Relationship of the overtraining syndrome with stress, fatigue, and serotonin

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ABSTRACT

The requirements of the competitive sports have caused severe consequences in athletes involved in high level training. The changing in the aesthetic standards has leaded individuals to search for physical exercises to reduce their body mass, to increase their muscular mass as well as their aerobic fitness. It is quite common that athletes and non-athletes exceed the limits of their physical and psychological capacities causing the development of the overtraining syndrome, which is defined as the neuroendocrine disorder (hypothalamohypophysial), resulting from the imbalance between the demand of the exercise and the possibility of assimilation of the training, causing metabolic changes with consequences comprising not only the performance, but also other physiological and emotional aspects. The high level of physical, sociocultural and psychic stress are factors that contribute to such outcome, as well as to neuroendocrine changes caused by nutritional aspects that lead to serotoninergic fluctuations. Changes in the brain serotonin level can be associated to the occurrence of the physical fatigue, and this may be chronically settled, constituting one of the symptoms of the whole overtraining syndrome. Deficiencies or imbalances in neurotransmitters and neuromodulators can also be caused by severe or prolonged stress. The aim of this reviewing study was to analyze those factors that synergistically contribute to the outcome of the overtraining syndrome.

Keywords: Physical exercise. Neurotransmitters. Cerebral function.

INTRODUCTION

The focus given to the health services in controlling the sedentarism through the regular practice of exercises[1] and the changing in the aesthetic standards have lead individuals to search for a reduction in their body mass, to increase the muscle mass through physical exercises in addition to the traditional aerobic fitness. On the other hand, high level athletes suffer the harmful consequences that come from pressures provoked in the present context of the highly demanded sportive practice. It is verified that athletes and non-athletes can develop the overtraining syndrome that has as its major cause the wrong management of the training in terms of its volume and/or intensity and/or recovering pauses[2].

Primarily observed in athletes, the overtraining syndrome is characterized by metabolic changes, reduction in the athletic performance, and the response to the training in healthy individuals, incidence of bruises and viral and bacterial infections due to the fall in the immunological resistance, alterations in the mood, constant fatigue, etc. This set of signs and symptoms cause chronic fatigue in the individual, and etiology of such signs and symptoms involves the imbalance of the cerebral neurotransmitters, as well as a decrease in the serotonin levels (5-HT), that by its turn is derived from the tryptophan, an aminoacid delivered by a high-protein diet[3]. It is possible that the energetic metabolism, which is secondary to the endocrine changes, be changed in the overtraining syndrome, and thus, consequently affecting the fatigue as well.

Studies have demonstrated that deficiencies or imbalances in the neurotransmitters and neuromodulators can be caused by severe or prolonged stress[4].

Other factors can predispose individuals to the syndrome, such as a high number of competitions, monotony of the training, trainers and relatives' high expectations of outcomes, the individual structure of the personality, the social environment, preexisting medical conditions, environmental factors (altitude, temperature and humidity), and even the lack of professional guidance as to the correct practice of the physical exercises[5]. Several situations seem to be related to the overtraining syndrome, and despite its extended list of signs and symptoms, a definitive diagnosis criterion and its biochemical-metabolic mechanism are yet to be discovered[6,7].

Aiming to understand such mechanism, this reviewing work has the purpose to analyze those factors that synergistically contribute to the outcome and maintenance of the signs, symptoms, and imbalances that characterize it.

STRESS

Stress can be defined within a psychological perspective as the individual perception related to the imbalance between the physical or psychological demands, and their resources to face them in an activity that is regarded important, such as, for instance, the sportive action to the athlete[8]. It can be differentiated in *eustress*, or positive stress, characterized by the mobilization of every physical and spiritual strength in a status of strong excitement causing feelings of joy, satisfaction and happiness[9], and *distress*, or negative stress, that represents a damaging situation to the body, which can be acute whenever it is intense, and it is installed in a quite short period of time, or chronic, whenever it is gradually installed for a longer period[8].

