Original Research Article

The effect of biomays on lipoprotein receptors in the dynamics of development of experimental atherosclerosis

Abstract

In Asia, wheat sprouts (OP) has long been used as a traditional herbal medicine. Polikozanol, vitamins and polyunsaturated fatty acids - have different biological activity: anti-inflammatory, antioxidant, antidiabetic and lipid-lowering.
Aim: Investigate the effect of biomays on lipoprotein receptors in the dynamics of development of experimental atherosclerosis
Material and methods of research: We decided to study the effect of the domestic drug "Biomays" in the treatment of experimental atherosclerosis. The study involved 5 groups of rabbits: 1st - intact (normal), 2nd - rabbits with hypercholesterolemia, 3rd - treatment with ultrax, 4th - treatment with biomice, 5th - received mixed treatment. Investigated the concentration of LOX-1 and LDLR on the 60th, 70th, 80th and 90th days of hypercholesterolemia.

Results. Thus, the combination of Biomays and Ultrox has the most beneficial effect on LOX-1 and rLDL parameters than monotherapy. In animals treated with both statins and Biomays, plasma LOX-1 ligand levels were maintained at lower levels than untreated rabbits.
Conclusion. We have found that the use of a statin in combination with dietary supplements "Biomays" (Maysara) has a synergistic effect improves the expression of r LDL and LDL uptake.

Key words: atherosclerosis, lipoproteins, LDL receptors, LOX -1.

Introduction

Atherosclerosis is associated with a violation of lipid metabolism, mainly with the effect on the vessels of atherogenic forms of lipoproteins. First of all, these are modified (oxidized or methylated) low-density lipoproteins (LDL) [2,3].

Strong concentration of oxidized low-density lipoproteins (oxLDL), as well as reactive oxygen species (ROS) and some cytokines (TNFα, TGF-β) provoke an increased expression of lectin- type oxidized LDL receptors (LOX-1) on endothelial cells [4]. Further, LOX-1 triggers ROS generation, activates NADPH-dependent oxidases, and subsequently stimulates redox -dependent proteins (MAPK (p38, ERK1/2, JNK) and NF- κB), and induces the biosynthesis of many proteins involved in atherogenesis [5]. In addition, the interaction of LOX-1 with oxLDL can trigger the process of apoptosis in cells and damage to the endothelial lining [4,5]. In turn, the secretion of ROS by the endothelium promotes the formation of oxLDL in the blood, which leads to the formation of a vicious pathogenetic circle and the progression of atherosclerosis.

Thus, the formation of foam cells in atherosclerotic plaques is promoted by scavenger receptors SR-A1 (scavenger receptor) and SR-B2, and SR-E1 helps to disrupt the barrier function of the endothelium, as a result of which oxLDL and monocytes (precursors of foam cells) penetrate into the intima of the main arteries. SR-E1-dependent activation of endotheliocytes and myocytes of contractile vessels may be involved in the pathogenesis of hypertension and many other vascular diseases [6–9].

SR - E1 (LOX -1) is a key receptor for oxLDL on endotheliocytes and vascular myocytes. It is a 50 kDa transmembrane glycoprotein. It was originally identified in bovine aortic endothelial cells, where it plays an important role in binding, internalizing, and degrading ox - LDL [10]. Later it was found that it is expressed

in many other cells - in macrophages, vascular smooth muscle cells, cardiomyocytes, platelets and fibroblasts. In addition, LOX -1 promotes endothelial dysfunction and apoptosis, as well as the formation of foam cells in macrophages and vascular smooth muscle cells. mediators (angiotensin II, cytokines, overt stress and advanced glycation end products) as well as some conditions (diabetes mellitus, hypertension and dyslipidaemia) activate LOX -1 [11-13]. ox - LDL and several other molecules act as ligands for the LOX -1 receptor. Tumor necrosis factor-alpha (TNF - α), interleukin-1 (IL -1), interferon-gamma (IFN-γ), and modified lipoproteins (glycoxidized LDL, lysophosphatidylcholine, and ROS) induce LOX -1 expression. In vivo, hypertension and diabetes, obesity, ischemia, reperfusion, heart failure, psychological stress, and HIV infection have been shown to increase LOX-1 expression [14,15].

