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Biology of Stress and Physical Performance

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Abstract

Regular physical training leads to physical capacity and optimal sports performance, and although this relationship is usually linear, the athlete's adaptation is conditioned by multiple factors: environmental, genetic and psychological. Studies have shown that between 70 and 85% of successful and unsuccessful athletes can be identified using psychological measures of personality and mood, a level higher than chance, but insufficient for the purpose of selecting athletes. The research indicates that the mood of the athletes exhibits a dose-response relationship with their adaptation to the training load; This finding has shown potential to reduce the incidence of overtraining syndrome in athletes who undergo rigorous physical training, through early detection using scales of perception of their mood and physiological measures such as the testosterone / cortisol index. Thus, the genetic and epigenetic modifications of the factors that regulate the hypothalamic-pituitary-adrenal axis and, therefore, the response to stress, have recently been associated with a detrimental effect on physical performance and early manifestations of the overtraining syndrome and the abandonment of training and competences.

Keywords: stress, psychopathology, cortisol, anxiety, sports performance

1. Introduction

Physical exercise corresponds to a set of activities of which multiple health benefits have been documented, especially in the prevention of a number of diseases [1]. It is known that regular physical training leads to a physical capacity and a certain sports performance, and in this sense, it is worth mentioning that the physical capacity and sports performance are conditioned by many factors: the intensity and type of training, the energy expenditure of the race (distance,

feeding, hydration, climatic conditions, etc.), and the condition of the athlete's health, his anthropometric and morphometric characteristics, and his psychological condition before and during the competition [2]; determining then according to the foregoing that the athlete has a complex phenotype influenced by multiple environmental, genetic, and psychological factors [1, 3].

The effects of anxiety on sports performance have been the main target of study of sports psychology in recent times [4]. Stress is a feeling of physical or emotional stress marked by an increase in the activity of the body's homeostasis systems, and anxiety is a feeling of fear, restlessness, and worry (you are neurogenic); people who frequently present these emotions may have an anxiety disorder within which a series of psychopathological entities are included [5, 6]. Anxiety can have an impact on several aspects of the sport; for example, anxiety is associated with the interruption of sports activities, less pleasure during competition, and deterioration in sports performance [6]. On the other hand, a number of researchers have associated anxiety disorders with dysfunctions of the hypothalamic-pituitary-adrenal (HPA) axis regulatory mechanisms, within which synaptic modulation through neurotransmitters, its receptors, and regulatory mechanisms takes on particular importance. It is in this instance where molecular biology and genetics have marked the understanding of these entities in the last 20 years; so today, the genetic and epigenetic factors that affect the functionality of proteins involved in the neuromodulation of the HPA axis are the target of multiple publications and research projects.

1.1. Theoretical framework

The study of anxiety, its antecedents, its relations with other psychological variables, and its consequences has been the target of theoretical and empirical attention within the psychology of sports for a long time [7]. Alterations in the concentration and the reactivated physiological stress are considered as two components of the anxious response, and an attempt has been made to establish a relationship between the cognitive and somatic consequences of these in sports performance [6, 7]. Stress is a feeling of physical tension (physiological stress) or emotional stress (neurogenic stress), and anxiety is a feeling of fear, restlessness, and worry. People who frequently present these emotions may have an anxiety disorder that includes panic disorder, agoraphobia, social phobia, post-traumatic stress disorder, obsessive-compulsive disorder, and generalized anxiety disorder; each anxiety disorder has different symptoms, but all symptoms are grouped around an irrational and excessive fear or dread [5, 6]. Anxiety is a multidimensional construct that is constituted by two main components: cognitive anxiety (i.e., worrying thoughts about one's performance) and somatic anxiety (i.e., individual physiological changes, for example, sympathetic hyperactivity, respiratory changes, changes in blood pressure, etc.) [5]. In long-distance athletes, the changing situations in the course of training and competition, together with the presence of anxiety disorders, could be caused by maladaptive fatigue syndrome (overtraining syndrome) characterized by anger, hostility, anxiety, confusion, depression, sadness, lack of energy, and apathy, which has as a consequence of a bad performance and/or the abandonment of training and skills [3, 8, 9].

The model of mental health and sports performance suggests that there is an inverse relationship between psychopathology and sports performance [9]. This model postulates that as an athlete's mental health deteriorates or improves performance it must fall or rise accordingly [3, 8].

