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NO-DEPENDENT PROCESSES IN BIOLOGY, MEDICINE AND LIVESTOCK

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INTRODUCTION

In recent decades, biological science has been focused on the study of thin mechanisms that underlie biochemical processes in the body of plants, animals and humans, which have been well investigated in the previous days. On the one hand, such studies are of great scientific interest, on the other – the results of these searches subsequently become the basis for the development of absolutely practical solutions. And this applies not only to the field of humanities, the results of experiments of complex design and super-modern methodological approaches often become the basis for the development of "landing" practices that are widespread in everyday veterinary medicine. In this regard, we have focused on the topic relevant and actual, first of all, for human medicine in recent times, in particular it important for the development of methods of prevention and treatment of cardiovascular diseases. The literary data and the results of our own investigations show the evidence of actuality of this them also for veterinary practice and livestock in general.

In a number of scientific studies conducted at the end of the XX century, the participation of nitrogen monoxide (NO) in many physiological processes has been shown, that began to be called NO-dependent processes. These include: – relaxation of smooth vessel muscles, transmission of neural signals in the central and peripheral nervous system, higher nervous activity, secretion of histamine by mast cells, intestinal peristalsis, erection, destruction of bacteria and tumor cells by T-killers.

For us, the role of nitrogen monoxide in the development of immunological reactions is important. In particular, it is known that NO plays the role in the effects of immune cells, affects proliferation, maturation, differentiation, elimination of damaged and neoplastic cells,

selection of lymphocytes in which auto-reactive clones occurs[1,2]. NO contributes to the migration and recirculation of T-lymphocytes, changes the ratio of the T-helper–suppressor link, slows down the age-related thymus involution, and increases the cytolytic properties of NK cells and IFN synthesis[3]. The deficiency of NO is the cause of unfinished phagocytosis and reproduction of microorganisms in phagocytes. It serves the effector of macrophages and neutrophils[4].

NO hyperproduction inhibits proliferation and increases apoptosis of lymphocytes and macrophages, exhibits cytotoxic and immunogenic effects, causes the development of secondary immunodeficiencies. Synthesis of NO in macrophages occurs for increasing TNF-α levels, which is combined with an increase in the content of the acute phase proteins and reactive oxygen species, (ROS)[5]. At the same time, a high level in Ca^{2+} cells and generation of ROS, including NO, mediate the implementation of apoptosis and free radical processes[6,7].

1. NO synthase system

In the human body, NO is synthesized from the amino acid L-arginine under the influence of the NO synthase (NOS) enzyme. Currently, three isoforms of the enzyme are isolated: neuronal, inducible and endothelial[8]. The structure of NOS includes: heme (protorfirin IX), FAD, FMN, calmodulin and (6R) -5, 6, 7, 8 – tetrahydro-L-biopterin (BH_4). Starting from the C-terminal part in the structure of NO-synthase the following domains are distinguished: 1 – Reductase domain (FAD, FMN), which

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[8] Förstermann U., Sessa W.C. Nitric oxide synthases: regulation and function. Eur. Heart J. 2012; 33(7): 829–837.

catalyzes the transport of electrons from NADPH to an oxygenase domain; 2 – a calmodulin contingent domain that provides transportation of electrons with FMN to a heme and stimulates the transport of electrons from FAD to FMN; 3 – an oxygenase domain comprises a heme, the binding site of amino acid L-arginine and BH4[9,10].

Name	Gene(s)	Location	Function
Neuronal NOS (nNOS or NOS1)	NOS1 (Chromosome 12)	• nervous tissue • skeletal muscle type II	• multiple functions (see below)
Inducible NOS (iNOS or NOS2) Calcium insensitive	NOS2 (Chromosome 17)	• immune system • cardiovascular system	• immune defense against pathogens
Endothelial NOS (eNOS or NOS3 or cNOS)	NOS3 (Chromosome 7)	• endothelium	• vasodilation
Bacterial NOS (bNOS)	multiple	• various Gram-positive bacteria	• defense against oxidative stress, antibiotics, immune attack

Fig. 1. Classification of NOS

Neuronal NO synthase is expressed in nerve tissue, skeletal muscles, cardiomyocytes, bronchial epithelium and trachea, and even in vascular endothelium[11], participates in memory mechanisms, coordination between nervous activity and vascular tone, the implementation of pain irritations[12]. Inducible NO synthase is activated under the influence of various physiological and pathological factors (cytokines, endotoxins), when there is a need. Under the influence of endothelial NO synthase there is a synthesis of physiological levels of nitrogen monoxide[13]. Formed from L-arginine NO activates smooth muscle cells the guanilate cyclase, stimulating synthesis of cGMP, which, in turn, causes vasodilation.

