KAPITEL 2 / *CHAPTER 2* [2]
THE EFFECT OF NITROGEN OXIDE AND ITS METABOLITES ON THE HUMAN ORGANISM, THE ROLE IN THE ORIGIN OF PATHOLOGICAL PROCESSES

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An important biological mediator of physiological processes in the human body is nitric oxide II (NO) [21, 34, 38, 43], which regulates blood pressure and antimicrobial protection [2].

The amino acid L–arginine and nitric oxide synthases (NOS) NOS play a major role in the formation of NO. They are found in the endothelium, vascular myocytes, neurons, lymphocytes, neutrophils, platelets, macrophages, fibroblasts and hepatocytes [6, 10, 36, 37]. Stress and hypoxia alter NOS activity [47]. There are several NOS: endothelial (e-NOS), constitutive (c-NOS) and inducible (induced) (i-NOS). Endothelial NOS is activated under the influence of large amounts of calcium and synthesizes endothelial NO, which diffuses into vascular smooth muscle cells [20]. Constitutive NOS is constantly located in the cytoplasm of cells, is the main factor protecting the body from infection, ischemia, increased thrombus formation and many other injuries [41]. With a small amount of free calcium, c-NOS is inactivated. Inducible NOS (i-NOS) is not always present in cells and its activity does not depend on the level of calcium ions in the cell [33, 40]. i–NOS synthesizes NO only in pathological conditions (stress, cardiovascular diseases, tumors, etc.) under the influence of glucocorticoids, estrogens, interleukin-1β, γ-interferon, □-tumor necrosis

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factor, □-transforming growth factor, endotoxins and cytokines [28]. There are 20 cells in which i–NOS is expressed, which ensures the synthesis of NO by the vascular endothelium and protects the body from bacteria, viruses, cancer cells [35, 45]. Tumors contain a lot of i–NOS, which synthesizes NO, which increases vascular permeability, increases the access of nutrients to tumors and accelerates their growth.

NO has a short half-life (2–50 sec). In living organisms, NO is quickly converted into metabolites (nitrites or nitrates), which reduces its toxic effect. When the process is disturbed, peroxynitrite (OHOO–) is formed, which decomposes into NO2 and hydroxyl radical (OH–). Peroxynitrite activates the processes of lipid peroxidation (LPO). Glutathione radicals are formed, which from an antioxidant become a prooxidant [7, 31]. In tissues, NO is a free radical that has strong lipophilic (easily diffuses through cell membranes) and hydrophilic (easily converts into nitrites, nitrates, peroxynitrite and nitrogen oxides) properties.

When the NO system is activated, POL processes increase, and hypoxia intensifies in tissues. Hypoxia stimulates the synthesis of NO in the vessels, its expression by i-NOS, increases the level of dinitrosyl iron complexes and S-nitrosothiols (NO depot). In severe and chronic hypoxia, the level of L-arginine in the blood decreases, NO synthesis is suppressed, and its inactivation is accelerated. In moderate hypoxia, the level of NO increases [27].

In the endothelium of vessels, NO and lipid prostacyclin (PG-I2) are formed from arachidonic fatty acid and the amino acid L-arginine. NO maintains a low tone of the arterial wall (dilatory effect), and prostacyclin stabilizes the thromboresistance of the endothelium. With increased destruction of NO by polymorphonuclear leukocytes, the regulation of tone is blocked.

During stress, NO exhibits protective properties and forms a rapid and long-term adaptation [15], in which NO production in organs increases or decreases. During short-term and immune stresses, the amount of NO increases, and during long-term and severe stresses, it decreases. After adaptation, the NO level is restored. Stress increases the amount of NO and endothelin in the blood [38], which affect the development of atherosclerosis and vasospastic reactions and damage the gastric

mucosa. When the heart adapts to stress and physical exertion, NO synthesis increases.

