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ACTIVATION OF NEUTROPHILS IN PATHOLOGICAL CONDITIONS OF ISCHEMIA AND CARDIOVASCULAR CONSEQUENCES, ROLES OF NITRIC OXIDE /NO/ AND PHARMACOLOGICAL WAYS OF REGULATION

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Major role in the pathogenesis of the changes development in the heart tissue due to anoxia during myocardial infarction play activated polymorphonuclear leukocytes. Under conditions of hypoxia activated neutrophils are generating oxygen free radicals and releasing the contents of their granules with a number of lysosomal enzymes. There are very interesting to have different possibilities of pharmacological regulation of this kind of pathology of a high activated neutrophils. For example, stimulation of adenylate cyclase by prostaglandin E2 (PGE2) in neutrophils can leads to an increase of intracellular cAMP levels in neutrophils, and then to reduction of leukotrienes formation and to reduction of the inflammatory processes degree.

The use of compounds in pharmacotherapy, which are inhibitors of the enzyme phosphodiesterase (cAMP degrading enzyme) can also enhance the effect of elevated concentration of cAMP and thus leads to suppression in the activation processes of neutrophils and also platelets. The compounds, which can inhibit the process formation from arachidonic acid (AA) some active metabolites by activated neutrophils, are also important during heart ischemia. Moreover, we have known a synergistic effect between stimulators of c-AMP and c-GMP (by EDRF/NO) in the white blood cells and platelets. Endogenous EDRF/NO is synthesized from the aminoacid L-arginine by the enzyme NO-syntase, mainly in the vascular endothelium as well as in other cells. NO is constitutively secreted by endothelial cells but its production is modulated by a number of exogenous chemical and physical stimuli, whereas the other known mediators (PGI2, Endothelin-1 and PAF) are synthesized primarily in response to changes in the external environment. Both endogenous and exogenous NO (liberated from NO-donors) may bind to the heme enzyme - guanylate cyclase. This effect is stimulated by guanylate cyclase and then followed by the increase of the c-GMP production in the cells. Reduction of endogenous NO formation in the absence of substitution, lead to a number of causes pathological changes in a front of acceleration of aterothrombosis process, higher activation of platelets and more opportunities for their adhesion and aggregation particularly in ischemic and hypoxic conditions, the shrinkage of blood vessels, reducing the blood flow through the coronary arteries, and in the case of beginning myocardial infarction to extend the zone of ischemia and necrosis of hemodynamic consequences. Reduced endogenous production of NO and thus the deficiency occurs in conditions of excessive production and release of active vasoconstriction compounds (leukotrienes, in front of leukotriene B4 as well as thromboxane A2 and endothelin-1) deepens further reduced vascular flow, leading to coronary artery spasm. Pharmacological ability to regulate the biosynthesis of endogenous NO with elevation of NO level in cells in various stages of pathological condition because of heart ischemia can be also conducted by NO-donors a compounds that can release from their structure egzogenous nitric

oxide (NO). Moreover, negative effects of oxygen free radicals overgeneration by activated polynuclear granulocytes during ischemia and hypoxia condition can be regulated by free radicals scavengers. The knowledge of different mechanisms with pathologic consequences activation of neutrophils during aseptic inflammation caused by ischemia and hypoxia as well as these processes possibility of pharmacological regulation are necessary to proper introduce and effective conduction of optimal pharmacotherapy of cardiovascular pathology caused by ischemia and hypoxia.

Key words*: hypoxia, septic and aseptic inflammation processes, neutrophils, free oxygen radicals, lysosomal enzymes, endothelium, nitric oxide (NO), NO-synthase, NO-donors.*