Oxidized ox-LDL via LOX -1 plays a critical role in atherogenesis. It affects several types of cells (endothelial, cell vascular smooth muscle (VSMC), fibroblasts, macrophages and platelets) in the atherosclerotic pathway. Involvement in the development of endothelial dysfunction, apoptosis, monocyte migration and macrophage differentiation, smooth muscle proliferation and migration, and plaque destabilization are some of the critical steps in atherosclerosis [10]. The LOX -1 receptor is currently being investigated as a potential biomarker for cardiovascular disease, as well as a therapeutic target in the modification of atherosclerosis and related diseases.

Cholesterol is the main component of cell membranes, a precursor for the synthesis of bile acids and steroid hormones. [16-17]. Most of it is produced by the

liver, delivered to other organs by LDL particles, which pack cholesterol. High plasma levels of LDL cholesterol (LDL-C) (hypercholesterolemia) are a strong risk factor for atherosclerotic cardiovascular disease (CVD) [18]. Therefore, the reduction of its content in serum has traditionally been considered as the main one in the treatment of this disease.

The liver removes LDL from the blood using LDL receptors, a cell surface protein. It binds to LDL particles and ensures their uptake by cells through endocytosis. [18]. Stimulation of LDL receptor is tightly regulated in response to the amount of intracellular cholesterol through transcriptional and post-translational pathways. Transcription of the r LDL gene is controlled by protein-2, which binds the sterol regulatory element (SREBP - 2) [19]. When intracellular cholesterol levels are low, SREBP -2 located on the endoplasmic reticulum (ER) membrane is transported to the Golgi apparatus. There, the SREBP -2 transcription domain is cleaved by two Golgi proteases : Site -1 and Site -2. (S1 P and S2 P). The cleaved mature form of SREBP -2 then moves to the nucleus, where it activates target genes including 3-hydroxy-3-methyl-glutaryl-coenzyme A-, reductase (HMGCR), and rLDL [20]. It has also been shown that rLDL is regulated by post-translational mechanisms, proprotein convertase subtilisin/ kexin type 9 (PCSK9) binds to the extracellular domain of rLDL on the cell surface. This prevents the return of r LDL to the plasma membrane after lysosomal degradation , endocytosis degradation [10]. And it is known that inducible degrader rLDL (IDOL), ubiquitin ligase E 3, triggers the degradation of rLDL mediated by the mechanism of lysosomal degradation [21]. These pathways regulate the amount of r LDL in the liver . Drugs have been developed that act on one of these pathways, increase rLDL levels and increase the clearance of LDL particles from the blood, i.e. for the treatment of hypercholesterolemia [22,23].

Statins are a class of drugs used to lower blood cholesterol and are commonly prescribed for cardiovascular disease, including stroke. Statins inhibit the activity of HMGCR, an enzyme that slows down the rate of cholesterol biosynthesis, which reduces its content in the liver [23]. In response to a decrease

in intracellular cholesterol levels, the proteolytic process of SREBP 2 is enhanced and active SREBP 2 moves to the nucleus, where it binds to the rLDL promoter , thereby inducing rLDL expression and LDL uptake. Although statins have been shown to be effective drugs for the treatment of patients with high LDL-C, many patients have developed resistance or intolerance to this drug [24]. Therefore, new cholesterol-lowering alternatives to statins are needed. Recently, the Food and Drug Administration (FDA) approved the use of monoclonal antibodies against PCSK 9 - alirocumab and evolocumab, which inhibit the activity of PCSK 9. They have emerged as a valuable adjunct to LDL-C lowering therapy [25]. These PCSK 9 inhibitors narrow the degree of degradation of rLDL and increase serum LDL-C clearance. Several clinical trials have demonstrated that PCSK 9 inhibitors can be used in patients with statin side effects or in combination with statins to enhance their effect [26]. But the high cost of these drugs has become a major problem limiting their widespread use. To date, IDOL inhibition is also considered a strategy for lowering LDL-C levels . Although an effective therapy targeting IDOL has yet to be developed, several recent studies have shown that natural compounds such as docosahexaenoic acid and xantholhumol increase the content of rLDL in the liver, suppressing the expression of IDOL [27]. These fatty acids are also contained in our domestic preparation Biomays. In addition, it was found that a cyclic peptide that disrupts homodimerization IDOL, as an inhibitor of IDOL, increases the level of rLDL in the human hepatocellular carcinoma cell line (HepG 2) [28].

