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Mini Review

Endotelial Dysfunction of Cavernosal Arteries: Role of Nitrogen Oxide, Influence of Long Range Infra-Red Radiation

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Abstract

The article provides survey of bibliography related with biological effect of nitrogen oxide. The survey covers issues of endothelial dysfunction of cavern arteries and methods of its identification. In particular, interaction of interagency range infra-red radiation with biological objects of various complexity has been considered. Data collection demonstrates that effects of terahertz range infra red waves in biological systems is possible on molecular, cell, organ and system level of regulation.

Keywords: nitrogen oxide; endothelial dysfunction; long range infra-red radiation

Introduction

For over 30 years, the problem of nitric oxide (NO) has been one of the key in modern biology and medicine. In 1987, the reaction of the formation of NO inside the cells of a macroorganism was discovered, which led to the discovery of a previously unknown regulatory system of the human body and mammalian animals - the nitric oxide system [1]. In 1998, R. Furchgott, Luis J. Ignarro, Ferid Murad - were awarded the Nobel Prize in the field of physiology and medicine for the discovery of the role of "nitric oxide as a signaling molecule in the cardiovascular system" [2,60]. Nitric oxide is called a "molecule of the XX century" [3]. NO is a universal regulator of physiological and metabolic processes in a single cell and in the body as a whole; in addition, it performs intercellular interactions, functioning as a signaling molecule in almost all organs and tissues of humans and animals [4-6]. NO is able to quickly diffuse through the membrane of the cell synthesizing it into the intercellular space and is also easy to penetrate into target cells, which defines NO as a neurotransmitter [7,8]. Thanks to the study of nitric oxide, a new principle of signal transmission in biological systems was established: NO is formed in some cells, penetrates through membranes and regulates the functions of other cells [3]. Endogenous NO is involved in many vital physiological processes. This is a universal modulator of various body functions, such as interneuronal communications, synaptic plasticity, the state of receptors, intracellular signal transmission, the release of other neurotransmitters [8]. Inside the cell, NO activates some enzymes and inhibits others. The main physiological targets for NO are considered to be soluble guanylate cyclase [3-9]. Activation of soluble guanylate cyclase causes an increase in cyclic guanosine monophosphotase (cGMP), which in turn leads to a decrease in the intracellular Ca2 + content [3]. According to many authors, the ability to regulate the intracellular concentration of Ca2+ ions is one of the most important properties of NO [10]. Endogenous nitric oxide exists and is continuously synthesized in organs, tissues and cells by enzymatic means with the participation of NO synthases (NOS) - enzymes that use the amino acid L-arginine as the sole substrate [11]. Three NOS isoforms were studied: endothelial, neuronal, and macrophage [12,13]. Endothelial NOS is found in vascular endothelial cells, platelets, myocardium and endocardium [65-67]. Neuronal NOS is found in the neurocytes of the central nervous system and peripheral plexuses of the autonomic nervous system (ANS). Neuronal and endothelial NOS have many common properties; they are combined together and called constitutional

NOS [1-13]. Constitutional NOS is calcium dependent, because Ca2 + is required for its activation.

In addition to constitutional NOS, "inducible" or "calcium-independent" NOS is also distinguished. It is found in macrophages, hepatocytes, fibroblasts, smooth muscle cells of blood vessels, the gastrointestinal tract and genitourinary system, muscle cells of the heart and uterus [1, 13-15]. Inducible NOS appears in cells only after induction with bacterial toxins and some inflammatory mediators - cytokines [1, 13, 14, 60.66.68]. In cells at rest, it is not detected. Produced by inducible NOS NO is primarily intended to protect the host organism, helps to reduce the activity of borderline inflammatory cells, the death of microorganisms and intracellular parasites, inhibiting platelet aggregation and improving local blood circulation [7]. Inactivation of NO is carried out by hemoglobin of the blood with the formation of nitrosohemoglobin, which decomposes to methemoglobin [1]. An excess of NO can be bound upon its interaction with superoxide radicals, thiols, and metals (especially Fe2 +) [16]. Undesirable effects have also been described in NO; they are caused by the formation of the strongest oxidizing agent, peroxynitrite, which arises in the reaction of NO with the superoxide anion [13]. High concentrations of NO exert a cytotoxic or cytostatic effect on any cell without differentiating whether it is a normal host cell, tumor cell, or macrophage [1-3]. The half-life of the NO molecule is calculated in seconds, therefore its effect extends only to nearby cells [1]. Currently, one talking about the multifunctionality of the action of NO, which is sometimes the opposite. So, it became known that NO can both enhance lipid peroxidation (LPO) processes in cell membranes and inhibit them, cause both vasodilation and vasoconstriction, induce apoptotic cell death and have a protective effect against apoptosis induced by other agents [3-17]. NO is characterized by both anticarcinogenic activity and mutagenic effect [18]. It is believed that the various effects of NO are determined by various NO signaling pathways (which depend on the relative rate of NO formation, redox reactions, as well as combinations of oxygen, a superoxide radical, and other biological molecules) and the sensitivity of cell systems to a particular signaling pathway [17]. The final effect of NO in the vessels may depend on the place of its generation, local concentration and interaction with other tissue components [16].