Septic and aseptic inflammation processes in the tissues are accompanied by accumulation and activation of polymorphonuclear leukocytes, neutrophils. These cells are able to adhere to the blood vessel wall, migrate through the vessel wall and the destruction of not only microorganisms, but also its own tissues, which have been damaged or changed by ischemia and /or influencing inflammatory processes by immunological processes [1, 2]. An example of aseptic inflammation that runs from the activation of neutrophils, activated with the action of main mechanisms of humoral and cell-mediated immunity is a ischemic area of myocardial infarction. Major role in the pathogenesis of the development of these changes in the heart tissue due to anoxia during myocardial infarct seem to play just activated polymorphonuclear leukocytes, and also other types of leukocytes. These cells are involved in the destruction of damaged and dead tissue, and in the preparation of repair processes leading to the formation of scar tissue, also modulate repair processes. Migration of neutrophils takes place in the first hours of ischemia and then also through the vascular endothelium and is largely associated with the activation of the components of complement system appearing in a relatively high concentration of highly active immune component C3 and C5a complement, which show strong chemotactic and chemokinetic activity. Activated complement components, especially C5a, have a strong activating effect for neutrophils. This leads to an increase in adhesion of neutrophils to vascular endothelium, and the appearance of granulocytes aggregation, and then to increase the peripheral resistance and in consequence decrease of blood flow in the ischemic area of myocardial tissue [1, 2, 3]. The role of neutrophils in the process of myocardial ischemia is associated not only with the mechanical disturbances due to the appearance in the circulation of the neutrofils circulating aggregates and their adhesion to endothelial cells. Activation of neutrophils, due primarily to the component of the complement C5a, which causes the increase of glucose metabolism, mainly in pentose cycle alternating circuit, with simultaneous increase in the consumption of oxygen, which is referred to as “oxygen burst” [1]. This process is accompanied by activation of an enzyme catalyzing the production of complex molecules of oxygen and simultaneous oxidation of NADPH oxidase localized in the cell membrane and the formation of highly biologically reactive superoxide anions O_2^-, then under the influence of the enzyme superoxide dismutase (SOD) they are converted to hydrogen peroxide (H_2O_2). Superoxide anions are converted by the enzyme myeloperoksydase in the presence of Cl^-, Br^- and other highly reactive compounds such as hypochlorous acid (HOCl), hypobromous acid (HOBr), which in the presence of water are decomposed to release singlet oxygen $1O_2$ molecule [1, 2, 4, 5].

Discovered in 1980 nitric oxide EDRF/NO by Furchgott and Zawadzki, a strong vasodilatatory factor, that is produced and released by the vascular endothelium, was originally named as Endothelium Derived Relaxing Factor (EDRF) [6]. It is a vasodilator, modulating vascular tone, blood pressure and hemodynamics, a important role for angina, heart failure, pulmonary hyper-

tension and also erectile dysfunction. In addition, its powerful antioxidant, anti-inflammatory and antithrombotic actions are antiatherogenic with antiatherothrombotic activity [6]. NO is synthesized from the amino acid L-arginine by the enzyme NO-syntase, mainly in the vascular endothelium as well as in other cells. L-arginine due to oxidative dezimination is converted to the final product - NO and L-citrulline, but one of the intermediate product is N-hydroxy-L-arginine. NO is constitutively secreted by endothelial cells but its production is modulated by a number of exogenous chemical and physical stimuli, whereas the other known mediators (PGI2, Endothelin-1 and PAF) are synthesized primarily in response to changes in the external environment [7, 8]. In the process of NO production may interfere with acting as a brake - the so-called inhibitors of the biosynthesis of endogenous NO. These are false substrates for the enzyme - NO synthase. These compounds can include, among others NG-monomethyl-L-arginine NG-mononitro-L-arginine. These inhibitors of endogenic NO biosynthesis compounds can significantly increasing systemic vascular resistance with subsequent increased blood pressure, including also pathological conditions related with increased production of nitric oxide / NO/ (for example overproduction of NO in septic shock). For impaired NO formation occurs in the process of atherogenesis, which has important clinical consequences, mainly concerning the cardiovascular system and also immune system. NO also plays a important regulatory role in the central and peripheral nervous system. Decreased NO level leads to vasoconstriction with higher permeability and even more deeper tissue hypoxia with simultaneous stimulation of platelets to adhesion and aggregation [7, 8].