The term *stress* means the status generated by the perception of the stimulus that cause emotional excitement, and upon the perturbation of the homeostasis, it triggers an adaptation process that is characterized among other changes by an increasing adrenaline secretion, producing several systemic manifestations with physiological and psychological disturbances[10]. It has been observed that the overtraining syndrome is generally caused by a sum of multiple stressing events in the life, such as physical training, sleep loss, exposition to stressing environments (humidity, cold, altitude, and heat), and change of residence, occupational pressures, and interpersonal difficulties. Thus, the overtraining can be understood within the Hans Seyle's classical context of the General Adaptation Syndrome (GAS)[11].

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The GAS is composed by three phases: alarm, resistance, and exhaustion. All these three phases involve hormonal responses trying to re-establish the balance. In the first phase, the body recognizes and reacts to the stressing factor(s). In the resistance phase, it is already able to make the appropriate psychological adaptations with no damages.

In terms of training, the overreaching causes a temporary decrease in the body's functioning, followed by an adaptation that overpasses the initial level of such functioning. The exhaustion phase can be reached whenever the body is under stress for a long period of time. At this point, his defense system is overloaded causing a lack of the adaptations, and his ability as to the psychological adequacy is lost for a period of time. Although much of the overtraining symptoms are similar to the resistance and exhaustion phases of the Seyle's GAS, this model is unable to clarify the very mechanism of the overtraining syndrome[12].

NEUROANATOMIC ASPECTS OF THE RESPONSE TO THE STRESS

The stress has its roots in the animal's defense reactions that come to answer to the dangers found in its environment. Different cerebral structures are involved in different defense strategies, depending on the level of the threats perceived by the individual. Trials with animal models has evidenced that in potentially dangerous situations, the structures involved would be the septo-hippocampal system and the tonsils. These structures receive information gathered by different sensorial systems, thus creating a representation of the outside world.

The septo-hippocampal system initially performs the conferee function, comparing the sensorial data synthesis at that moment with those predictions that take into account the memories stored in several spots of the Central Nervous System (CNS), as well as the action plans generated by the prefrontal cortex. Whenever there is coherence between both representations, the septo-hippocampal system continues to exert its conferee task. However, whenever it is detected a discrepancy between what is expected and what happened, the septo-hippocampal system starts in generating an inhibition of the behavior, an increasing vigilance level, driving the individual's attention to possible sources of danger. When the danger signs are clear but still are far away, the tense immobility reaction is quite common, whose neural substrate is probably the ventral portion of the periaqueductal gray matter (PGM) of the mesencephalon[13,14].

The PGM seems to be the major structure responsible by the fight and escape schedule that is analogically related to the panic attacks[13]. The PGM, together with the hypothalamus schedules the behavior, hormonal and neurovegetative manifestations of the defense reactions. It was also verified that the stimulation of the serotonergic way, which is originated in the medial nucleus of the Raphe, and preferably innervates the septo-hippocampus, determines the behaviorist inhibition that characterizes the defense[15].

NEUROTRANSMITTERS AND STRESS

Seeking to understand the neurophysiology that involves the anxiety and the stress, substances such as noradrenaline, dopamine, serotonin, melatonin, acetylcholine, and choline, glutamine, aspartate, glycine, taurine, histamine, GABA, adenosine, and inosine, cholecystokinin (CCK) have been studied. Several of these neurotransmitters are synthesized through precursors delivered by the food, and they are directly influenced by the diet. Therefore, proteins, carbohydrates, and fat, which are the major constituents of the diet, act not only as energetic substrate, but also as precursors of several neuroactive substances.

According to Prasad[16], the use of neurotransmitter precursors as dietetic supplements both in humans and in animals has presented profound effects on the neurochemistry and in the behavior. Dunn *et al.*[17], in their experimental trials, have shown alterations in the neurotransmitter levels in animals during chronic exercises, mainly in the serotonin (5-HT), dopamine, acetylcholine, and in neuromodulators such as cytokines and ammonia. Zanker *et al.*[18] observed an increase in the glutamine concentration after exercises in individuals having replete reserve of glycogen, suggesting that the higher glycogen availability into the muscle and liver during prolonged exercises stimulates the release of glutamine by those organs.

Presently, it is believed that the serotonin has a double role in the regulation of the defense behavior. The signs of danger would stimulate the defense system through the tonsils, and at the same time, they would activate the serotoninergic neurons of the dorsal nucleus of the Raphe, that will innervate both the tonsils and the PGM through different nervous ways.

