The effect of tobacco smoke ingredients on immunity with special reference to chronic obstructive pulmonary disease

Uticaj sastojaka duvanskog dima na imunski sistem sa posebnim osvrtom na hroničnu opstruktivnu bolest pluća

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Introduction

Tobacco smoke consists of several thousand toxic and carcinogenic substances 1. Ingredients of tobacco smoke have numerous extremely harmful effects on human health and are related to the occurrence of various diseases such as respiratory infections, chronic obstructive pulmonary disease (COPD) and lung cancer 7. The increased incidence of these diseases in smokers is possibly caused by the effects of tobacco on the function disorder of the immune system. Whereas the acute effect of smoking on the function of the immune system is less known, chronic exposure to tobacco ingredients causes a decreased function of T-lymphocytes 3.

Nowadays it is considered by the World Health Organization (WHO) that smoking cessation is the single most effective and cost effective way to reduce exposure to COPD risk factors 4.

Tobacco smoke might affect the function of the immune system 5. Numerous studies in vitro and in vivo have demonstrated so far that there is an immunosuppressive effect of tobacco smoke on T and B-lymphocytes 6, 7.

During smoking, a smoker inhales both the smoke and the particles. Among the particles inhaled, a thousand of ingredients are taken in the most important of which are nicotine, various carcinogens, metals and others. Nicotine is the main immunosuppressive ingredient of tobacco smoke 6. Numerous investigations have demonstrated that tar and nicotine have an extremely toxic effect on the immune system 8. The effect of tobacco smoke ingredients on immunity depends on the doses of substances, as well as on the duration of exposure.

Investigations of effects of tobacco smoke on the function of the immune system

Various experimental investigations have been carried out warning that smoking imposes the occurrence of various diseases due to an impaired function of the immune system 6, 8. Numerous investigations have also been carried out to explain this phenomenon 6, 7.

Active smokers suffer from influenza more frequently and have the lowest concentration of antibody titre against influenza virus 9, 10. In order to recognize the difference in the immune responses of smokers and non-smokers, their reactions in the production of antibodies after vaccination against hepatitis B virus (VHB) have been studied 11. Active smokers have a significantly lowered immune response to the applied vaccine than non-smokers, because their production of antibodies against VHB is significantly lower than in non-smokers. A significant effect of the intensity of smoking on the function of the immune system has been confirmed.

The first exposure to cigarette smoke might start in utero, when a fetus is exposed to blood-borne metabolites from a mother. Neonates and infants might be exposed passively to tobacco smoke at home if a sibling smokes. Children under 2 years, who are passively exposed to cigarette smoke, have an increased prevalence of respiratory infections and are at a greater risk for developing chronic respiratory symptoms later in life 12.

By investigating concentrations of immunoglobuline in the blood of children, the effect of smoking parents on the immunity of children, exposed to tobacco smoke at home, is studied at the same time 13. It has been proven that the chil-
dren whose parents are smokers have a disbalance in the function of the immune system with a significantly lowered production of total immunoglobulin G (IgG) as compared with those whose parents are non-smokers. Studies have not confirmed, however, a significant effect of passive smoking on the concentration of other immunoglobulins. The survey of parents who were active smokers have shown that their children have more frequent respiratory and allergic diseases than the children who live in the environment without tobacco smoke 13.

Active smokers might have the decreased values of serum immunoglobulins except for IgE which has an increased concentration 14.

There is a higher risk of contracting infections with human immunodeficiency virus (HIV) in active smokers than in non-smokers 15.

The mechanism of the action of ingredients of tobacco smoke on immunity has not been fully explained yet.

There is a close link between the functions of the neuroendocrine and immune systems because they both receive signals through substances such as cytokines and hormones which act as neurotransmitters and exert influence on the receptors of both systems. Nicotine from the air ways is quickly absorbed by the lung circulation and then passed through the brain barrier and got into the central nervous system (CNS). It is a classical sympathicoadrenal stimulant. There are several explanations for the communicaton of the immune and nervous systems, but the most acceptable one is through the hypothalamus – hypophysis – adrenal axis 16. Nicotine stimulates this axis together with the production of corticotropic releasing hormone from the hypothalamus which results in a faster secretion of adrenocorticotrophic hormone (ACTH). Tobacco smoke and nicotine increase the concentration of norepinephrine and epinephrine in plasma. ACTH together with kateholamines show an inhibitory influence on the immunological response of the organism. On the other hand, activating nicotine receptors in the brain, stimulates the function of the autonomic nervous system, which then affects the function of visceral organs including the lymph nodes, as well. Noradrenaline from the sympathetic part of the nervous system has influence on adrenoreceptors of T-lymphocytes. The effect of parasympathetic nervous system on the function of T-lymphocytes is still not explained well enough. Investigations showed that tobacco smoke causes the dysfunction of both T- and B-lymphocytes 17.

