Paton JY, Ahola S, McCann DC, McGuinness D, Hillary CR and Oja H. 2000. The role of acute and chronic stress in asthma attacks in children. *Lancet* 356: 982-987.
- 20) Shi Y, Devadas S, Greenelth KM, Yin D, Allan Mufson R and Zhou JN. 2003. Stressed to death: implication of lymphocyte apoptosis for psychoneuroimmunology. *Brain Behav Immun* 17 Suppl 1: S18-S26.
- 21) Stone AA and Bovbjerg DH. 1994. Stress and humoral immunity: a review of the human studies. *Adv Neuroimmunol* 4: 49-56.
- 22) Yin D, Zhang Y, Stuart C, Miao J, Zhang Y, Li C, Zeng X, Hanley G, Moorman J, Yao Z and Woodruff M. 2006. Chronic restraint stress modulates expression of genes in murine spleen. *J Neuroimmunol* 177: 11-17.
- 23) Angeli A, Masera RG, Sartori ML, Fortunati N, Racca S, Dovio A, Staurengi A and Frairia R. 1999. Modulation by cytokines of glucocorticoid action. *Ann N Y Acad Sci* 876: 210-220.
- 24) Johnson JD, Campisi J, Sharkey CM, Kennedy SL, Nickerson M, Greenwood BN and Fleshner M. 2005. Catecholamines mediate stress-induced increases in peripheral and central inflammatory cytokines. *Neuroscience* 135: 1295-1307.
- 25) Mossner R, Mikova O, Koutsilieri E, Saoud M, Ehli AC, Muller N, Fallgatter AJ and Riederer P. 2007. Consensus paper of the WFSBP Task Force on Biological Markers: biological markers in depression. *World J Biol Psychiatry* 8: 141-174.
- 26) Zorrilla EP, Luborsky L, McKay JR, Rosenthal R, Houldin A, Tax A, McCorkle R, Seligman DA and Schmidt K. 2001. The relationship of depression and stressors to immunological assays: a meta-analytic review. *Brain Behav Immun* 15: 199-226.
- 27) Capuron L and Miller AH. 2004. Cytokines and psychopathology: lessons from interferon-alpha. *Biol Psychiatry* 56: 819-824.
- 28) Reichenberg A, Yirmiya R, Schuld A, Kraus T, Haack M, Morag A and Pollmacher T. 2001. Cytokine-associated emotional and cognitive disturbances in humans. *Arch Gen Psychiatry* 58: 445-452.
- 29) Brydon L, Harrison NA, Walker C, Steptoe A and Critchley HD. 2008. Peripheral inflammation is associated with altered substantia nigra activity and psychomotor slowing in humans. *Biol Psychiatry* 63: 1022-1029.
- 30) Brolinson PG and Elliott D. 2007. Exercise and the immune system. *Clin Sports Med* 26: 311-319.
- 31) Walsh NP, Gleeson M, Pyne DB, Nieman DC, Dhabhar FS, Shephard RJ, Oliver SJ, Berman S and Kajeniene A. 2011. Position statement. Part two: Maintaining immune health. *Exerc Immunol Rev* 17: 64-103.
- 32) Walsh NP, Gleeson M, Shephard RJ, Gleeson M, Woods JA, Bishop NC, Fleshner M, Green C, Pedersen BK, Hoffman-Goetz L, Rogers CJ, Northoff H, Abbasi A and Simon P. 2011. Position statement. Part one: Immune function and exercise. *Exerc Immunol Rev* 17: 6-63.
- 33) Perry C, Pick M, Bdoelach N, Hazan-Halevi I, Kay S, Berr I, Reches A, Harishanu Y and Grisaru D. 2013. Endurance exercise diverts the balance between Th17 cells and regulatory T cells. *PLoS One* 8: e74722.
- 34) Xiang L, Rehm KE and Marshall GD Jr. 2014. Effects of strenuous exercise on Th1/Th2 gene expression from human peripheral blood mononuclear cells of marathon participants. *Mol Immunol* 60: 129-134.
- 35) Pedersen BK and Hoffman-Goetz L. 2000. Exercise and the immune system: regulation, integration, and adaptation. *Physiol Rev* 80: 1055-1081.
- 36) Nieman DC. 1997. Immune response to heavy exertion. *J Appl Physiol* 82: 1385-1394.