Material and methods of research: We decided to study the effect of the domestic drug "Biomays" in the treatment of experimental atherosclerosis. The study involved 5 groups of rabbits: 1st - intact (normal), 2nd - rabbits with hypercholesterolemia, 3rd - treatment with ultrax, 4th - treatment with biomice, 5th - received mixed treatment.

Biomays is dried wheatgrass powder. We studied the effect of biomays on the concentration of LOX-1 and rLDL in animals with experimental atherosclerosis.

Experimental atherosclerosis was reproduced by daily intragastric administration of cholesterol (0.2 g per kg of body weight for 2 months). Ultrox (Nobel Farm, Turkey) was used as a statin , which was administered at 0.6 mg/kg. Biomays (ORION-SKORPION LLC, Uzbekistan) was administered at the rate of 142 mg/kg 2 times a day.

Investigated the concentration of LOX-1 and LDLR on the 60th, 70th, 80th and 90th days of hypercholesterolemia.

In the dynamics of the development of experimental hypercholesterolemia, the concentration of LOX-1 and LDLR determined by enzyme immunoassay using RayBio ® ELISA Kit (USA) at the Institute of Biophysics and Biochemistry at the National University of Uzbekistan. Mirzo Ulugbek.

The data obtained were processed using the STATISTICA 7.0 software package. Quantitative data are presented as the median (Me) of the upper and lower quartiles (25 and 75%). Qualitative variables were compared using the chi-square test or Fisher's exact method. Quantitative variables with a normal distribution of a trait were compared using the Student's t-test, and in the case of a distribution different from normal, using the Wilcoxon rank test for dependent variables and the Mann-Whitney U-test 18 for independent groups. The Kruskal-Wallis test was used to compare several independent groups . Relationships between were determined by correlation analysis using nonparametric Spearman test and linear regression analysis.

First, we set the concentration of LOX -1

In intact rabbits, the result was taken as normal. It turned out that in rabbits with atherosclerosis, this indicator was significantly increased. On days 60, 70, 80, and 90, these excesses were 23.9; 40.8; 42.7 and 55.8%, respectively (Table 1).

Table 1.

LOX concentration -1 and rLDL (pg /ml) in the blood serum of rabbits with experimental atherosclerosis (n =6)

Index	Intact group	Study days			
		60-	70-	80-	90-
LOX –1(pg / ml)	52.7±3.29	65.3±3.2	74.2±2.4	75.2±3.3	82.1±3.4
rLDL	75.4±2.3	64.2±2.1	51.5±1.2	44.3±1.45	36.6±0.64

Note. Significant difference from intact groups $p< 0.05$.

Our figures are consistent with those of Chen , M. et al . [10], who observed a similar increase in the content of oxidized lipoproteins in the endothelium of an early atherosclerotic lesion cell. An increase in LOX-1 in the later stages can give negative effects that may be associated with the development of atherosclerotic complications - plaque rupture and thrombosis.

The content of p LDL in the dynamics of experimental atherosclerosis decreased from the norm by 14.86; 31.7%, respectively, compared with intact animals, then on the 80th and 90th days the decrease in the content of rLDL was 41.25 and 51.46%, respectively.

Therefore, the LOX-1 marker and rLDL proved to be significant and are excellent diagnostic tests in predicting atherosclerosis. They have high sensitivity (SE) - 0.77, 0.84 and specificity (SP) - 0.83, 0.9 diagnostic efficiency (AUC) 0.8 and 0.85, respectively. These tests can be a good predictor of the development atherosclerosis, pathogenic RR for LOX-1 (3.6; 95% CI 1.3-10.5) and for rLDL (5.5; 95% CI 1.5-19.7) (Table 2).