The biological effects of NO are of particular interest to cardiologists, since NO is a neurotransmitter, a powerful hemostasis factor, antiplatelet agent, endogenous vasodilator [9,13,19-24], has a stress-limiting effect [25], and is directly involved in the modulation of the immune response [15], is a universal regulator of the central and peripheral nervous systems [3-8]. However, the main mechanism of the vasodilating effect of NO is directly related to the functioning of guanylate cyclase, only its soluble form, and is mediated through the activation of soluble guanylate cyclase with the accumulation of cGMP, which subsequently leads to the release of Ca2 + from muscle cells and ultimately to vasodilation [14]. It has been proven that NO is involved in the relaxation of vascular smooth muscle [3, 26, 27-31]. Thus, the regulatory system of nitric oxide affects the main pathogenetic mechanisms of the development of cardiovascular pathology: platelet hemostasis, hemocoagulation, rheological properties of blood, the functional state of the endothelial and smooth muscle components of the vascular wall, stress-limiting factors, and lipid peroxidation. Diseases of the cardiovascular system can develop either as a result of a decrease or as a result of an uncontrolled increase in the concentration of NO in the body.

Thus, for cardiologists, the issues of maintaining the physiological level of concentration and the functional state of endogenous NO in the human body are extremely relevant both scientifically and in practice. Vascular atherosclerosis begins with functional changes in the endothelium. Endothelial dysfunction (EnD) is an important clinical correlate of atherosclerosis in the early phase of its development and is closely associated with cardiovascular risk factors such as arterial hypertension (AH), smoking, elevated cholesterol, diabetes mellitus (DM), and obesity. EnD should be considered as a violation of the balance between vasodilating and vasoconstrictor factors, caused by a decrease in the production of some and an increase in the synthesis of others [32,33, 61-64].

An important role in the development of EnD is played by hypercholesterolemia. Low density lipoprotein cholesterol (LDL) is infiltrated in the walls of blood vessels, which undergoes oxidation and its oxidized forms accumulate in the intima, which attracts monocytes. The latter stimulate the release of oxygen radicals, thereby enhancing the oxidative stress of the endothelium. It was found that oxidative stress, which leads to an increase in lipid peroxidation, blocks the synthesis of protein and nucleic acids, inhibits glycolysis, and inhibits the activity of enzymes (glucose-6-phosphatase, adenylate cyclase, guanylate cyclase, etc.), which causes dysfunction of many tissues. EnD also develops in patients with diabetes. A significant decrease in endothelium-dependent dilatation of peripheral arteries in patients with diabetes compared with healthy people was noted.

A negative effect on endothelial function has tobacco smoking. In smokers, basal NO secretion is reduced, platelet aggregation is increased, anti-atherosclerotic protection is reduced. EnD progresses with age, which is associated with a decrease in endothelial synthesis of NO and an increase in the reactivity of endothelium to vasoconstrictors. The activity of some isoforms of NO synthetase changes with age. An increase in inducible NO synthetase can indirectly lead to ED, causing damage to the smooth muscle cells of the cavernous bodies of the penis [34]. Thus, EnD is a systemic disorder affecting the entire vascular bed. At present, they put an equal sign between En and erectile dysfunction (ED arteriogenic form). The risk of ED increases in the presence of hypertension, diabetes, hypercholesterolemia, cardiovascular disease (CVD) and those diseases that is closely associated with En [35].

Currently, methods are being sought to create pharmacological guanylate cyclase activators based on chemical structures (donors) that provide the possibility of the formation of endogenous nitric oxide in the body, regulation of its concentration and reactivity [9-11]. Unfortunately, preparations based on the described compounds have not yet been introduced into clinical practice. In

addition, pharmacological correction of the NO content may be accompanied by the appearance of undesirable side effects, since currently there are no available methods for determining the concentration of nitric oxide in the bloodstream in the clinic. In connection with the foregoing, it is of interest to detect EnD in a timely manner and use narrow-spectrum (far range) infrared (IR) radiation as a potential regulator of the nitric oxide cycle. As one know, each substance, and therefore each intermolecular bond, has its own specific spectrum, both radiation and absorption. This means that body tissues have selective sensitivity, which supports their vital functions. Therefore, it is advisable to use narrow spectra of the far infrared range for successful treatment and diagnosis. It is such narrow-spectral emitters developed on the basis of oxide ceramics at the Institute of Materials Science (Tashkent, Republic of Uzbekistan). The spectrum of their radiation lies in the range from 8 to 50 μm. This means that the quantum energy of radiation converted by ceramics is within the limits of the quantum energy of a person's own radiation or below it, and, accordingly, cannot have a negative effect on the physiological processes of the human body [36, 37].