Studies have shown that between 70 and 85% of successful and unsuccessful athletes using general psychological measures of personality structure and mood can be identified, a level higher than chance but insufficient for the purpose of selection of athletes [10]. Research indicates that responses of athletes' mood states exhibit a dose-response relationship with their training load; this finding has shown potential to reduce the incidence of overtraining syndrome in athletes who undergo rigorous physical training [3]. Other studies show a deleterious effect of stress and anxiety on sports performance in various sports [3, 4, 8, 9].

1.2. Anxiety disorders' neurobiology

The biological foundation of anxiety disorders focuses on HPA axis dysfunction that leads to an increase in axis activity and an exacerbated response mediated by the neuroendocrine system of cortisol and catecholamines [11]. An important regulator of this axis is the serotonergic system that would play a key role in the regulation of the HPA axis, regulating its function at least in two levels: on the one hand, by activating neurons that release CRF and, on the other, by regulating the activity of CRF and cortisol at the synaptic level [12]. In this setting, the serotonin reuptake (SERT, 5-HTT) regulates the serotonin (5-HT) levels at the synaptic level [13]. More than 12 different features of human behavior and other systemic pathologies have been associated with variations of the SERT gene (SLC6A4) [13, 14]. The reduced expression of the gene and the function derived from a significant variation in the region of its transcriptional control (serotonin transporter gene-linked polymorphic region; 5-HTTLPR) are linked to multiple psychopathological conditions, including anxiety disorder [15, 16]. Serotonergic neurons are located mainly in the dorsal and middle raphe nuclei (DRN and MRN) of the brain stem; the projections of these neurons release 5-HT through the entire forebrain and brainstem modulating a variety of neuronal activities [17]. The largely neuromodulatory effects of 5-HT are mediated through 14 subtypes of receptors that are grouped into subfamilies according to their primary signaling mechanism, within which is the 5-HT_{1A} receptor, which in studies in humans and rodents it has been suggested that it would participate in the etiology of anxiety and depression disorders and their treatment [18]. The 5-HT_{1A} autoreceptor is a G_i-protected coupled receptor (GPCR) and is located in the soma and dendrites of the serotonergic neurons in the raphe nuclei; its activation induces neuronal hyperpolarization and therefore a lower release of 5-HT. The 5-HT_{1A} postsynaptic receptor is expressed mainly in pyramidal neurons and in GABA (gamma-aminobutyric acid)-releasing interneurons [18]. The reduction of levels of autoreceptors and postsynaptic 5-HT_{1A} receptors has been reported in patients with social phobia, as well as in the cortical regions of patients suffering from panic disorder [18, 19].

Another important mechanism of regulation of the HPA axis occurs in the release of corticotropin-releasing factor (CRF) and its binding to its specific receptors CRF_{1R} and CRF_{2R} (corticotropin-releasing factor receptor-1 and receptor-2), which regulate and modulate the activity of the HPA axis [20]. The release of CRF from the periventricular nucleus of the hypothalamus induces the release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary and the consequent activity of this on the adrenal gland to initiate the release of cortisol [21]. Scientific evidence shows that central regulation of CRF release is mediated by the CRF-binding protein (CRF-BP), a protein that binds to CRF and binds to the CRF_{2R} receptor,

producing an additional feedback to modulation of the HPA axis [20–22]. Several studies show an increase in the expression of CRF-BP in the amygdala, anterior pituitary, and portal circulation after an increase in the release of CRF [21]. In addition, in CRF-BP knockout mice, an anxious behavior and an increase in the concentration of CRF and therefore the levels of ACTH and cortisol were demonstrated [21]. CRFR2 is suggested to play a fundamental role in recovery from the state of stress to calmness; is abundantly distributed in the raphe nuclei of the midbrain, in those that regulate serotonergic neuronal activity; and has been shown to regulate behavioral consequences of stress [23]. It is suggested that the CRF2 receptor is necessary for the proper functioning of the 5-HT_{1A} receptors in the raphe nuclei, and they are the key to a successful recovery of tension. This altered serotonergic function in knockout mice - / - for the CRF2 receptor probably contributes to its phenotype sensitive to stress and anxiety [23, 24].