Activated neutrophils under conditions of hypoxia in addition to generating oxygen free radicals, release the contents of their granules, ie, allowing a number of lysosomal enzymes dissolve, then absorb the revised antigenic tissue. Among these may be mentioned enzymes such as elastase, acid hydrolases (such as beta-glucuronidase), myeloperoxydase, and others enzymes [1, 2, 4, 5]. Neutrophil activation also leads to increased synthesis and release of pharmacologically very active metabolites of arachidonic acid, mainly products of lipooxygenation. Under the influence of 5-lipoxygenase from arachidonic acid (AA) are generating leukotrienes, particularly leukotriene B4. That has a very potent chemotactic and chemokinetic action for neutrophils and has the capacity to ability longer stimulation neutrophils to generation of O_2^- anion, and production of leukotrienes C4 and D4, a strong contracting substances for vascular smooth muscle as well as the production of thromboxane A2 (TXA2) from arachidonic acid (AA) by cyclooxygenase. Thromboxane A2 rapidly activate platelets to aggregation and also constrict of vascular smooth muscles Lysosomal enzymes, oxygen free radicals and active metabolites of arachidonic acid (leukotrienes) released from activated neutrophils sharing in the processes of removing dead tissue but also acts destructive to healthy surrounding tissue, so they can expand the zone of ischemia, for example myocardial infarction zone [1, 5, 7, 8, 9].

There are different possibilities of pharmacological inhibition of stimulated neutrophils excessively, which can determine the degree of ischemic injury and myocardial tissue with insufficient oxygen. Ischemia and myocardial anoxia leads to the formation of aseptic inflammation primarily goes from activation of platelets and polymorphonuclear granulocytes, neutrophils, their adhesion to the vascular endothelial cells and aggregation [10]. These processes intensify of ischemic hypoxic zone of myocardial area largely by activating components of the complement (C5a mostly), which have a strong chemotactic and chemokinetic activity. Neutrophil activation leads to an increase in the intracellular concentration of calcium ions, to form highly reactive oxygen free radicals (superoxide anions mainly O_2^- and also hydroxyl radicals, singlet oxygen and hypochlorous acid, which are destructive factors for act on the sur-

rounding cells and tissues, for endothelial damage and myocardial tissue during infarction. All these processes lead to a deeper ischemic area to the surrounding tissue edema, increased permeability of blood vessels and can lead to induction of arrhythmias. Generation of hydroxyl radicals, which inactivate the enzyme prostacyclin synthase, leading in this condition to a reduction in endogenous production of prostacyclin PGI2. Moreover, the reduction production and inactivation of nitric oxide - NO also leads to increased platelet activation and increases contraction of coronary vessels. The changes of concentration of free calcium ions plays important role in the process of neutrophils activation [1, 7, 8, 9, 10]. The rapid increase in the concentration of free calcium ions leading to the activation of these cells and are as strong activating factor for regulation activity of the enzyme 5-lipoxygenase, which is required to activate a higher concentration of free calcium ions than cyclooxygenase. Pharmacological compounds which may reduce intracellular free calcium ions concentration, thereby may reducing the activity of the enzyme 5-lipoxygenase and arachidonic acid as well as process of lipooxygenation and thus reduce the production of leukotriene B4, C4 and D4 by activated neutrophils [1, 5, 9]. The process of neutrophil activation may play an important role in changing the concentration of cyclic nucleotides: cAMP and cGMP, increase in the cells concentration of these cyclic nucleotide leads to a reduction in the bioavailability of free calcium ions and thus to inhibition of the 5-lipooksygenation activity, leading to decrease leukotrienes production by activated neutrophils. Similar effects are found in platelets, where an increase in the concentration of cAMP and cGMP reduces and inhibits their activation. In effects of these process we can see supression of platelets adhesion and aggregation [7, 8]. In the case stimulation of adenylate cyclase by prostaglandin E2 (PGE2) in neutrophil, it leads to an increase in intracellular cAMP levels in neutrophils, then to reduction of leukotriene formation as well as to reduction degee of inflammatory processes. On the other hand, the use of compounds in pharmacotherapy, which are inhibitors of the enzyme phosphodiesterase (cAMP degrading enzyme) enhances the effect of cAMP and thus leads to suppression in the activation processes of neutrophils and platelets. Pharmacologically active compounds that are released from their structure egzogenic nitric oxide (NO): “NO-donors” (eg, the active metabolite of molsidomine: SIN-1), stimulates the enzyme guanylate cyclase and in consequence elevate production of cGMP in these cells. A synergistic effect between stimulators of c-AMP and c-GMP in the white cells and platelets and compounds which can inhibit of proces formation of arachidonic acid active metabolites by activated neutrophils are also important in condition of heart ischemia [7, 8, 10, 11].