Investigating bronchoalveolar lavate (BAL) in smokers suffering from COPD and asthma, has revealed that there is an increased number of alveolar macrophages and neutrophil leukocytes 17. Compared with non-smokers, alveolar macrophages of smokers seem to be active in terms of showing the ability of secreting microsomal and lysosomal enzymes, an increased production of oxygen radicals and activation of myeloperoxidase, as well as an increased migration and haemotatic response. However, in spite of the cited functions, the alveolar macrophage of a smoker is extremely deficient in phagocytosis and/or bactericidal function which greatly affects the immune response of the host 18.

Smoking stimulates aggregation of alveolar macrophages but significantly diminishes their function. Macrophages have an important role in immune response because of their different activites, among which the most important are phagocytosis, haemotaxis, preparation and presentation of antigens for B- and T-lymphocytes. These cells can secrete hydrolytic enzymes, products of oxygen metabolism, cytokines: interleukin 1 (IL-1) and interleukin 6 (IL-6), metabolites of arachidonic acid, tumor necrosis factor alpha (TNF-α) and others. A reduced degree of phagocytosis of alveolar macrophages in smokers is connected with a decreased response of the immune system and inadequate defense against various respiratory infective agents 18. An increased number of alveolar macrophages and neutrophil leukocytosis in smokers causes inflammation in mucous walls of the airways. The following products, collagenase and elastase, are also released from these cells and they lead to the destruction of alveolo-capillary membranes which is clinically manifested as pulmonary emphysema, or they can cause chronic obstructive bronchitis because of the increased production of mucus in the airways 18.

It has been noted that in smokers there is an increased level of CD8 T-lymphocytes in relation to non-smokers 19-21. Histopathological investigations of bronchial biopsy have shown that the number of T-lymphocytes, especially CD8 cells (cytotoxic cells), is increased in smokers with COPD 22,23. The role of these cells in the occurrence of inflammation in this disease is not yet fully explained. These cells can partly contribute to the development of COPD because of the release of perforins, granyme-B and TNF-α, which cause cytolysis and apoptosis of epithelial alveolar cells, which is all responsible for continuation of inflammation.

The results of histopathological investigations of bronchial biopsy, BAL, and induced sputum have shown an increased number of alveolar macrophages in small and large airways in smokers. These cells act as a conductor in the development of inflammation, on the basis of the release of various mediators such as TNF-α, interleukin 8 (IL-8), and leukotrien B4 (LTB4), which provoke the development of neutrophil inflammation 24. Tobacco activates macrophages and epithelial cells to produce TNF-α which stimulates gene 8 for IL-8, which leads to the accumulation and activation of neutrophils. This process takes place by means of the activation of transcription factor-kB (NF-kB).

The effect of tobacco smoke ingredients on immunity in patients suffering from chronic obstructive pulmonary disease

In recent years attention has been particularly focussed on the appearance of immunosuppression of the organism after active and passive smoking 11,13.

Smoking is an important risk factor for the occurrence of various lung diseases, the most serious among them being COPD 2.

Under the influence of tobacco inflammatory cells are activated and they release various mediators. Among them are powerful proteinases, oxidants and toxic peptides. These mediators are capable of destroying the lung structure in patients with COPD and/or maintain neutrophil inflammation.

There is increasing evidence that an oxidant/antioxidant imbalance, in favour of oxidants, occurs in COPD. Tobacco smoke is one of the well-known risk factors for oxidative stress in smokers. Markers of oxidative stress have been found in the epithelial lining fluid, breath and urine of cigarette smokers and patients with COPD. Hydrogen peroxide (H₂O₂) and nitric oxide (NO) are the direct measures of oxidants generated by cigarette smoking or released from inflammatory leukocytes and epithelial cells. Oxidative stress contributes to COPD in the variety of ways. Oxidants can react with, and damage, a variety of biological molecules, including proteins, lipids and nucleic acids and this can lead to cell dysfunction or death, as well as to damage the lung extracellular matrix. Oxidative stress contributes to the proteinase-antiproteinase imbalance by inactivating antiproteinases, such as alpha-1 antitrypsin. Oxidants also promote inflammation.

Figure 1 shows the influence of tobacco smoke on activation of macrophages, neutrophils and epithelial cells which produce mediators of inflammation.

The presence of macrophages, neutrophils, eosinophils and T-lymphocytes is different in healthy people, smokers or sufferers from COPD and asthma. Therefore a significant increase of neutrophils was noted in smokers in relation to non-smokers, and the number of these cells is even greater in smokers suffering from COPD (p < 0.05).

It has been noticed that the number of CD8 lymphocytes in smokers is in negative correlation with forced expiratory volume in the first second (FEV₁). We have already said that in smokers the number of CD8 lymphocytes tends to increase which is connected with the decrease of FEV₁ value.

**Conclusion**

Various ingredients of tobacco smoke and nicotine in particular, can influence immunity. Smoking leads to immunosuppression of T- and B-lymphocytes as well as to disturbed function of alveolar makrophages, in the form of decreased phagocytosis. Tobacco smoke stimulates alveolar makrophages, neutrophils to release the mediators of inflammation which can damage the lung structure of smokers suffering from COPD or asthma.

**REFERENCES**