Two molecules that participate in the regulation of the HPA axis and that have been reported as factors that can be therapeutic and observational targets in the pathophysiology of stress deregulation and anxiety disorders are substance P (SP) and enzyme-converting angiotensin (ECA). SP has been an important target in the study of the pathophysiology of pain; however, in the last time, it has been shown to be involved in the regulation of mood states, and studies using antagonists of its neurokinin-1 receptor (NK1R) show antidepressant effects in humans [25]. In rodents, treatment with NK1R antagonists has been shown to increase the release of 5-HT from the dorsal raphe nucleus (DRN), suggesting local interactions between SP and serotonin in the desensitization of 5-HT_{1A} receptors. This interaction represents a new element in the complex neuronal circuits proposed in mood regulation [26, 27]. Angiotensin-converting enzyme (ACE) has been one of the main molecular markers associated with physical performance in humans, especially insertion/deletion polymorphism; in recent studies it has been associated with hyperactivity of the HPA axis and increased secretion of cortisol in patients under stress [28, 29]. The presence of this polymorphism has been recently implicated with various behavioral disorders and increased mortality in patients with cardiovascular disease who present with depression [28, 30]. The proposed model for neuroendocrine regulation of the HPA axis is observed in **Figure 1**.

1.3. Genetic polymorphisms as factors associated with stress and anxiety

The 5-HTTLPR polymorphism of the SLC6A4 gene coding for 5-HTT corresponds to a genetic variant in which an insertion/deletion of a fragment of 44 base pairs (bp) occurs in the gene, where the short variant or deletion (short allele or S) results in less transcriptional activity and greater vulnerability to affective disorders (**Figure 2**) [31].

Another important study target of the serotonergic system is the 5-HT_{1A} receptor, which plays an important role in the self-regulation function of the central serotonergic system [32]. Studies of the -1019C > G variant of this gene show an association between this polymorphism and the risk of suicide, not being associated with depression. The dysfunctions of this receptor observed in 5-HT_{1A} - / - knockout mice show an increase in anxious traits and stress sensitivity in these animals [33, 35]. The presence of the -1019C > G polymorphism of this gene increases the inhibitory feedback tone of the 5-HT synapse, by increasing 5-HT_{1A} autoreceptors in the raphe nucleus

[36, 37]. Studies in animals and cell culture show that the increase in activity of the HHA axis goes hand in hand with a decrease in the expression of the postsynaptic 5-HT1A receptor [36].

The polymorphism rs1875999 (also known as CRF-BPs11) of the CRF-BP gene is produced by the exchange of nitrogenous bases in the 3'UTR position of the gene, where a T (thymine) is exchanged for a C (cytosine). The TT genotype for this variant is associated with substance dependence, alterations in eating behavior, and mood disorders [22, 38, 39]. Another polymorphism associated with stress regulation is the variant rs2267717 of the CRF2R gene located on chromosome 7, which has been linked to anxiety and mood disorders in men and women [40].

The activity of substance P in the brain as a stress modulator is carried out through its interaction with NK1R, a protein that is densely distributed in brain regions that modulate the stress response. Antagonists of this receptor have been shown to be effective for the treatment of anxiety and depression [41]. The NK1R gene is located on chromosome 2p13.1 and contains five exons. The polymorphism rs6715729 (G > A), a silent mutation located in exon 1 of the NK1R gene, has been associated with substance dependence and stress hyperactivity [42, 44].

The I/D polymorphism (rs1799752) of the ECA gene corresponds to an insertion or deletion of a 287 bp fragment in intron 16 of the gene. The presence of the deletion allele (D) has been associated with increased levels of angiotensin II and release of plasma cortisol. On the other hand, the insertion allele (I) has been related to greater resistance to fatigue. Multiple studies

