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ODDÍL 5. LÉKAŘSKÉ VĚDY

*§5.1 ANTI-INFLAMMATORY ACTIVITY OF RESVERATROL IN CORONARY HEART DISEASE (***Chekalina N.I.**, Poltava State Medical University of the Ministry of Health of Ukraine)

Introduction. Treatment of Coronary Heart Disease (CHD) remains an open pressing issue of modern medicine. Worldwide, despite the numerous methods of correction of CHD that are being developed, there has been no improvement in the situation with morbidity and mortality. In developed countries, CHD remains in the first place in the structure of mortality from all causes [1].

In Ukraine over the past decade, CHD accounted for 65-68% of all deaths in the structure of cardiovascular diseases (CVD). Among the able-bodied population in Ukraine, CHD leads to disability in 38.5%, and the average age of patients becomes younger [2, 3]. Показник кількості років життя, втрачених через інвалідність, з причини ІХС, в Україні у чоловіків складає 27 %, у жінок – 33 % [4].

The pathogenesis of CHD is based on atherosclerosis (AS). The development and progression of AS is mediated by numerous factors of external and internal influence that are characteristic of the modern environment. This is chronic stress, hypodynamia, high-calorie nutrition, excess xenobiotics entering the body, environmental pollution [3]. In Ukraine, the most significant factor contributing to the increase in cardiovascular pathology in the population is the war. In conditions of severe mental stress, especially in regions in a state of humanitarian catastrophe, malnutrition, the inability to timely seek medical help and the impossibility of appropriate full-fledged therapy makes a decisive contribution to the statistics of morbidity and mortality from CHD [5].

There are international protocols for the provision of medical care at IHD, on the basis of which national standards are created [6]. But the state of the problem requires the search for new effective methods of effective therapeutic effect in order to improve the quality and increase the life expectancy of patients with CHD.

Plant polyphenols are one of the promising means of treating coronary artery disease with a reasonable pathogenetic direction [7]. Known representatives of polyphenols include the flavonoid quercetin [8]. The soluble form of quercetin showed effectiveness, in particular, in reducing the necrosis zone in patients with acute myocardial infarction and in improving the central hemodynamic parameters in patients with heart failure [9, 10].

Today, a representative of polyphenols stylben resveratrol attracts great interest in the treatment of patients with cardiovascular pathology [11]. Resveratrol is dedicated to our analytical scientific research.

Presentation of the main material. One of the leading mechanisms of action of polyphenols, including resveratrol, is the influence on the molecular mechanisms of pro-inflammatory signaling, which mediates a decrease in the level of chronic systemic inflammation (CSI) [11, 12].

At the same time, one of the leading components of the development of AS is the activation of CSI [13, 14, 15]. Under conditions of activation of CSI, oxidation of low-density lipoproteins (LDL) occurs, Oxidized LDL acquire autoantigenic properties, forming circulating immune complexes with autoantibodies [16, 17]. CD4 + T cells that accumulate in the vascular intima during the formation of atherosclerotic damage increase the expression of receptors for oxidized LDL and chemokines. Increased transcriptional activity of nuclear factor kappa B (NF-kB) leads to enhanced production of proinflammatory cytokines (CK), which in turn activate endothelium [17, 18].

Inhibition of pro-inflammatory activation in AS and CHD is a pathogenetically justified target of drug exposure.

Resveratrol belongs to phytoalexins, is 3,4,5-trihydroxy-trans-stilbene produced by plants under the conditions of their defeat by bacteria or fungi [19, 20]. Resveratrol is found in more than 70 plant species. Red wine may contain from 0.1 to 14.3 mg/l of resveratrol [21]. For the first time, a scientific article on the biological activity of resveratrol was published in 1939 by the Japanese scientist Michio Takaoka. This initiated a broad scientific interest in resveratrol and the search for its therapeutic properties in various areas of clinical medicine. Cured antioxidant, anti-inflammatory, immunomodulatory, angioprotective, cardioprotective, neuroprotective, anticarcinogenic, estrogen-modulating, osteoprotective, geroprotective and other properties of resveratrol, which made it possible to use as a component of treatment regimens of various groups of diseases [22, 23, 24]. For medical use, resveratrol is extracted from plant raw materials by reverse-phase chromatography, as well as by chemical synthesis [21].