NO is hydrophobic gas, a simple molecule capable of performing a universal regulator of many biological functions. This is primarily due to

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the fact that it can exist in three chemical forms: neutral radical NO, nitroxyl (anion) NO- and nitrosonium (cation) No +. With a violation of synthesis of NO, many pathologies are associated, including arterial hypertension, atherosclerosis, ischemic heart disease, bronchial asthma, primary pulmonary hypertension, obliterating lesions of lower extremities, diabetes, erectile dysfunction, thrombocytosis, allergic diseases. Currently, research aimed at studying the role of NO in ignorance of pregnancy and the growth retardation of the fetus[7].

The synthesis of NO in the body occurs from the amino acid L-arginine. In the body L-arginine synthesized from glutamine, glutamate and proline by intestinal-renal axis in humans and animals. The break down of arginine passes in various ways, with the participation of a number of enzymes – arginises, NO-synthase, arginine-glycine-amidin transferase and arginine decarboxylase. As a result, nitrogen oxide, polyamines, proline, glutamate, creatine and agmatine are formed[14].

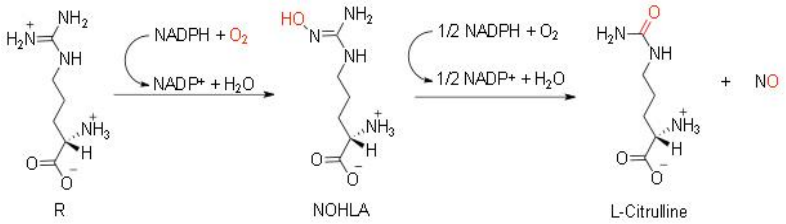

Fig. 2. NO synthesis, by Knowles R.G., S. Moncada

The peculiarity of NO synthesis is as follows: 1 – for catalytic conversion NOS uses L-arginine as a substrate only in a pair with other components (L-homoerginin, N^G-methyl-L-arginine), which are co-substrates; 2 – by-products are L-citrulline and nitrogen oxide; 3 – the reaction passes into two stages to form an intermediate – N-hydroxy-L-arginine (OH-Arg); 4 – both stages of the reaction require O_2 as a co-substrate and NADPH, as an electron donor; 5 – for the synthesis of L-

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citrulline molecules, 3 electrons are spent[12-14]. NO synthase convert L-arginine into an equimolar amount of L-citrulline and NO[15].

Constitutive forms of NO-synthase provide biosynthesis of a small amount of nitrogen monooxide, which in the mucous membranes of the digestive system regulates secretion, blood flow, motility, takes part in maintaining the structure and function of the mucous barrier, processes of intercellular integration, transmission of information in non-adrenergic and non-cholinergic neurons[15,16].

Endothelial NOS ($_E$NOS) is localized in endothelial cells of the vessels associated with the membrane and plays a major role in maintaining cardiovascular homeostasis, functional condition of blood vessels and angiogenesis[8]. In the vessels the NO, synthesized by $_E$NOS of endotheliocytes, takes part in various processes – inhibits platelet aggregation, inhibits the production by monocytes of chemoatractant protein-1 and granulocyte-macrophage colony-stimulating factor, changes the permeability of capillaries, inhibits the proliferation of smooth muscles, inhibits the interaction of leukocytes with endotheliocytes, reduces blood pressure. Inhibition of basal secretion of NO by inhibiting $_E$NOS leads to a rapid prolonged increase in blood pressure[17].