The serotonin would facilitate the active defense reactions in the tonsils, and it would inhibit them in the PGM. Therefore, the serotonin-mediated responses would have an adaptation sense, as for levels of potential or distal danger it is convenient that the fight and escape behaviors are inhibited, making possible for the individual to choose the best strategies that means: careful exploration, and behaviorist inhibition[14]. Serotonin could even to increase the anxiety, acting on the tonsils in order to restrain the panic, acting on the PGM[15].

At least five different serotonin receptors were identified in the cellular membranes, each of them with a sole molecular structure, pharmacological action, and anatomic distribution into the central nervous system. These receptors have a fundamental role in the overtraining syndrome. Studies indicate that the sensitivity changes, or low regulation of the central and peripheral serotonin receptors are associated to the fatigue during prolonged exercises[19], and to the body adaptation in the resistance training[20].

More recently, a case study performed by Uusitalo *et al.*[21] reported a decreased reabsorption of the cerebral serotonin, as well as signs of clinic depression in the advanced phases of the overtraining syndrome, evidencing that the highest stress levels, as those experienced during intense and prolonged physical strength without the necessary recovery time are related to the risk of the reduced cerebral serotonin, due to the imbalance between its synthesis and degradation. Such deficiency is part of the neurophysiologic basis in the depressive mood, and a worsening in the performance, since the serotoninergic activity is particularly involved in the maintenance of the controlling process of the information and in the motor activity. As the high serotoninergic activity during the stress leads to a high level of usage of the serotonin, the continuing stress can lead to a functional lack in the production of such neurotransmitter, and the deficiency of food originated precursors can decrease its cerebral synthesis[3].

FATIGUE

Fatigue can be defined as the set of manifestations produced by the work or prolonged exercises, which has as consequence a decreasing functional capability in keeping or continuing the expected outcome[20].

Several works in the Physiology area defines the term *fatigue* as "incapacity to maintain the power outcome" both in resistance exercises and in the overtraining states[10,20,22-24]. Its etiology has brought a great interest, mainly due to its multifactor feature, and it can be divided in two components: peripheral and central fatigue. That division takes into account interactive metabolic factors affecting the muscles (peripheral fatigue) and the brain (central fatigue) upon the accomplishment of an intense physical work in athletes and other individuals[6].

In resistance sports, the overtraining syndrome is characterized by a persistent fatigue and apathy. Some researchers have been

studying such fatigue, but its nature is yet to be clearly explained. It can be muscular fatigue, and it may be related to the depression or even resulting from diseases.

In general, the muscular fatigue involves a lack of ability in generating energy in a sufficient amount o maintain a given physical activity. The specific energetic path responsible by the muscular fatigue depends on the endurance and intensity of the event. It is possible that the energetic metabolism that is secondary to the endocrine changing is altered in the overtraining syndrome, and consequently affecting the fatigue as well.

Several diseases are associated to the fatigue, including anemia, mononucleosis, hypoglycemia, hypothyroidism, and the chronic fatigue syndrome[25].

Several case reports have demonstrated that the worsening in the sportive performance is associated to persisting viral infections for prolonged periods of time[26]. Whatever may be the cause of the fatigue in the overtraining syndrome, it is clear that there are more questions than definitive answers.

SEROTONIN AND CENTRAL FATIGUE

The hypothesis that the exercise affects the protein and aminoacid metabolism has been revaluated, and they significantly contribute to the outcome in prolonged exercises[27-33]. The serotonin has an important role in investigating the development of the central fatigue, acting in the formation of the memory, in the lethargy, in the sleep and mood[33], in the suppression of the appetite[34-38], and in the alterations of the strength perception[39].

Those training induced alterations in the metabolism of the nutrients have been proposed as one of the factors that contribute to the overtraining syndrome. The "Central Fatigue Hypothesis" connects the signs and symptoms of the syndrome to similar symptoms than those that appear whenever there is an increasing concentration in the cerebral neurotransmitter serotonin[40]. It has been demonstrated that the cerebral serotonin level depends on the free in the plasma tryptophan that increases whenever the free fatty acid concentration increases. Due to the increase of the free fatty acid in the plasma levels during the resistance training, this theory proposes that the levels of cerebral serotonin increase before the presence of the overtraining[41,42].

