Review DOI: 10.5604/20831862.1019662 Biol. Sport 2012;29:255-261

EFFECT OF EXERCISE ON THE LEVEL OF IMMUNOGLOBULIN A IN SALIVA

Accepted for publication 23.09.2012

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ABSTRACT: The aim of this paper is to describe the structure, production and function of secretory immunoglobulin A (sIgA) as well as changes of its concentration caused by exercise of various intensity and duration. Immunoglobulin A is the main class of antibodies present in the body secreted fluids such as saliva, tears or mucus from the intestines. It is generally recognized that IgA, due to its dominance in the immune system of mucous membranes, is the first line of defence against harmful environmental factors. The secretion and composition of saliva depends on the activity of the sympathetic and parasympathetic nervous systems. Physical activity, stimulating the autonomous nervous system, may reduce the amount of saliva and/or inhibit its secretion. The relationship between physical activity and the suppression of the immune system is not fully understood, but it is known that moderate intensity exercise can improve immune defences, while extreme effort can reduce them by creating an increased risk of upper respiratory tract inflammation (URTI). In athletes, the lowest risk of upper tract infection was connected with the case of moderate intensity exercise. It is now believed that the relationship between exercise volume and the risk of URTI has the shape of the letter "J". This means that both too little and too much physical activity may increase the risk of upper respiratory tract infection. Training optimization and correct balance between exercise and rest periods may reduce the risk of adverse changes in the immune system and decrease the frequency of URTI.

KEY WORDS: immunoglobulins, secretory IgA, exercise

Introduction

Immunoglobulins are a heterogeneous group of proteins of the immune system. All immunoglobulins are composed of four polypeptide chains: two light (L) and two heavy (H), joined by disulfide bonds in macromolecular compound. Numerous studies of the molecules of the immunoglobulin distinguished the variable part (Fab), responsible for recognition and binding of epitopes, and the constant part (Fc). The structural differences within the variable part determine the antigenic specificity of immunoglobulins, while the structural differences observed in the constant part determine their effector functions, associated with the activation of the complement [13].

Based on structural differences in constants heavy chains, immunoglobulins have been divided into five classes (isotypes): IgG, IgA, IgM, IgD, and IgE, in which there are different types of the heavy chain: γ, α, μ, δ, and ε, respectively. The result is that individual proteins differ in physicochemical and biological properties. The IgG and IgA classes of immunoglobulins are divided into subclasses: IgG1, IgG2, IgG3, IgG4, and IgA2, IgA1, respectively.

Immunoglobulin G, the basic immunoglobulin in the blood, appears during the first and second immune responses by activating the complement system and macrophages. It is the only class of antibody that has the ability to pass through the placenta.

Immunoglobulin A is the main class of antibodies present in the body secreted fluids such as saliva, tears or mucus from the intestines. The meaning of IgA in serum is still unclear. It was postulated that this immunoglobulin performs a complementary role in the neutralization of the pathogens, which defeated the mucosal barrier, as well as macrophage activation, and removal of immune complexes formed with the participation of this isotype [12].

The immunoglobulin M contains a μ heavy chain, which appears together with the peptide J, responsible for the initiation of polymerization to the form of pentamer IgM. Due to the large number of antigen binding sites, the IgM molecule binds very strongly with each pathogen. After binding to the antigen, the Fc portion activates the complement system, leading to the destruction of the pathogen. The immunoglobulin M is the class of antibodies, which appears as the first line of defence in the response to an antigen.

The immunoglobulin D is present on the surface of mature B cells and, in trace amounts, in various body fluids. The function of this class, however, is not entirely clear. The immunoglobulin E, after antigen binding, stimulates the mast cells, which in turn activate eosinophils involved in the elimination of parasites.

In recent years, much research was aimed at explaining how the exercise affects the immune system. It is known that stress induced by sport training causes changes in the lymphatic system, but so far it is not sufficiently clear what other changes occur in the human body.

The human lymphatic system keeps specific biological balance, thereby allowing the body's adaptation to the environment. It also has the ability to neutralize damaging agents - stressors. In a healthy subject, the properly functioning immune system comprises lymphatic cells (humoral immunoglobulins) and cells outside the lymph system (components of complement). The correct functioning of these elements determines the proper physiological state of the immune system, and thus a healthy organism.