Neuronal NOS ($_N$NOS), which is localized in a cytosol, synthesizes NO that participates in neurons as a neurotransmitter and a neuromodulator. Unlike classical NO neurotransmitters is not in vesicles, not released by exocytosis, not captured by nervous terminals after isolation and is not cleaved by enzymes[18]. The synthesized nitrogen oxide diffuses from the nerve terminals and its action ends after linkage with the substrate. $_N$NOS is present in the neurons of the central and peripheral nervous system and is calcium-calmodulin-dependent enzyme. By the way, various isoforms of NOS – $_N$NOS, $_E$NOS and $_I$NOS are identified in neurons. NO synthesized by the central nervous system participates in the

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processes of nociception, sleep, thermoregulation and regulation of microhemodynamics[19].

NO synthesized by $_{N}$NOS acts as a neurotransmitter in non-cholinergic non-adrenergic neurons of an enteral nervous system and takes part in the development of enteropathologies, including Crohn's disease, Chagas disease, ulcerogenic colitis, diabetes, etc. Under the conditions of various intestinal infections, the growth of $_{N}$NOS expression in the bodies of the neurons of the inner intramuscular, external intramuscular and the myenteric plexuses[20].

During the development of inflammatory processes and development of destructive damage in the mucous membranes of the digestive organs, the expression of inducible NOS ($_{I}$NOS, Mm 130 kD) in macrophages, neutrophils, epitheliocytes and endothelialocytes[21] increases. The $_{I}$NOS is not calcium-independent enzyme and are localized in cell cytosol. It is activated, first of all, by proinflammatory cytokines (IL-6, tumor necrosis factor-α). Expression of $_{I}$NOS leads to a sharp increase (in 10 and more times) of NO synthesis, which forms nitroxyl (NO^-), peroxynitrite ($ONOO^-$) and nitrosothiols, which violates the functions of intracellular proteins, plasma membrane and membranes of organelles, DNA structure[22].

The negative action of nitrogen oxide may be due to the fact that it interacts with iron sulfate centers of many respiratory chain enzymes, reducing their biological activity, has a high affinity for heme and nonheme iron and can form complexes with hemoglobin, myoglobin, cytochrome C, guanylate cyclase. NO may damage DNA by nitrosylation and disintegration of its structure. Peroxynitrite nitrosylates tyrosine residues of many proteins, superoxide dismutase and other copper-containing proteins. In high concentrations, its toxic effect is manifested in various pathogenetic states and is based on oxydation, nitrosylation reactions (NO^+ attachment) and nitration (NO_2^+ attachment)[17].

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The role of nitrogen oxide synthesized by $_{E}$NOS and $_{I}$NOS under inflammation is different. Thus, it is believed that $_{E}$NOS/NO has a protective effect, while the $_{I}$NOS/NO take part in the development of ulcerogenic mechanisms[16, 22]. Thus, in the conditions of experimental ulcer, the expression of $_{I}$NOS is determined in cells that are around destructive changes in the mucous membrane of animals and blocking the activity of the $_{I}$NOS/NO had a cytoprotective effect[23].

The proinflammatory effect of nitrogen oxide is observed in epithelial and endothelial cells and depends on the degree of $_{I}$NOS expression, the amount of synthesized peroxynitrite, activation of lipid peroxidation processes, production of proinflammatory cytokines. At high concentrations, NO detects a toxic effect by forming nitroso-oxidative stress[24].

In the study of the role of NO-synthase in animal experiments their blocking by non-selective or selective blockers or administration of NO donators were used. Most often, non-selective blockers – L-NMMA, L-NAME, L-NNA and selective $_{I}$NOS blockers – amino guanidine, 1400 W, GW 273629[25] are used.

The results of the research revealed ambiguity of changes of NO in ulcerogenic colitis and Crohn's disease on experimental models. Moreover the question arises about protective action of NO in case of damage to the large intestine, in other words, if changes in NO may be a marker of inflammation? Under conditions of ulcerogenic colitis there is an increase in expression of $_{I}$NOS and $_{M}$RNA, as well as infiltration of large intestine mucosa by neutrophils increases, oedema and destructive changes are observed. Introduction on this background of L-arginine led to an increase in NO and MDA, as well as the activity of glutathione peroxidase and

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glutathione content. The influence of the non-selective L-NAME blocker under these conditions reduced the level of oxidants[26,27].

When blocking an $_{I}$NOS by the selective 1400W blocker, the sharp decrease in edema and 68% reduced infiltration of neutrophils, by 26% reduced the area of structural damage to the mucous membrane have been shown. When introducing a L-NAME blocker, the effect was less pronounced than when blocking 1400W[28,29].