A similar alternative explanation admits that the ramified chain of aminoacids and tryptophan compete each other to reach the brain, and to penetrate into the hematoencephalic barrier.

According to this hypothesis, the decrease in the concentrations of the ramified chain aminoacids raises the level of the free tryptophan in the plasma and of the cerebral serotonin[22].

Up to this moment, the studies performed to determine the cerebral level of the tryptophan were made in animals. Those studies with rats present uniformity[43].

Data obtained from those studies support the above outlined hypothesis that the increase in the production of the serotonin in the brain, and its major metabolite (5-HIAA) has direct relationship to the accomplishment of prolonged exercises[44,45] and to the appearance of the fatigue signs. Both theories suggest that the cerebral serotonin increases up to the point that the fatigue and other overtraining syndrome's symptoms appear.

This is not the only neurotransmitter associated to the perception and development of the fatigue, but it is the one that is under study[46-48]. However, the big existing discrepancy between experimental protocols makes it difficulty to analyze the results. Even so, there are concrete evidences of the important role of the serotonin in the performance during prolonged exercises[20].

THE OVERTRAINING SYNDROME

In the medical literature there are several meanings to the overtraining syndrome that generally are associated to the overloaded training, called overreaching. The overloaded training is related to the hard training for a few days, followed by a short recovery period that in this case is essential. The physiological homeostasis of the body needs to be stimulated through the intense training in order to imrove the sportive performance capability. This process is called super-compensation.

Several days of intentionally heavy training are followed by a lighter training and resting for a few days, in order to reach the super-compensation and the performance climax. It is essential that the necessary time to achieve the super-compensation is recognized. If an athlete is not yet adapted before a new stimulus is given, there will be a progressive and higher imbalance[49].

The result is the overreaching, that is a set of transitory symptoms, signs and changes that appear during the heavy training, and they are diagnosed through tests.

Both the overreaching and the overtraining syndrome cause a decrease in the performance, as well as similar signs and symptoms, but they have different recovery time. The overreaching needs two or three weeks to re-establish the sportive performance of the athlete, but in the overtraining syndrome, this process takes months or even years[7,50].

The overtraining syndrome affects a considerable percentage of individuals involved in and resting intensive training programs. It is estimated the incidence rate is of 7% to 20% athletes per season[51-53]. Studies indicate that their signs and symptoms appear in more than 60% distance runners along their sportive carrier[51], and the syndrome was developed in more than 50% of the American professional soccer players along five months of competitive season, 21% of an Australian swimming team after six months of training for a national competition, and 33% of an Indian basketball team during a 6 weeks of a training period[54].

It is defined as a neuroendocrine disorder (hypothalamohypophysial) that results from an imbalance between the demand of the exercise and the functional capability, and it may be aggravated by an inadequate recovery, thus causing a decrease in the sportive and athletic performance, the incidence of bruises, neuroendocrine changes, alterations in the mood, constant fatigue, among other symptoms[8].

Athletes of all performance levels may develop the syndrome, and a relevant number of signs and symptoms have been associated to it. Fry *et al.*[49] listed more than 200 in their overtraining review in 1991[55].

But despite such extended list, up to this moment there are not yet quite established criteria[8], maybe due to the lack of a culture implying in a systematic evaluation routine for sportsmen.

The malfunction or imbalance in the autonomous nervous system was presented as the reason for the signs and symptoms of the syndrome[10]. There are several but not well evidenced theories on the origin and pathophysiological alterations of the overtraining syndrome. The alterations in the noradrenergic, serotoninergic and/or dopaminergic activity in the brain (specifically in the hypothalamic and suprahypothalamic regions) can cause hypothalamic disorders, but the function of the alterations in the neurotransmitters during the syndrome is yet unknown[56]. There is also lack of sufficient evidence for the hypothalamohypophysial-adrenal axle (HPA) alterations, as well as for the alterations in the hypophysial sensitivity. A quite intensive training period during a training program seems to reduce the adrenocorticotropic (ACTH) and the growth hormone[57] concentrations.

Peripheral alterations related to the overtraining syndrome can cause changing in the secretion of hormones and in the sensitivity of the peripheral endocrine glandules. These alterations also include a decreasing glycogen reserve, decreasing neuromuscular excitability, alteration in the adrenoreceptors sensitivity, and changing in the immunological function[7].