Structure of IgA

The history of the discovery of IgA goes back to the 1950's, when Slater et al. [63], during the study of globulins, discovered that one of the serum protein fractions demonstrates a particular characteristic during electrophoresis and has specific antigenic properties. In 1955, all these observations led to revealing the presence of a new, previously unknown, class of immunoglobulins.

It is generally recognized that IgA, due to its dominance in the immune system of mucous membranes, is the first line of defence against harmful environmental factors. It is believed that the concentration of secretory IgA (sIgA) varies depending on the physiological state and physical activity.

In each IgA molecule, there is an α chain, which can distinguish a variable part, lying in the N-terminal segment, and a fixed part, comprising the C-terminal segment, organized into domains: C_H1, C_H2, C_H3 as well as the hinge region, and the 18-amino acid peptide, called the tail section. This section is capable of covalent binding to the J chain and the formation of polymers. The immunoglobulin A is secreted in two forms: as a monomer and a dimer. In serum, IgA exists mainly in the monomeric form.

The secretory immunoglobulin A is synthesized locally by subepithelial plasma cells - pIgA. After creating a complex with pIgR (transmembrane segment), it undergoes endocytosis and is transported in endosomes to the luminar side of epithelium [50,56].

Until recently, it was thought that monomeric immunoglobulin A takes the shape of the letter Y [28], but Bohem et al. [5] presented a different structure of this immunoglobulin. They found that the area between the two antigen-binding elements is located at the ends of the Fab arms and is much higher in IgA1 (23 nm) than in IgG (13 - 16 nm).

The immunoglobulin A class is characterized by considerable heterogeneity. There are two subclasses: IgA1 and IgA2, which differ in structure and distribution, and occur in different proportions in tissues and organs of the human body [28,36,40]. The existence of particles IgA2m(1) and IgA2m(2) [39] was established in the 1970's. Subsequent studies confirmed the existence of a third variant isotype: IgA2(n) [9]. Each of these forms occurs in varying degrees of polymerization.

The difference between the subclasses of IgA applies only to 22 amino acids within the hinge region [41]. In the IgA2 molecule, there is a 13-amino acid deletion in this region, however the hinge region of the molecule IgA1 contains from three to five linked oligosaccharide domains, which are not found in IgA2. The immunoglobulin A1 is characterized by the presence of two oligosaccharide chains, connected by N-glycosidic bond in the domains: C_H2 (Asn263) and C_H3 (Asn459) of the constant α chain. The IgA2 contains two additional oligosaccharide chains, connected by the N-glycosidic bond to asparagine residues of C_H1 (Asn166) and C_H2 (Asn337) domains. The IgA2m(2) and IgA2(n) are the fifth N-linked region of C_H1 domain (Asn211) [60]. The increased number of linked oligosaccharide chains, in particular mannose residues, acts as a soluble receptor of bacterial type 1 fimbriae, weakening bacterial adhesion to epithelial cells [70].

The section linking monomer subunits - J chain - is a 137 amino acid peptide containing eight cysteine residues, which forms disulfide bridges with the tail section. This chain is involved in regulating the degree of polymerization of locally synthesized immunoglobulins, as well as their translocation through the epithelium onto the mucosal surface. The transcription of the gene encoding the J chain is located on chromosome 4. The main places of synthesis of this peptide are lymphoblasts and plasma cells found in lymphoid tissue, associated with the mucous membranes [26].

The secretory fragment (SC) is a glycoprotein composed of five domains (D1-D5), stabilized with one or two disulfide bridges. This part is synthesized by the epithelial cells of the digestive, respiratory, and genitourinary systems. The SC fragment, located in the cell membrane of the enterocyte, is the extracellular part of the receptor for polymeric forms of immunoglobulin, and may be a component of the secretory IgA and IgM immunoglobulins or it may exist as a free form [50].

The unique ability of the immunoglobulin A is polymerization, determined by the presence of the tail section, located in the area of C-terminal. It is known that the polymerization also requires the J chain, which probably causes conformational changes. Yoo et al. [71] observed that mutation of cysteine residues in the positions 15 and/or 79 in the J chain prevents the formation of IgA dimers. Another factor enabling the polymerization is the presence of enzymes catalyzing the reactions of forming disulfide bridges and covalent interactions in the tail sections as well as non-covalent interactions between the C_H2 and C_H3 domains of the monomers.