Oxygen free radicals generated by activated polymorphonuclear granulocytes in hypoxia condition, or by the fact that oxygenated blood flow during coronary artery reperfusion by pharmacological or invasive method, can be inactivated by the enzyme superoxide dismutase (SOD), glutathione peroxidase or by catalase. Ability of scavenging oxygen free radicals also have a coenzyme Q, tocopherols, and also mannitol [2, 5, 11]. Damage to cells of ischemic area caused by reperfusion is associated also with an increase in intracellular calcium ions. In this case may be important question, whether calcium channel blockers can be valuable preparations used to reduce the extent of ischemic damage to the area due to myocardial infarction, also caused by reperfusion. The importance of this group of drugs is limited. Although they increase the tolerance to ischemia, but only if it is given before the onset of ischemia, furthermore they do not limit infarct size, and they can influence the dynamics of reducing the ischemic area caused by myocardial infarction. Taking into account that they may lead to reduction of neutrophils activation, calcium antagonists may be useful in treating and reducing the effects of ischemia and

hypoxia caused by myocardial infarction. Of course, always be aware of their negative ino-and tonotropic action of calcium antagonists, which is crucial for them in the event of heart failure during myocardial infarction, low cardiac output as well as in cardiogenic shock [1, 5, 10, 11, 12].

Several known several types of the enzyme - NO synthase, which is dependent on NADPH. Constitutively NO synthasis, which occurs primarily in endothelial cells and nerve cells, is dependent on Ca2+ ions and the calmodulin. It is activated by an increase in intracellular calcium ion concentration, which is an increase in the endothelium cells is caused by mediators such as acetylcholine, bradykinin, histamine. The factor that causes nerve cells constitutively activated forms of NO synthase and the subsequent rise of endogenous NO production, an increase in the concentration of calcium ions caused by nerve impulse. From the constitutive NO synthase activity is dependent vascular wall tension or vascular resistance and blood pressure. Inducible form of NO synthase is independent of calcium and calmodulin. It is absent in non-activating macrophages and its activity appears only after activation of these cells or bacterial lipopolysaccharides, certain cytokines such as interleukin-1 beta or TNF-alpha (tumor necrosis factor). This creates a form-synthase endogenous NO as long as long as it is accessible to the substrate (ie, L-arginine). Induction of this form of the enzyme may also occur in the vascular smooth muscle cells and be controlled by interleukokin 8, TGF beta or by platelet derived growth factor (PDGF). Constitutive and inducible form of NO synthesis, it flawoprotein containing adenine mononucleotide FMN and FAD, is dependent on tetrahydrobiopterin (TH4). TH4 determine the activity of these enzymes, NO synthase. Both endogenous and exogenous NO may to bind to the heme enzyme - guanylate cyclase. The effect of this action is stimulation of guanylate cyclase and then increase the production of c-GMP in the cells. NO can simultaneously connect to various other enzymes containing -SH groups, resulting in a block and the inactivation of these enzymes. Intracellular growth of c-GMP concentration causes vasodilation (the vasodilatatory effect) and reduces the over-activity of activated platelets, and consequently reducing their mobilization for adhesion and aggregation, and the participation of activated neutrophils in inflammatory processes, including under aseptic conditions inflammation caused by ischemia and hypoxia. NO is rapidly destroyed by free radicals, anions O_2^-. The reaction of NO with O_2 anions can form highly reactive and toxic free radical ONOO-, which is a potent destructive not for foreign bacteria and other organisms that can cause inflammation, but also cause damage to other cells and tissues. Potential mechanism of cytotoxicity produced in excess and liberated nitric oxide NO and NO released by the exogenous chemical compounds (drugs: “NO donors”), which is associated with the nitrosylation by NO nucleic acids. Excessive nitrosylation may however lead to malignant transformation of cells. So after prolonged use of nitrates, NO-releasing drugs with cardiac indications should be kept in mind. Excessive formation and release of endogenous NO, and NO is supplied exogenously, can be so harmful [6, 7, 8, 10, 13]. Nitric oxide (NO) is generated in a variety of cells but and particularly in the endothelium and is an endogenous compound. Reduction of endogenous NO formation in the absence of substitution, lead to a number of causes pathological changes in a front of acceleration of aterothrombosis process, higher activation of platelets and more opportunities for their adhesion and aggregation particularly in ischemic and hypoxic conditions, the shrinkage of blood vessels, reducing the flow blood through the coronary arteries, and in the case of beginning myocardial infarction to extend the zone of ischemia and necrosis of hemodynamic consequences [10, 14, 15]. In this situation, reduced endogenous production of NO and thus the deficiency occurs in conditions of excessive production and release of active vasocon-