Table 2. Indicator marker s LOX-1 and rLDL in the dynamics of the development of atherosclerosis and predicting the outcome of the treatment of the disease

Indicators	SE	SP	AUC	R R	95%CI	P
LOX-1	0.77	0.83	0.8	3.6	1.3-10.5	>0.05
rLDL	0.84	0.9	0.85	5.5	1.5-19.7	>0.05

Increased expression of the LOX-1 gene is most noticeable in the endothelium of the arterial bifurcation [29]. Anatomical positions are generally considered to be susceptible to atherosclerosis. LOX-1 expression may be influenced by hemodynamic factors in vivo . In addition, LOX-1 stimulates not only endothelial cells.

It has been shown that it can be detected in SMCs and macrophages in vitro [30]. Activated platelets can also be recognized by LOX-1 [31]. Platelet binding is inhibited by a PS-binding protein, annexin V, whose activity is regulated by platelet agonists. Therefore, anionic phospholipids,

Table 3.

The content of LOX-1 (pg /ml) and rLDL after treatment with biomayse and ultrax in rabbits with experimental atherosclerosis, pg/ml (n = 30)

Index	Norm	Control	Group		
			3	4	5
LOX-1	52.7±3.29	82.1±3.4	62.8±1.71	60.2±1.71	50.3±2.15
rLDL	75.4±2.3	36.6±0.64	45.2±1.45	46.5±1.09	59.3±1.2

Note. Significant difference of all indicators from the control $p< 0.05$

exposed to the surface of activated platelets can serve as an epitope for LOX-1. Notably, platelet binding to LOX-1 enhances the release of endothelin-1 from endothelial cells, supporting the induction of endothelial activation. Targeted LOX-1 binding of platelets to the endothelium induces phenotypic changes in endothelial cells relevant to LOX-1 atherogenesis . The latter can connect both OxLDL and platelets affect endothelial function. These properties may provide a key to understanding the role of the endothelium in hemostasis and atherosclerosis [32,33].

After monotherapy ultrax and biomays, the LOX-1 level from the initial level decreased by 1.3 and 1.36 times respectively, and normalized when combined.

The content of p LDL after monotherapy biomays and ultrax increased by 27 and 23.5%, respectively, from the control group. The combination of drugs increased the content of rLDL more pronouncedly - by 62% compared with the control group.

Thus, the combination of Biomays and Ultrox has the most beneficial effect on LOX-1 and rLDL parameters than monotherapy. These observations are consistent with our earlier studies [34]. In animals treated with both statins and Biomays , plasma LOX-1 ligand levels were maintained at lower levels than untreated rabbits. In this study, we did not evaluate the reasons for the effect on LOX-1, but it is likely that biomayse contains vitamin E and PUFAs, and these antioxidants also reduce the expression of LOX-1 by reducing the content of the LOX-1 ligand, since OxLDL induces the expression of LOX-1. Thus, we suggest that the antioxidant effect of these agents suppressed the development of atherosclerosis by reducing the oxidative modification of LDL.

Conclusion

The identification of LOX-1 and the definition of its biological role in pathophysiological conditions provide new insight into the reasons for the uptake of ox-LDL by components of the vascular wall. Internalization ox-LDL causes a

cascade of events that can cause various diseases related to endothelial function, activity and damage. Endothelial cells can be activated by ox-LDL through LOX-1 in hypertension, diabetes mellitus, and hyperlipidemia. The most important risk factors for atherosclerosis per se, therapy targeting LOX-1 or LOX IN may be an effective strategy for the treatment of atherosclerotic and hypertensive diseases.

The action of biomays is primarily directed to the liver, where it binds and inhibits HMG- CoA reductase, and reduces cholesterol production. Against this background, the production of sterol-regulated membrane-bound transcription factors (SREBP) is activated and, accordingly, the number of LDL receptors on the membranes of liver cells increases. SREBPs also increase the amount of HMG-CoA reductase, but this does not increase since the enzyme is inhibited by statins .

LDL receptors remove LDL from the blood and deliver it to the inside of the cell, where they are digested by LDL, and the released cholesterol becomes available for metabolic purposes. The effect of the active substance in biomays - policosonol, is that the amount of cholesterol in the liver is maintained at a normal level, while the level of LDL cholesterol in the blood is maintained at a low level. LDL receptors do not bind HDL, so the protein content of this beneficial lipoprotein is not reduced.

Thus, when corrected by biomays and when combined with statins , the processes of lipid peroxidation are reduced, this drug reduced the duration of treatment in experimental animals.

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