Production of immunoglobulin A

The immunoglobulin A (IgA) is the major glycoprotein described in recent years. It is produced by mature B cells [36] in the blood and

is secreted into bodily fluids [31], such as saliva, tears, as well as nasopharyngeal, bronchial, intestinal and urogenital secretions [21, 38], and it penetrates freely through the mucous membranes.

The human body produces two types of immunoglobulin A: serum and secretory. Their total daily production is 66 mg per kg body weight [38,40]. The immune response of the IgA is triggered by many pathogens and is mainly induced locally in the mucous membranes.

The IgA secretion into saliva is stimulated by various factors such as stress or physical activity [14]. The secretion and composition of saliva depends on the activity of the sympathetic and parasympathetic nervous systems. The physical activity, stimulating the autonomous nervous system, may reduce the amount of saliva and/or inhibit its secretion [58].

The use of monoclonal and polyclonal antibodies against the IgA subtype IgA1 makes it possible to estimate the level of IgA1 and IgA2. The highest concentrations of immunoglobulins IgA1 was found in the nasal mucosa, where it represents 95%, and the highest concentration of IgA2 was observed in the colon (62%), compared to the total concentration of both subtypes of IgA [6,29].

In addition to changes in the amount of saliva, physical activity may also induce changes in concentration of some of its components, such as immunoglobulins and α-amylase [4]. Numerous studies have demonstrated an increased level of the total protein in saliva after strenuous exercise [8,24,25], explained by the higher activity of β-adrenergic receptors in the salivary glands [67]. Several authors have noted a significant decrease in the concentration of the salivary immunoglobulin A after a maximal intense physical exercise [16, 48,68], but the sIgA level did not change after the moderate exercise load [2,46].

The role of IgA in the human organism

It is well known that the salivary IgA is the predominant protein in mucosal humoral response, and it plays a key role in neutralizing toxins and removing pathogenic microorganisms, however, it does not reduce the number of symbiotic bacteria found in human intestine [36]. The secretory IgA is responsible for the agglutination of bacteria, inhibition of bacterial adhesion to epithelial cells of mucous membranes, the absorption of food antigens as well as neutralization of viruses, toxins, and enzymes produced by the microorganism [30], and neutralization of exotoxins [35].

It was also shown that the sIgA has the ability to neutralize and inhibit the intracellular release of virus particles. This occurs during transport of the antibody by epithelial cells with the secretory component (SC), which is a part of the transmembrane receptor protein of the IgA [27]. It has also been demonstrated that the anti-inflammatory role of the dimeric form of the IgA is associated with intracellular neutralization of bacterial antigens (e.g. lipopolysaccharide), involved in the proinflammatory activation of intestinal epithelial cells [18].

The secretory immunoglobulin A is a relatively small particle, secreted in large amounts, and it represents 70% of the total immunoglobulin produced by mammals. The IgA secreted by the intestinal mucosa induces changes leading to the preferential development of symbiotic bacteria in the gastrointestinal tract, which supports the mutualism between microorganisms, although this mechanism is still little understood [7]. The surface of the mucous membranes of the digestive, respiratory, and genitourinary systems of an adult human is more than 400 m^2, and is the major route of presentation for infectious, potentially harmful agents, therefore, the immunoglobulin A plays a key role in defence against pathogens.

The salivary immunoglobulin is the first line of defence to prevent colonization and development of pathogens, thus protecting the organism against infection [4,54]. The decreased level of the salivary immunoglobulin A is associated with an increased incidence of upper respiratory tract illness [42], thus it may be a useful biological marker of clinical predisposition to diseases of the upper respiratory tract [15].

The incidence of upper respiratory tract inflammation (URTI) is associated with sport training, although the nature of the upper respiratory tract infections is not fully explained, particularly among competitive athletes. Although the URTI is the most common cause of the admittance for the elite athletes in the sports medicine clinics, the question arises whether the analyzed respiratory diseases are actually caused by an infection, or whether they reflect other inflammatory conditions associated with exercise. Cox et al. [10] discovered the fundamental genetic polymorphism with high expression of genes encoding proteins with proinflammatory properties, such as interleukin-6. This cytokine increases the frequency of respiratory symptoms, although the same studies also showed that infections were not the only cause of the incidence of upper respiratory tract illness.