striction compounds (leukotrienes, in a front of leukotriene B4 as well as thromboxane A2 and endothelin-1) deepens further reduced vascular flow, leading to coronary artery spasm, to expand infarct zone as well as to a number of others important consequences extracardiac, such as changes in blood pressure and reduction of renal perfusion. Increase the effects of NO is possible by pharmacological intervention in the process of endogenous NO (eg, the substrate L-arginine), and reducing the rate of decomposition of NO (eg, drugs that inhibit the enzyme activity phosfodiaeterase-type5 (PDE5)) and most and, above all, by the substitution of exogenous NO. Increased production of endogenous NO can be achieved by providing a substrate for parenteral its formation, ie, the above-mentioned L-arginine, also activating the NO synthase addition, some compounds with antioxidant activity, which may prolong the operating time has already produced NO. In most clinical circumstances increases the NO concentration in the body giving the compounds having a built-in part of its structure in the form of NO, drugs NO-releasing directly or such drugs which metabolized after release NO. The most important "NO donors" include nitroglicerine (NTG), SIN-1 - the active metabolite of molsidomine and also sodium nitroprusside. Conventional nitrates using in pharmacotherapy are: glyceryl trinitrate (nitroglycerin, NTG), izosorbitolu dinitrate and mononitrate sorbitol. The mechanism of action of nitrates is associated with the presence of a group of NO3 which enzymatically in the presence of reduced glutathione (GSH) is reduced in the smooth muscle cells of the heart and to a highly active nitrogen oxide /NO/. The effectiveness of nitroglycerin and other nitrates containing NO3 group, depends on adequate stocks reduced GSH in smooth muscle cells and heart. In case of reduction of GSH occurs so nitrates tolerance and if it is necessary to increase the dose to achieve a similar clinical effect. Tolerance to nitrates can be stopped with eg. N-acetylcysteine, which increases the number of reduced GSH. Molsidomine is a compound from the chemical group of sydnoimine, that only metabolised in the liver, where it is converted to its active metabolite - SIN-1 and SIN-1A, and can only this structure directly release NO. Nitric oxide can be very quickly released immediately after parenteral administration of sodium nitroprusside, which is sometimes, but very rarelly can be used to rapidly reduce the pressure in clinical situations which require very rapid pharmacological intervention. The knowledge of nitric oxide /NO/ biological properties in the field of its regulatory role in maintaining the homeostasis of the organism is very important for treatment of several diseases. Pharmacological ability to regulate the biosynthesis of endogenous NO and in consequence NO level in cells in various stages are useful for the treatment of a lot of pathological conditions of deficiency of endogenous NO or excess of NO production [7, 8, 10, 11, 14, 15].

Understanding mechanisms of pathology, roles and negative effects of oxygen free radicals overgeneration by activated polymorphonuclear granulocytes in ischemia and hypoxia condition with action of liberated a number of lysosomal enzymes and autocoids because of aseptic inflammation caused by ischemia and hypoxia as well as knowledge action and effects of nitric oxide /NO/ in many pathological conditions of the cardiovascular system are necessary to proper introduce and effective conduction of optimal pharmacotherapy of cardiovascular pathology because of ischemia and hypoxia.