The short half-life of NO explains the difficulty of its detection in biological fluids, therefore, the final metabolites of NO (nitrites/nitrates) are most often determined, the amount of which in the blood of healthy adults is equal to 10 μmol/ml, and in children - 25 μmol/ml. The literature notes that the level of nitrites/nitrates in urine during the day does not change and does not depend on gender and age (except for newborns, where their amount in urine during the day is 2-3 nmol/ml, and at night – 14-16 nmol/ml). In the blood, the synthesis of NO is suppressed with age (aging of the body): in people over 75 years old, its level becomes lower (3-4 times) than at the age of 25-30 years. In the blood of healthy people, the level of nitrogen is 203 nmol/ml [28], in the bronchoalveolar substance the level of nitrites/nitrates is 0.8 nmol/ml [5].

In the late secretory phase of the menstrual cycle, the content of NO in the blood is higher than in the proliferative phase [32]. Estrogens increase the level of nitrites/nitrates – in pregnant women the amount of NO metabolites is higher (increases with the duration of pregnancy) than in non-pregnant women, and at the beginning of labor their level decreases significantly [29].

Increased NO level and its deficiency are harmful to the body. According to scientists, high NO level is the main factor in the development of pathological conditions of the body and the intensification of their inflammatory process, where an important role is assigned to i-NOS and c-NOS. There are contradictions in the literature regarding the role and effect of NO on the myocardium. Some authors believe that NO is a cardioprotector and reduces ischemic lesions of the myocardium [33]. In cardiovascular failure, the amount of NO in the blood plasma increases [2], which inhibits platelet aggregation and adhesion, prevents the development of atherosclerotic plaques and promotes diastolic relaxation of the myocardium. Significant accumulation of NO in the body damages blood vessels in diabetes, which contributes to complications. Elevated levels of NO inhibit the proliferation of lymphocytes and macrophages, increase their apoptosis and contribute to the development of secondary immunodeficiencies [43], tumors, shock, inflammatory and autoimmune diseases.

NO deficiency creates conditions for atherogenesis, vasoconstriction, thrombosis

and ischemia. According to other authors, inhibition of NO synthesis has a positive effect on the degree of heart damage during infarction [46]. With increased contractility of the heart, NO synthesis increases and oxygen demand decreases, and with blockade of NO synthesis, the heart's need for oxygen increases, which is present in its diseases.

In pathological changes in the heart, i-NOS appears in cardiomyocytes, resulting in an increase in the content of NO in the blood during myocardial infarction, myocarditis and cardiomyopathies. On the first day of myocardial infarction, there are several states of NO: inhibition or enhancement of its synthesis and the absence of changes. In mitral valve prolapse, the level of NO metabolites in the blood of children increases; in ischemic heart disease, chronic heart failure and arterial hypertension, NO synthesis is reduced [3, 25].

NO initiates apoptosis (stimulates the synthesis of the proapoptotic protein p53), which protects against infections and eliminates mutated cells. According to other literature data, NO inhibits the mechanism of apoptosis initiation, the disruption of which leads to the occurrence of pathological conditions and diseases. Chronic hypoxia and circulatory failure stimulate cardiomyocyte apoptosis, where NO significantly increases and contributes to cardiac hypertrophy [45].

High levels of NO metabolites are found in rheumatoid arthritis, cerebral vasculitis (in cerebrospinal fluid) [22, 26], their levels change in nodular thyroid pathology [4] and schizophrenia [19]. NO is an important mediator of the genitourinary, digestive and respiratory systems [16, 20, 21]. It has been noted in the literature that in nephritis and vesicoureteral reflux, the level of NO in the blood is reduced, in pyelonephritis (acute, chronic) and chronic glomerulonephritis the level of NO is increased. In remission of chronic glomerulonephritis, NO synthesis is suppressed [7]. NO stimulates bile secretion [11, 24], relaxes the smooth muscles of the walls of the gastrointestinal tract [41] and esophagus, regulates their activity [7] and affects their mucosa [11, 24]. Urinary excretion of nitrites/nitrates increases in infectious diarrhea [7] as a result of the vital activity of the intestinal microflora, in exacerbations of nonspecific ulcerative colitis and Crohn's disease, in which the level of NO in the colon mucosa increases [17]. NO is a factor of anti-stress resistance and

adaptation of the body in gastric and duodenal ulcers. Inhibition of its synthesis disrupts blood circulation in the mucosa and induces leukocyte adhesion to the vascular endothelium [21].