It is believed that the upper respiratory tract infections, caused by increased physical activity, are especially common among athletes in endurance sport disciplines. It has been shown conclusively that immunosuppression resulting from physical exercise increases susceptibility to infection, the symptom associated with a subdued immune system [49].

In recent years, there were many reports on the relationship between changes in the immune system and the risk of URTI in both active and sedentary individuals. It was found that there are differences between these groups in the incidence of respiratory disease frequency and in the IgA concentrations in secretions of the body, indicating the relationship between physical activity and the incidence of URTI [47,55]. In subjects, both who trained and who did not train, there is a negative correlation between the salivary IgA concentration and the risk of URTI [19,20]. It has been shown conclusively that prolonged exercise resulted in large decreases of the salivary IgA concentrations [22,33,34,55,65], while the increase in the salivary IgA occurs in response to short-term or moderate exercise [19,20,31]. Increasing of the salivary IgA concentration, observed after moderate exercise, can help to reduce susceptibility to URTI [1].

It is believed that the infectious causes of URTI include bacterial infections, which represent about 5% of cases, while the viral illness

ranged from 30 to 40% of cases. The bacterial and viral pathogens identified in these studies suggest that infections are caused by typical pathogens, the same as in the entire population of the upper respiratory tract infections [61].

It was noted that in athletes, the exposure to stressors of biological, physical, and psychological origin can induce neurological and endocrine changes, which affect the immune system as well as the increased incidence of symptoms of various illnesses, including respiratory diseases [51]. However, there is not enough direct evidence to support the contention that these are the mechanisms, specific to athletes, associated with susceptibility to infection or upper respiratory tract illness.

The body's response to exercise is also associated with regulation of the production and secretion of cytokines. Cytokines play an important role in the modulation of changes in the immune system during and after exercise, by increasing the risk of infection and the presence of local inflammation in the organism [66].

The effect of physical activity on the salivary IgA concentration

It is well known that a single bout of exercise or regular training may result in numerous changes in the immune system of athletes [23, 59]. Orysiak et al. [52] discovered exercise-induced decrease of white blood cells, which plays a role in defence against bacterial and viral infections. It has been confirmed that the salivary IgA level may depend on both the intensity and duration of training as well as the type of physical activity [31,43,59]. On the other hand, there were no changes in the concentration of IgG, IgA, and IgM in serum of young men participating in a 16-week continuous running training [57].

Most of the research shows that intensive, repetitive exercise causes a decrease in the salivary IgA levels and an increased susceptibility to upper respiratory tract infection in athletes [55]. In marathoners participating in a race over a distance of 160 km, Nieman et al. [47] showed that the secretion of the immunoglobulin A in saliva decreased by 10%. The same authors stated that 25% of the runners had developed URTI within two weeks after the end of the race. Gleeson et al. [22] presented the results, which show that long lasting training caused a decrease in the concentration of immunoglobulin A in saliva and an increase in the frequency of URTI. On the other hand, Francis et al. [20] have shown that, in competitive swimmers, the concentration of the salivary immunoglobulin A was significantly higher than in untrained persons. In addition, Wang et al. [69] reported that regular 12-week Tai chi chuan practice improved immune system function, and they demonstrated a lower frequency of incidence of URTI after training compared with sedentary persons.

Laing et al. [33], who studied twelve 28-year old athletes, reported an increase of the salivary IgA level from approximately 400 $mg \cdot l^{-1}$ to 450 $mg \cdot l^{-1}$ immediately after training, whereas two hours after the end of training, the IgA concentration was reduced to about 320 $mg \cdot l^{-1}$. These results confirm the research conducted by Steerenberg et al. [65] who showed a significant decrease in the salivary IgA concentration in the group of triathletes after a long lasting exercise. Also Libicz et al. [34], who studied athletes practicing triathlon, found a significant decrease in the salivary IgA level after the competition. On the other hand, Slivka et al. [64], studying eight cyclists during 21 days of training, did not observe any changes in the concentration of sIgA in relation to its concentration on the first day of training. A moderate physical effort reduces the risk of infection due to the positive changes taking place in the immune system [53] by increasing the immune response to pathogens [37].