One of the main properties of long-range infrared radiation is the dependence of the effects on the phase of biological development and on the initial state of the object: the long-range infrared radiation practically does not affect the normal functioning of a healthy organism, and if pathology occurs, it can regulate its functioning within the limits inherent in this biological species, which is confirmed experimentally and is consistent with the literature [38-41]. Currently, a positive effect of long-range IR radiation on the functional properties of platelets and rheological parameters during blood irradiation of patients with angina pectoris in vitro has been revealed [42-44], as well as the restoration of initially disturbed rheological parameters and functional activity of platelets during IR irradiation long-range emitter of white rats in a state of immobilization stress [45]. Infrared radiation in the terahertz range causes an increase in the production of nitric oxide by vascular endothelium, which is accompanied by the normalization of reduced basal and induced vasodilating activity in animals in a state of acute immobilization stress [46]. The course of exposure to terahertz waves in animals with prolonged stress causes an increase in the concentration of nitrites - stable metabolites of nitric oxide [47] and [48], a decrease in the concentration of endothelin I in the blood serum, helping to normalize the balance of production of vasoconstrictor and vasodilator substances by endothelium, that is, prevents the development of endothelial dysfunction. According to a number of modern authors, the irradiation of infrared radiation from the terahertz range can not only increase the synthesis of endogenous nitric oxide and increase its reactivity, but also increase the duration of the existence of nitric oxide in cells [49]. Studies have been published on the effects of infrared radiation of the terahertz range on changes in LPO processes [58]. One of the first works in which the possibility of assessing the state of the endothelial function of the cavernous arteries was studied was the study of R. Virag [50]. The essence of the technique is ultrasound (ultrasound) of changes in the diameter of the cavernous arteries after their temporary compression. The increased blood flow, after elimination of compression, exerts pressure on the arterial wall, which causes the endothelial cells to release NO and dilate [51]. In addition, short-term tissue ischemia causes an increase in lipid peroxidation products, which cause pre-stimulation of blood and tissue phagocytes with the release of primary radicals (NO, O2). The degree of expansion of the arteries reflects the ability of endothelial cells to synthesize and secrete NO and its bioavailability [52]. A similar technique has been used for a long time to assess the state of endothelial function of peripheral arteries, including the femoral, radial and brachial [53]. The main diagnostic method for the arteriogenic form of ED is pharmacodopplerography (FDG) of the penile vessels using intracavernous injections of vasoactive drugs or oral phosphodiesterase-5 inhibitors (PDE-5). However, FDG does not allow detecting violations of the arterial blood flow of the corpora cavernosa at the stage of functional vascular damage, especially on the background of pharmacological induction of erection [54]. In addition, FDH has disadvantages: firstly, injection of drugs into the cavernous body is in most cases accompanied by fear and pain from patients, which leads to activation of sympathetic impulse and a decrease in the diagnostic value of the obtained parameters [55]; secondly, the technical features of the study (dose, composition of the drug) affect the diagnostic value. The FDH technique using PDE-5 inhibitors is devoid of these drawbacks; however, the results largely depend on the degree of sexual arousal and have a rather high cost and duration of the study in time [56]. Completely new possibilities in the early diagnosis and treatment of EnD may appear when using narrow-spectrum IR emitters. As indicated above, NO complexes with hemoproteins are photosensitive and decompose with the release of NO; the release of primary radicals, as a protective reaction, by phagocytes of blood and tissues, on the stimulation of IR emitters. Most of the biochemical reactions that occur in the human body are photochemical and are in resonance in the field of human own radiation, therefore, the speed and consistency of their course are strictly dependent on the power of this radiation [36, 37]. The mismatch and change in the rates of the occurring photochemical reactions, this is the accumulation of lipid peroxidation products, intermediate aggressive compounds (peroxynitrite and metabolic products in the cycle of nitric oxide NO2-, NO3-, NO +, NO-, NO2.- radical, etc.), excessive concentration of primary radicals with their negative effect on the functional abilities of cells, protein synthesis, enzymes, nucleic acids, etc. It is logical that if you supply energy from the outside that corresponds to the radiation of the human body, this will help coordinate the rates of chemical reactions and restore processes.

Thus, the infrared radiation of the terahertz range is capable of changing the morphological and functional state of tissues and individual organs, which affects the functioning of the organism as a whole. The literature data indicate that the electromagnetic waves of this range are characterized by a powerful regulatory effect on many processes in the body. The biological effects of the infrared radiation of the terahertz range are realized at the molecular, cellular, organ, and systemic levels [57].

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