It's well known that income in the blood of various biologically active substances changes the functioning of ion channels, membrane enzymes and receptor apparatus, affects the processes of lipoperoxidation and the level of activity of NOS and arginase in blood lymphocytes[30]. The NO system reacts to physiological and pathological changes in the body, which allows assessing the degree of influence of a certain factor and quickly reproducing them[31]. According to the literature data[32,33], under the conditions of stress in the body the activation and-NOS determined.

2. Investigation of NO-processes in piglet

All above mentioned facts allow using the investigation of NO-system not only for the purposes of human medicine investigations, but also for

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animal biology and veterinary practice. Our own studies have shown the influence of vitamin and mineral preparation “Vitarmin” on the activity of NO-dependent protection mechanisms in lymphocytes of piglet under stress conditions of weaning from sows.

Fig. 3. “Koviscyn” preparation (Ковісцин in Ukrainian)

According to our study[34]of the NO generation system, after weaning in lymphocytes of piglet of the control group, the activity of the total NOS increased, especially on the 1st and 5th day ($P < 0.05$) after weaning, compared with the period before weaning.. In these periods, a tendency towards a decrease in the activity of the total NOS in lymphocytes of blood of piglet of the experimental group, compared with control. From these data it follows that the “Koviscyn” (Ковісцин in Ukrainian) components contribute to a gradual reduction in lymphocytes of the expression of NOS, which was enhanced as a result of weaning from sows. The decrease in the activity of NOS after the actions of “Koviscyn” can be determined as a decrease in the production of interleukins and peroxinitrite, and the

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availability to cells of L-arginine, its influence on NF-kB, as well as by blocking the synthesis of cyclooxygenase-2. Between NOS and cyclooxygenase there is an interrelation, NO donators increase its activity and PG E2[17].

At the same time, in the first five days after weaning in lymphocytes of piglet of the control group has been observed an increase in the activity of arginase, which led to an increase in urea content. Thus, on the 1st day after weaning of urea content in lymphocytes of pigs, in comparison with the period before weaning, increased by 3.9 times, and on the 5th day – 3.5 times. During studies, the activity of arginase in the blood of piglets of the experimental group reduced and on the 5th day after weaning was 1.7 times lower, compared with control. The urea content in lymphocytes after the introduction of "Koviscyn" also decreased on the 10th day after weaning was at the level of values before weaning.

CONCLUSSIONS

The physiological phenomena connected with NO-dependent processes in human and animal body have been established as a meter of common evidence in many branches of contemporary biological science and medicane. Specific physiological, biochemical and molecular mechanisms that underlie these phenomena are clearly elucidated during last decades and summarized in our paper. The achievement of these results allows to elaborate the system of medicamental and instrumental influences on these processes in human medicine and health. By the way, there are some achievements in biology of domestic animals and veterinary practice, to some of them our scientific collective has the direct connection. In our paper we try to show the physiological significance of NO-dependent processes and the role of nitrogen monoxide in functioning of various organs, systems and tissues of human and animal body. Significant emphasize was done on the role of L-arginine and NO synthases – the key enzymes of reviewed processes. Special attention was attracted to the results of our own studies of NO-dependent mechanisms in body of domestic animals, mainly pigs, and prospective of such investigations for the sake of veterinary medicine.

SUMMARY

During last 30 years a lot of physiological phenomena connected with NO-dependent processes in human and animal body have been described. Moreover, specific physiological, biochemical and molecular mechanisms that underlie these phenomena are clearly elucidated. The achievement of

these results allows elaborating the entire system of medicamental and instrumental influences on these processes in human medicine and health. By the way, there are some achievements in biology of domestic animals and veterinary practice. Our short review is dedicated to all of these questions. We try to show the physiological significance of NO-dependent processes and the role of nitrogen monoxide in functioning of various organs, systems and tissues of human and animal body. Significant emphasize was done on the role of L-arginine and NO synthases – the key enzymes of reviewed processes. Special attention was paid to the results of our own studies of NO-dependent mechanisms in body of domestic animals and prospective of such investigations for the sake of veterinary medicine.

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