The only effective treatment is the prolonged rest that makes impossible to the athletes to participate in competitions, and may

lead to a loss of motivation, and even to abandon the sports. Thus, the best way to avoid the syndrome to manifest is the prevention.

Since up to this moment there are no physiological or biological markers that allow an early diagnosis of the syndrome[12], the use of instruments that allow to find measurements to the mood[12] have demonstrated effectiveness in detecting the initial signs of the overtraining syndrome, preventing its complete development, and avoiding the inactivity period[58,59].

It is considered highly susceptible individuals to develop the syndrome:

- Highly motivated athletes;
- Athletes presenting high outcome;
- Athletes coming back early to the training before their complete recovery;
- Self-trained athletes and non-athletes;
- Individuals with no qualified technical guidance[60].

The overtraining can be distinguished in basedovoid (sympathicotonic) and Addisonian (parasympathicotonic). The first one is characterized by the predominance of stimulation processes and an intense motor activity. The recovery after loads is insufficient and late.

This form of overtraining is easy to be diagnosed, since the athlete feels sick, and there are several indicator signs and symptoms, such as: anorexia, loss of body weight, sudoresis, headache, lack of energy, increase in the basal heart rate and in the blood pressure, irritability, insomnia, inappetence, difficulty to concentrate, arrhythmia, increase in the acute response to the catecholamines, adrenaline, and noradrenaline, etc.[10]. It is a prolonged response to the stress that precedes the exhaustion, and attacks younger athletes in anaerobic sports involving speed, strength and power.

Excessive amounts of training, anxiety and accumulation of competitions with insufficient recovering intervals are generally mentioned as factors that cause sympathicotonic overtraining.

The anxiety of being obliged to produce maximal strength in the everyday train, and to compete in a great amount of events can be emotionally stressing, particularly in quite anxious athletes[61].

The parasympathicotonic originated syndrome is characterized by predominant inhibition processes, physical weakness, and lack of motor activity. The athlete may express that he is not feeling tired, but he is not able to mobilize the necessary energy to participate in a sportive event. The resting athlete may present no symptoms, but these symptoms can supervene in a furtive and sudden way. It may appear depressive and neurohormonal manifestations, apathy and low resting heart rate[62].

This kind of syndrome affects highly trained athletes in aerobic sports, such as the triathlon, long distance swimming, marathon, and road cycling, and it is quite common in older individuals with a longer sportive life[5,6].

Several physiological alterations that occur in the overtraining syndrome have been described, but up to this moment, none of them was considered solely reliable to be accepted as a diagnostic test[63,64]. Some of them are: decrease in the maximal heart rate[57,65-67], alterations in the lactate concentration in maximal strength or in its threshold[64], reduction in the night excretion of the noradrenaline, increase in the serum cortisol (catabolic action), decrease in the testosterone (anabolic action)[7,64,68], and alterations of the kinase creatine and urea[69].

CONCLUSIONS

The overtraining syndrome has a great relevance within the sportive field, mainly for elite athletes who are searching to overcome their limits, and those who submit themselves to a physical activity practice with no specialized guidance.

The early diagnosis and prevention of the development of the whole situation, as well as to propitiate the maximum performance achievement demands in the full knowledge of the physiological and psychological processes involved in the physical adaptation before the stimulus he is submitted to.

External factors such as stress, interpersonal and environmental relationships have significant importance in this context, and important parameters must be considered in evaluating situations whenever the overtraining is observed.

The overtraining syndrome is defined as a neuroendocrine disorder, in which the serotonin seems to have an important role in the physiology, along with other neurotransmitters. But the study needs to be deepened together with nutritional aspects related to the tryptophan and the aminoacid levels of the ramified chain that can be involved in the central fatigue.

The development of the overtraining syndrome involves several internal (biological) and external (environmental) factors that must be identified and controlled in order to avoid it is settled down.

Athletes, individuals involved in physical activities and rehabilitation, trainers, sports and health scientists would be benefited by the discovery of a simple, specific and sensitive test that allow to make the diagnosis of the syndrome. On going studies are focused to validate instruments in the early detection of the overtraining syndrome in Brazilian athletes and non-athletes.

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