The main argument for the use of resveratrol in cardiology and angiology is its high tropicity to myocardiocytes and endotheliocytes. Thus, resveratrol realizes the main biological properties in relation to the myocardium and vessels in dilution 30 times lower than for its effectiveness against hepatocytes [22]. Instead, the well-known polyphenol silymarin has a high tropism for hepatocytes, and by influencing pro-inflammatory mechanisms, reduces the activity of cytolysis [12, 22].

Pro-inflammatory synnal transduction, the key factor of which is NF-kB, mediates pathogenetic links in the development of AS and CHD [13]. Found scientific evidence that the effectiveness of resveratrol against these pathological conditions is associated with its effect on CSI [25, 26].

Special attention of researchers to the study of polyphenols was attracted after the publication of the results of population studies of the phenomenon of the Mediterranean diet. It was found that the relatively low risk of CVD in the inhabitants of this region is justified by the high content of polyphenols, in particular, resveratrow in their diet [27, 28, 29].

More than a hundred large-scale clinical studies of the effectiveness of resveratrol are presented at the http://www.clinicaltrials.gov/, which demonstrates high scientific interest in it and opens up prospects for wide clinical application.

Consider the molecular mechanisms that realize the anti-inflammatory activity of resveratrol and affect the pathogenetic links of AS and CHD.

The anti-inflammatory effect of resveratrol is, as already noted, to inhibit signaling involving NF-kB [25]. Inducers of pro-inflammatory signaling can be tumor necrosis factor α (TNF α), other CK, lipopolysaccharides, Main target cells of pro-inflammatory stimuli – monocytes, endotheliocytes, dendritic and other immunocompetent cells [30, 31]. It was found that the reduction of NF-kB transcriptional activity by resveratrol occurs by inhibiting inhibitor-kappa B kinase β (IKKβ), which is responsible for the degradation of inhibitor protein kappa B α (IkB α) [25].

Among the existing mechanisms of inhibition of transcriptional activity of NF-kB are stimulation of the PRARγ protein, production of IkB α, blocking of the MAP kinase signaling pathway (mitogen-activated kinases), blockade of the signaling cascade involving phosphatidylinositol-3-kinase (PI3K) and protein kinase B (Akt), inhibition of TAK1 kinase (a kinase activated by transforming growth factor- β), activation of transcription factors FOXO (Forkhead box proteins), SIRT activation, inhibition of Gadd45b protein expression (beta gene induced growth inhibition and DNA damage), etc. [33, 34, 35].

Resveratrol activates sertuins involved in maintaining the viability of cardiomyocytes and prevents degenerative processes in the human body [36, 37].

Resveratrol has been proven to activate FOXO via SIRT1, enhancing FOXO translocation into the nucleus with reduced pro-inflammatory signaling. Also, resveratrol activates SIRT6 by deacetylating histone H3, reducing the transcriptional activity of NF-kB [35].

In vivo studies have shown that the stimulatory effect of resveratrol on SIRT1 is mediated by the activation by resveratrol of adenosine monophosphate activated protein kinase (AMPK), one of the key regulators of intracellular metabolism [38].

Also, the metabolic effects of resveratrol are realized by its effect on the receptor-activator of proliferation by gamma peroxisome (PGC-1 α), which is involved in the regulation of cellular respiration and lipolysis [39, 40]. The properties of resveratrol in an experiment in a diet with a load of fat components to activate SIRT1 and PGC-1α, which provides antioxidant and endothelioprotective effects [39].