Farzanaki et al. [17] demonstrated that in female gymnasts, aged from 11 to 13 years, low-intensity exercise increases the amount of the salivary immunoglobulin A secretion. On the first day, these gymnasts have been training only in the morning, while on the second day they trained twice, in the morning and in the evening. The physical effort reached the intensity of 60 to 80% of maximum heart rate. The immunoglobulin A concentration on the first day before training had a value above 5.0 $mg \cdot dl^{-1}$. Immediately after training, it increased to about 11.5 $mg \cdot dl^{-1}$, and two hours later, it decreased below the initial value (3 $mg \cdot dl^{-1}$). On the second day after the morning training, the IgA concentration in saliva was 4 $mg \cdot dl^{-1}$ and it increased to 5 $mg \cdot dl^{-1}$ immediately after training, however before and after the evening workout the IgA concentrations were 6.2 and 5.0 $mg \cdot dl^{-1}$, respectively.

Cunniffe et al. [11], leading research on elite rugby players throughout the season, showed that the largest decreases of the sIgA concentration occurred in the months with the highest exercise loads, while at the same time there was an increase in the incidence of URTI.

It is unclear what is the effect of exercise at maximal intensity but short duration on the salivary IgA level. Research, conducted on seven athletes subjected to 30s Wingate test of arms and legs, shows that the maximal effort during leg cycling caused a small increase in the salivary IgA to the value of 112 ± 32 $mg \cdot l^{-1}$ compared with the value before effort (105 ± 39 $mg \cdot l^{-1}$), but arm cranking caused a significant increase of the IgA levels, from 125 ± 81 to 147 ± 69 $mg \cdot l^{-1}$ [25].

The relationship between the concentration of salivary IgA and the URTI risk in trained and untrained subjects has been repeatedly confirmed. It was noted that the risk of URTI varies depending on the volume and intensity of exercise. During prolonged exercise at a high load level, the IgA decreased, and simultaneously the risk of upper respiratory tract infection increased. However, moderate short-term exercise increases the level of sIgA and decreases the risk of URTI. Klentrou et al. [31] found that the level of salivary IgA after exercise increases after the moderate load and after regular exercise. Fondell et al. [19], who studied 1509 subjects divided into groups of men and women aged 20-60 years, active and physically inactive, have found that physical activity reduces the incidence of upper respiratory tract illness. The risk reduction was observed in both smokers and nonsmokers, and in men and women, regardless of age.

It has been shown that regular exercise can cause favorable changes in the immune system in the elderly, as reported by Akimoto et al. [1] who studied a group of healthy subjects (18 males and 27 females) over 60 years of age, subjected to regular (twice a week) training for one year. Initially, the concentration of immunoglobulin A in saliva was 24.7 $\mu g \cdot ml^{-1}$, while after the fourth month there was an increase to 27.2 $\mu g \cdot ml^{-1}$, and after 12 months of physical activity the concentration of sIgA was 33.8 $\mu g \cdot ml^{-1}$.

The relationship between physical activity and the suppression of the immune system is not fully understood, but it is known that moderate intensity exercise can improve immune defences, while the extreme effort can reduce them by creating an increased risk of URTI. Nieman [43] showed that in athletes the lowest risk of upper tract infection was connected with the case of moderate-intensity exercise. It is now believed that the relationship between the volume of exercise and the risk of URTI has the shape of the letter "J". This means that both too little and too much physical activity may increase the risk of upper respiratory tract infection [45]. Although exercise-induced decrease in defence function of the immune system seems to be transitory, it could be suggested that immediately after training or hard exercise loads the competitors should be isolated from large groups of people [3]. On the other hand, training optimization and correct balance between exercise and rest periods may reduce the risk of adverse changes in the immune system and decrease the frequency of URTI.

ACKNOWLEDGEMENTS

This work was supported by Ministry of Science and Higher Education (grant PB 75 from the Józef Piłsudski University of Physical Education, Warsaw, Poland.

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