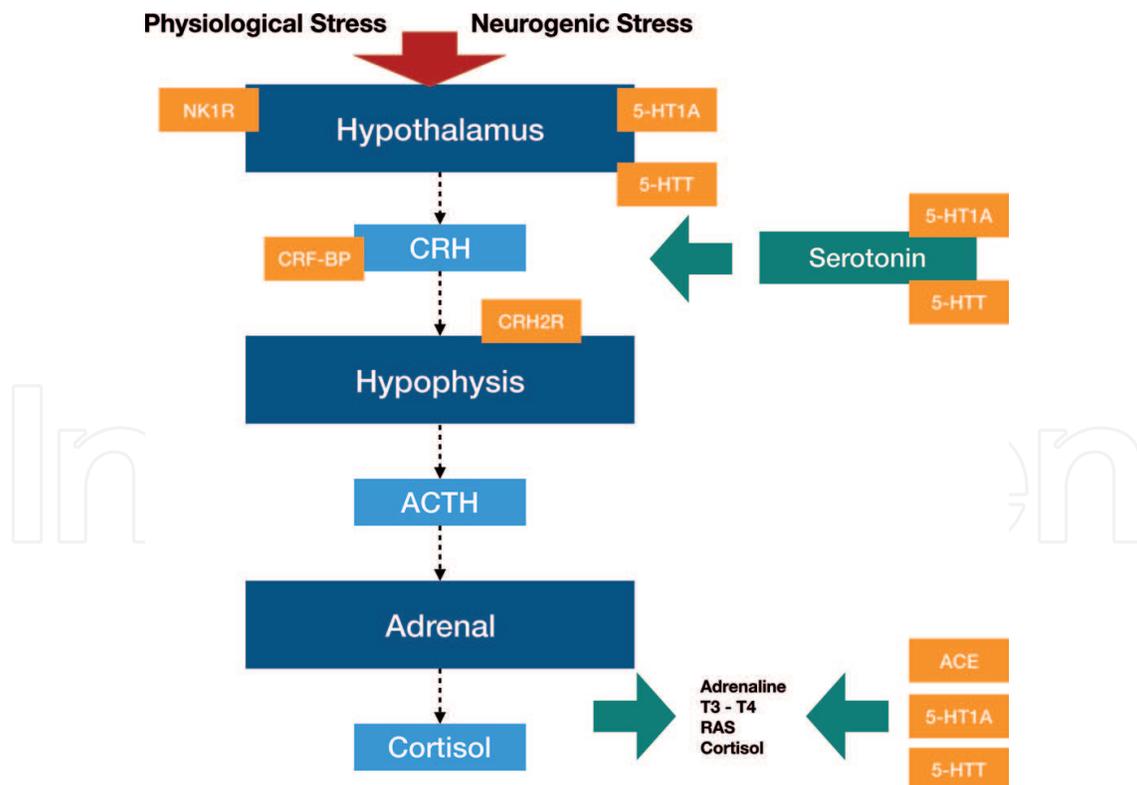


Figure 1. Hypothalamic-pituitary-adrenal (HPA) axis and proposed regulatory model for substance P (NK1R) receptors, serotonin reuptake (5-HTT), serotonin type 1a receptor (5-HT1AR), receptor corticotropin-releasing factor type 2 (CRF2R), angiotensin-converting enzyme (ACE), and corticotrophin-releasing factor-binding protein (CRF-BP), triiodothyronine (T3), tetraiodothyronine (T4), renin-angiotensin-aldosterone system (RAAS).

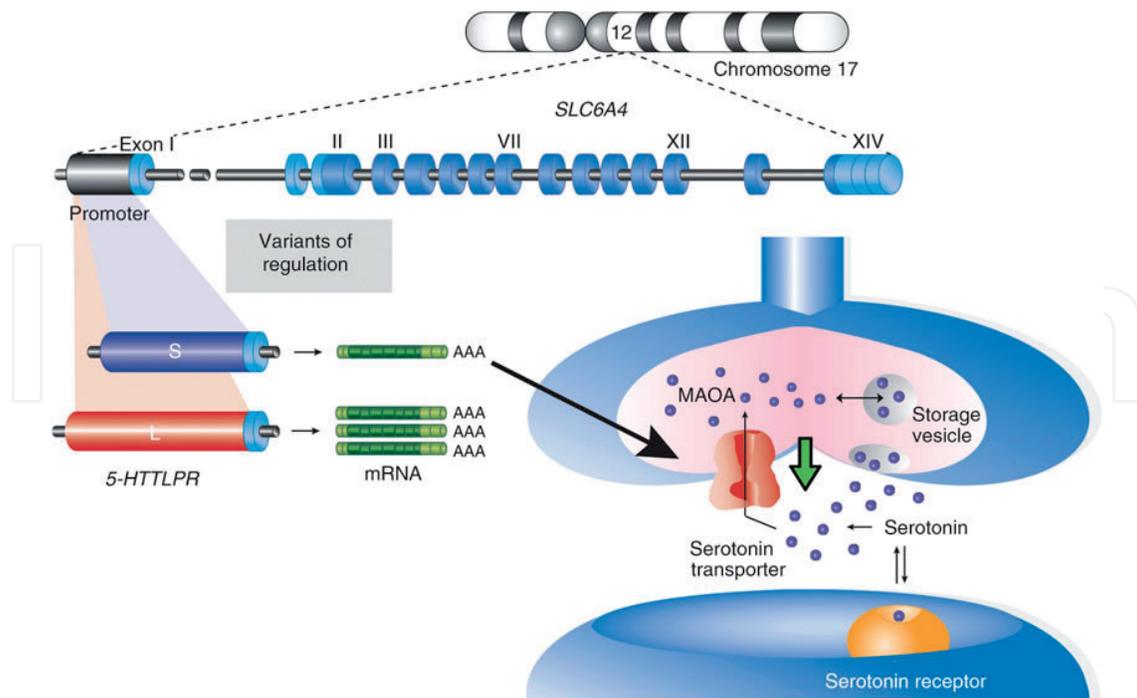


Figure 2. Effect of allelic variation of the serotonin transporter. The 5-HTTLPR (purple) short allele of the SLC6A4 gene reduces 5-HTT expression, as indicated by the green arrow leading to higher concentrations of serotonin in the synaptic cleft. The S allele is associated with personality traits related to anxiety disorder. MAOA, monoamine oxidase type A; L, long allele (red) (Adapted from Canli & Lesch (2007)).