In vivo studies have shown that adenosine monophosphate-activated protein kinase (AMPA) is one of the mediators of the effects of resveratrol. These findings were made on the basis that the metabolic effects of resveratrol are not realized in AMR-deficient mice [32]. Therefore, the use of resveratrol in pathological conditions in the mechanism of development of which AMRK is involved, including AS and myocardial ischemia, is pathogenetically justified.

With the participation of resveratrol, there is an increase in the content of adenosine monophosphate (cAMP) in cells, which is an intermediate messenger in the molecular cascade with the participation of AMPK, SIRT1 та PGC-1α [39, 40].

Resveratrol showed the ability to reduce the expression of intercellular adhesion molecules (ICAM-1) and vascular cell adhesion molecules (VCAM-1) on the endothelium by reducing pro-inflammatory signaling involving NF-kB [31].

Donnelly L.E. and colleagues determined the ability of resveratrol to interfere with CK-stimulated expression of cyclooxygenase-2 (COX-2) and inducible NO· synthase (iNOS) in the bronchial epithelium. The results provided the basis for similar studies on vascular endothelium. Identical conclusions were supported by the determination of the mechanism of action of rssveretrol, which was in this study, also in the blockade of pro-inflammatory transduction with the participation of NF-kB [41].

Resveratrol has direct antioxidant activity due to its chemical structure. Containing 3 hydroxyl groups, resveratrol is a scavenger of hydroxyl radicals, peroxide radicals, superoxide anion radicals. In this way, resveratrol participates in endothelioprotection, promotes the synthesis of NO. endothelium, reduces oxidative stress in CHD Resveratrol has direct antioxidant activity due to its chemical structure. Containing 3 hydroxyl groups, resveratrol is a scavenger of hydroxyl radicals, peroxide radicals, superoxide anion radicals. In this way, resveratrol participates in endothelioprotection, promotes the synthesis of NO. endothelium, reduces oxidative stress in CHD Resveratrol has direct antioxidant activity due to its chemical structure. Containing 3 hydroxyl groups, resveratrol is a scavenger of hydroxyl radicals, peroxide radicals, superoxide anion radicals. In this way, resveratrol participates in endothelioprotection, promotes the synthesis of NO· endothelium, reduces oxidative stress in CHD [42]. Resveratrol also increases the bioavailability of NO by activating endothelial production of eNOS [43].

It was found that the anti-inflammatory activity of resveratrol is also realized due to the inhibition of anaphylatoxin C5 (C5a). In

vitro neutrophils inhibited the release of inflammatory proinflammatory CK - interleukins 1, 6 and TNF-a. Resveratrol also reduced extracellular signal-regulated kinase (ERK) mediated phosphorylation, which reduced pro-oxidant effects [44]. The ability of resveratrol to block TNF α expression in myocardial and vascular endothelial cells and inhibit nicotinamide dinucleotide phosphate oxidase (NADRH oxidase) activity was determined [41, 44].

Having estrogen-stimulating activity through the mediation of the corresponding receptors, resveratrol increased the vasodilation of arterioles, and the synthesis of endothelium $NO^{\cdot}$. Obtained nvuk data on high sensitivity to resveratrol of coronary arterioles [45].

Having a direct and indirect antioxidant effect, resveratrol increases the activity of antioxidant enzymes - superoxide dismutase, catalase, hemoxygenase 1 (HO-1), enzymes of the glutathione system, which is found in cardiomyocytes and vascular endothelium [19, 43, 45]. Also, resveratrol suppresses the formation of reactive oxygen species in the endothelium of the coronary arteries [7, 11].

Resveratrol has properties to reduce platelet aggregation and inhibit eicosanoid synthesis obtained in experimental animals with hypercholesterolemia [20, 46]. The property of resveratrol to block lipoxygenase and components of the arachidon cascade - hydroxygenases, thromboxane B2, etc. Resveratrol inhibits the formation of thromboxane A2 in activated platelets, which is also a metabolite of arachidonic acid [47].

Resveratrol is found to interact with GPIIb/3a receptors, GPIa/IIa collagen receptor and integrin aII b β 3 activated platelets [23].