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Резюме

РЕЗУЛЬТАТЫ АКТИВАЦИИ НЕЙТРОФИЛОВ ПРИ ИШЕМИИ И СЕРДЕЧНО-СОСУДИСТЫХ ЗАБОЛЕВАНИЯХ, РОЛЬ ОКСИДА АЗОТА (NO) И ФАРМАКОЛОГИЧЕСКИЕ СПОСОБЫ РЕГУЛИРОВАНИЯ

Рутовски Я.А.

Показаны механизмы патологии, роль и негативные последствия повышенной генерации свободных радикалов кислорода активированными полиморфоядерными гранулоцитами при ишемическом и гипоксичном состояниях, изменения, вызванные высвобождением ряда лизосомальных ферментов из-за асептического воспаления, вызванного ишемией и гипоксией. Рассмотрены влияние и механизм действия оксида азота на фоне ряда патологических состояний сердечно-сосудистой системы.

Ключевые слова: гипоксия, септические и асептические воспалительные процессы, нейтрофилы, свободные кислородные радикалы, лизосомальные ферменты, эндотелий, оксид азота (NO), NO-синтаза, NO-доноры.

Резюме

РЕЗУЛЬТАТИ АКТИВАЦІЇ НЕЙТРОФІЛІВ ПРИ ІШЕМІЇ ТА СЕРЦЕВО-СУДИННИХ ЗАХВОРЮВАННЯХ, РОЛЬ ОКСИДУ АЗОТУ (NO) І ФАРМАКОЛОГІЧНІ СПОСОБИ РЕГУЛЮВАННЯ

Рутовський Я.А.

Показано механізми патології, роль і негативні наслідки підвищеної генерації вільних радикалів кисню активованими поліморфоядернимі гранулоцитами при ішемічному і гипоксічному станах, зміни, викликані вивільненням ряду лізосомальних ферментів через асептичного запалення при ішемії та гіпоксією. Розглянуто вплив і механізм дії оксиду азоту на тлі низки патологічних станів серцево-судинної системи.

Ключові слова: гіпоксія, септичні та асептичні запальні процеси, нейтрофіли, вільні кисневі радикали, лізосомальні ферменти, ендотелій, оксид азоту (NO), NO-синтаза, NO-донори.

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ВИКОРИСТАННЯ АНАЛІЗУ ВАРІАБЕЛЬНОСТІ СЕРЦЕВОГО РИТМУ ДЛЯ ОЦІНКИ СТАНУ ВЕГЕТАТИВНОЇ ДИСФУНКЦІЇ У ПАЦІЄНТІВ ІЗ СТАНОМ ВІДМІНИ ВНАСЛІДОК ВЖИВАННЯ АЛКОГОЛЮ

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У статті наведені результати досліджень щодо використання методу оцінки варіабельності серцевого ритму у пацієнтів із алкогольним абстинентним синдромом без делiріозного синдрому в умовах реанімаційного відділення. Дослідження проводилися в перший день госпіталізації пацієнтів у клініку. Отримані дані порівнювалися із варіантами норми відповідних показників варіабельності серцевого ритму. Отримані результати свідчать про значну вегетативну дисфункцію в пацієнтів із алкогольним абстинентним синдромом та про наявність кореляційних зв'язків між показниками варіабельності серцевого ритму і показниками гемодинаміки.

Ключові слова: варіабельність серцевого ритму, вегетативна дисфункція, алкогольний абстинентний синдром, стрес-індекс Баєвського.

В даний час в Україні є тенденція до збільшення кількості хворих, які зловживають психоактивними речовинами. Однією з проблем сучасної медицини є збільшення частоти гострих психозів у хворих із залежністю від психоактивних речовин, найчастіше вони розвиваються в стані відміни від вживання алкоголю під час лікування з приводу різних соматичних захворювань, черепно-мозкових травм і т.д. [10].

Стан відміни з делірієм та психотичні розлади внаслідок вживання алкоголю займають одне з перших місць серед гострих екзогенних психозів, що вимагають інтенсивної терапії. Історична практика показує, що в умовах економічної та соціальної нестабільності зростання захворюваності білою гарячкою приймає епідемічні масштаби. На підставі сучасних даних алкогольні делірії за смертністю (20% випадків при відсутності ліку-