associate RCT with sports performance, and ACE has recently been proposed as an important regulator in the secretion of cortisol and regulator of the HPA axis [29, 45]. The genotype I/I is associated with a lower activity of the ACE in plasma and tissues and the presence of the D/D genotype with a higher concentration of ACE in the plasma and a greater cardiac activity of the enzyme and also with an improvement in performance in sprint sports [46, 47]. The I allele has been associated with greater physical endurance in elite long-distance runners, rowers, and mountain runners [48]. It has been proven that the presence of the D allele increases the ejection fraction and the pulmonary systolic blood pressure [47], in addition to increasing the CRF and ACTH levels of the HPA axis [45]. Recent evidence shows that triathletes who competed in the ironman of South Africa who had higher levels of plasma ECA had a lower performance on the cycling and jogging tests [49].

1.4. Epigenetic modulation

The complex mechanisms that modulate gene expression are the focus of study at present, with epigenetics being one of the main sciences of analysis and observation. The term epigenetics has been defined as “heritable changes in gene expression that occur without an alteration in the nucleotide sequence of DNA.” Thus, an epigenetic mechanism can be understood as a complex system to selectively use genetic information, activating and deactivating various functional genes. Epigenetic modifications may involve the methylation of cytosine residues in DNA and/or changes in the structure of chromatin that regulate gene expression [47]. Methylation and histone modifications induce transcriptional changes in DNA. Along

with their susceptibility to external influences, epigenetic patterns are highly specific to the individual and may represent an important avenue of analysis to understand the predisposition toward high or low physical performance capabilities. In this context, epigenetics combined with classical genetics could broaden our knowledge of the genotype-phenotype interactions of athletes [48]. It is suggested that epigenetic effects may also play an important role in determining athletic potential and athletic performance, and in the future, they will be of importance in determining the characteristics of an athlete [48]. Currently, in addition to methylation and modification of histones, the activity of microRNAs (miRNAs) and their role in the regulation of gene expression have been included in the study of epigenetic control mechanisms. The miRNAs are small noncoding ribonucleic acids (RNAs), which play a vital role in the regulation of gene expression. They play an important role in posttranscriptional regulation through direct binding with messenger RNAs (mRNA). Currently, several reports relate the regulation exerted by miRNAs on the phenotypic characteristics of skeletal muscle and their participation in the conditioning factors of athletic performance in athletes who practice long-distance sports [49].

There are few reports of epigenetic modifications in the genes associated with stress and anxiety, and there are no precedents that link genetic and epigenetic factors with anxiety and sports performance.

2. Conclusion

The relationship between sport and mental illness in any athlete can occur in one of the three ways: firstly, sport can somehow cause or worsen a mental illness; secondly, the athlete's psychiatric symptoms can somehow attract him to sports, maybe as a way to deal with the symptoms or because the symptoms are somehow adaptable for the sport; and, thirdly, there may not be an obvious relationship between sport and mental illness. A low prevalence of psychiatric disorders in athletes was assumed for a very long time, both by health professionals and by the general public. This bad assumption could have come from a general cultural inclination to idealize the athletes and their health, which excludes the possibility of having psychiatric illnesses. Athletes were taught to be tough and to focus on physical performance and physical signs that interfere with optimal ability at the expense of mental symptoms. On the other hand, mental disorders in general, and in particular among high-level athletes, are stigmatized, and this situation is perpetuated by the general public and the media, as well as sports clubs and health professionals. This has led to a lack of research and an underdevelopment of specific psychiatric treatment facilities for athletes.

Finally, it is important to mention that several authors have tried to establish the association between genetics and sport. However, previous reports only report associations between genetic variants and anxiety disorder, with no information regarding the association between genetics, anxiety disorder, and sports performance. Our data demonstrate, in an unprecedented way, that sports performance and behavioral disorders, with genetic and epigenetic variations as markers, constitute an important factor to be taken into account when assessing the athletic performance of an athlete.

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