NO has an antimicrobial effect [2]. It suppresses the action of pathogens of infectious diseases and eliminates them from the body [1]. NO deficiency contributes to the multiplication of pathogens in cells, exacerbation of the disease and its chronic course [2]. In infections, the depression of the effects of NO increases, which significantly disrupts hemocirculation, damages the endothelium and disorganizes tissues. The level of NO increases in the vascular wall [10] and in the moisture of exhaled air during sepsis and inflammatory infectious processes [1], and decreases in HIV infection. High concentrations of NO act cytotoxically or cytostatically [2], and NO deficiency in macrophages is the cause of incomplete phagocytosis and the multiplication of microbes in them [1, 35].

In healthy people, NOS activity is low. NO (more than 90%) is formed in the nasal cavity, 50–70% of which is self-absorbed and enters the lungs. The amount of NO is reduced in smokers [9] and in healthy individuals during physical exertion. The level of NO depends on alveolar clearance, cardiac output, ventilation and oxygen content in exhaled air.

NO relaxes the bronchi. Increased synthesis of NO promotes adequate bronchodilation and enhances the function of the ciliated epithelium of the bronchi. In the nasal cavity, nasopharynx and paranasal sinuses, the concentration of NO is much higher than in the lower respiratory tract: in the bronchi – 3–11 parts per billion (ppb) (parts per 1 billion water molecules), in the nasal cavity and nasopharynx – 1000 ppb [9]. In exhaled air condensate (EAC), the level of nitrites/nitrates in children is higher (2.8 μmol/l) than in adults (1.5 μmol/l).

The metabolic transformations of NO in bronchopulmonary diseases have been studied [23, 30], during their adaptation to hypoxia [15, 27]. The level of NO is reduced in EAC of children with bronchial asthma, and in adults it is increased compared to healthy individuals. The level of NO increases during exacerbation of bronchial asthma and decreases during chronic bronchitis and taking corticosteroids. The severe course

of bronchial asthma correlates with a higher level of NO in EAC and bronchoalveolar substance [9].

In inflammatory processes of the respiratory system, NO accumulates in exhaled air, and in the respiratory tract - the products of its metabolism, which is observed in bronchitis, acute respiratory viral infection and some extrapulmonary diseases [47]. Cytokines and endotoxins inhibit the activity of cNOS, which leads to spasm of the respiratory tract [28, 37]. When activating the POL processes, NO participates in the formation of free radicals that damage the respiratory tract and inhibit adaptation mechanisms.

There have been attempts to study NO in phthisiology [13, 14]. In active tuberculosis, NO increased in leukocytes. In children with disseminated forms of tuberculosis, the level of nitrites in the blood serum is higher than in local forms [18]. The literature contains information on the state of NO metabolites in patients with pulmonary tuberculosis (affected and not affected by the consequences of the Chernobyl accident), and also highlights the issues of the relationship between metabolic changes in NO, LPO and the spectrum of fatty acids of blood lipids and CVP in these patients. The role of NO in the pathogenesis of tuberculosis has been established. Correction of NO levels can affect the effectiveness of treatment of patients with this disease [13, 14] and contribute to the elimination of the inflammatory process in the bronchi and the reduction of cavities several times.

Conclusion.

NO takes part in the regulation of many functions of the body, synthesizing nitrogen-containing compounds, which under certain conditions are converted back into NO. It activates and inhibits chain free radical reactions. Excessive or insufficient production of NO is the cause of the development and adverse course of respiratory diseases, since NO is a factor of nonspecific protection of the body.

Studies of the NO system expand and deepen some questions of pathogenesis in many diseases (including bronchopulmonary and tuberculosis), determine the possibility of corrective therapy for these patients. This is important and essential in the formation of consequences and residual changes of the pathological process.