Cardioprotection is achieved by a number of mechanisms, oneof which is preconditioning. Myocardial preconditioning can be achieved by increasing the expression of antioxidant enzymes, chaperone proteins, adenosine A1-retseptoriv, etc. Adenosine A1-retseptori involved in K + channel discovery involving G proteins

[15, 48, 49]. Resveratrol promotes myocardial preconditioning by activating phosphokinase C, a number of MARK, PI3K, A1 and A3 receptors of adenosine, ADP-dependent K + channels, and by activating synthesis NO· [49, 50, 51]. Also, resiveratrol inhibits proliferation of fibroblasts in the myocardium and slows the migration of smooth muscle cells into the vascular wall, blocking the activity of matrix metalloproteinases [52].

The angioprotective anti-atherosclerotic effect of resveratrol, mediated by the ability to block the signaling cascade associated with the endothelial growth factor in smooth muscle cells of the arteries, was determined. Cardioprotective effect of resveratrol, also associated with its inhibition of ATI-dependent myocardial hypertrophy [52, 53].

In the experiment, under the influence of resveratrol, the viability of cardiomyocytes was increased by activating SIRT1 and preventing ATII-dependent apoptosis [53]. SIRT1 activation, which increased up to 10-fold with resveratrol, reduced insulin resistance [39].

The ability of resveratrol to significantly increase the transcriptional activity of the Nrf2 gene, which realizes its effect through NADPH reductases, is determined [54]. Activation of Nrf2 mediating the induction of HO-1, as well as an increase in the activity of p38 kinase and RI3K under the influence of resveratrol, provided cardioprotection in an experiment in myocardial ischemia [54, 55]. Induction of the Nrf2 pathway also increases SIRT1 transcription [55]. This can also justify the cytoprotective effects of resveratrol and the feasibility of its use in CHD.

Resveratrol has been found to inhibit the activity of the channel A1 the transient receptor potential (TRP), which is involved in the processes of inflammation, peroxidation and nociception, in particular, due to the Ca++ transmembrane flux [56].

Tome-Carneiro J. and co-authors identified 6 transcription factors associated with inflammation that are significantly activated

or inhibited under the influence of resveratrol, and 27 extracellular factors that are involved at different levels of pro-inflammatory reactions and are regulated by the use of resveratrol in patients with stable CHD [29].

Based on data obtained by other researchers, we conducted our own studies to study the effectiveness of resveratrol in patients with stable CHD. Along with a decrease in the levels of pro-inflammatory CK, under the influence of resveratrol in patients with CHD, there was a decrease in the number of endothelial microparticles circulating in the bloodstream with markers of inflammatory activation $CD32^+$ and $CD40^+$, which indicates an improvement in the state of the endothelium, anti-inflammatory and angioprotective properties of resveratrol [57].

Taking into account the data of our correlation-regression analysis, the increase in the levels of pro-inflammatory GC and inflammatory activation of the endothelium in patients with CHD are independent predictors of left ventricular systolic and diastolic dysfunction (LV) [58, 59]. Under the influence of resveratrol, the diastolic function of LV improved in patients with CHD in terms of the ratio of transmitral flow phases [60].

Also, in patients with CHD under the influence of resveratrol, we determined a decrease in the number of episodes of depression of the ST segment with daily Holter electrocardiogram (ECG) monitoring by 37.1%, which was significantly different from patients who were on standard therapy with CHD. Under the influence of resveratrol, the daily number of supraventricular extrasystoles decreased by 47.2% [60].

The effects of resveratrol obtained in our study can be considered directly related to the anti-inflammatory effect found in it, which is consistent with the results of other researchers.

Conclusions. Thus, resveratrol has numerous molecular targets, through which cardio- and vasoprotection is carried out, has

anti-inflammatory, antioxidant, antinociceptive properties and numerous positive metabolic effects.

These data determine the feasibility of active use and further clinical study of resveratrol for the development of effective pathogenetically justified approaches to the treatment of coronary heart disease.

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