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HYPOTENSIVE EFFECTS OF STATINS. A PLACE FOR HYDROGEN SULFIDE IN THE PUZZLE?

Abstract: *Hypotensive effects of statins. A place for hydrogen sulfide in the puzzle?*

Lipid lowering 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors — statins — significantly diminish the risk of cardiovascular morbidity and mortality in patients with cardiovascular diseases. Moreover, some clinical trials results indicate that this group of drugs reduces blood pressure, especially in patients with hypertension. In the article pleiotropic effects of statins that might have influence on blood pressure are discussed. Recent data on the role of gaseous messenger hydrogen sulfide (H₂S) in cardiovascular biology and kidney physiology are presented with the focus on the latest findings of atorvastatin increasing H₂S tissue concentration in kidneys.

Key words: statins, blood pressure, arterial hypertension, hydrogen sulfide, kidney, mouse

Słowa kluczowe: statyny, ciśnienie tętnicze krwi, nadciśnienie tętnicze, siarkowodór, nerka, mysz

INTRODUCTION

Lipid lowering 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors — statins — are the most commonly administered drugs in the treatment of lipid disorders worldwide [1]. Clinical trials results indicate that statins decrease all cause mortality and cardiovascular mortality, the incidence of cardiovascular events — transient ischaemic attacks and stroke, acute coronary syndromes and coronary revascularization rates in patients after myocardial infarction and in groups of high cardiovascular risk [2, 3]. This beneficial impact on the cardiovascular system results not only from statins' lipid-lowering action but also from a wide variety of effects they exert on atherosclerotic plaques, endothelium and their antioxidant and anti-inflammatory properties [4]. Interestingly, it has been lately also proclaimed that HMG-CoA reductase inhibitors reduce blood pressure, especially in patients with hypertension [5, 6]. The mechanisms of this action are not clear. Different biological systems are pos-

tulated to be involved. Here we discuss their possible role in light of the recent data on hydrogen sulfide — an important cardiovascular function and blood pressure regulator [7].

PLEIOTROPIC EFFECTS OF STATINS

HMG-CoA reductase is the rate controlling enzyme of the mevalonate pathway that produces cholesterol and other isoprenoids, so statins decrease cholesterol synthesis but also isoprenoids generation, mainly farnesyl pyrophosphate and geranyl pyrophosphate. These compounds normally attach post-translationally to intracellular signaling proteins including nuclear lamins, guanosine triphosphates — Rho, Rac, Rap and Ras, G-proteins and enable proper sub-cellular localization and trafficking of intracellular proteins. Since those modified proteins control diverse cellular function, statins exert additional effects beyond lipid lowering and resulting from altered isoprenoids system. Furthermore, numerous studies have shown that HMG-CoA reductase inhibitors have a broad array of anti-inflammatory, antiproliferative and immunomodulatory actions, described commonly as pleiotropic effects (Table 1) [1, 8].

Table 1 — Tabela 1

Pleiotropic effects of statins
Pleiotropowe działanie statyn

↓ ET-1	↓ LDL oxidation	↑ NO
↓ IL-6	↓ histamine release by basophils	↑ CO
↓ VCAM-1 and ICAM-1	↓ interferon gamma-induced MHC class II expression	↑ PPAR-α
↓ PDGF	↓ T-cell activation	↑ apoA-I expression
↓ NF-κB activation	↓ monocyte activation	↑ PI3K/Akt
↓ endothelial cell activation	↓ leukocyte-endothelial cell adhesion	↑ inhibition of leukocyte function antigen-1
↓ CRP	↓ proinflammatory cytokines (MCP-1, TNF-α)	↑ resistance to complement
↓ ROS	↓ PAI-1	↑ t-PA
↓ factor XIII	↓ thrombin	↓ factor Va

ET-1 — endothelin 1, IL-6 — interleukin 6, VCAM-1 — vascular cell adhesion molecule-1, ICAM-1 — intercellular cell adhesion molecule-1, PDGF — platelet-derived growth factor, NF-κB — nuclear factor kappa-light-chain-enhancer of activated B cells protein complex, CRP — C-reactive protein, ROS — reactive oxygen species, LDL — low density lipoproteins, MHC — major histocompatibility complex, MCP-1 — monocyte chemotactic protein-1, TNF-α — tumor necrosis factor α, PAI-1 — plasminogen activator inhibitor-1, NO — nitric oxide, CO — carbon monoxide, PPAR-α — peroxisome proliferator-activated receptor α, apoA-I — apolipoprotein A-I, PI3K/Akt — phosphatidylinositol-3-kinase/Akt pathway, tPA — tissue plasminogen activator

MECHANISMS OF STATINS HYPOTENSIVE ACTION

One of the most important mechanisms postulated to contribute to blood pressure decrease elicited by statins is the improvement of endothelial function [9, 10]. During statin therapy vasorelaxant mechanisms amended and arterial stiffness in long-term observations declined [11, 12]. Increased nitric oxide (NO) bioavailability was reported, while levels of oxidatively modified low-density lipoprotein (ox-LDL) and endothelin-1 (ET-1) fell [13–15]. Vasocostrictive and pressory effects of angiotensin II and norepinephrine were reduced while susceptibility to vasorelaxant action of angiotensin converting enzyme inhibitors, angiotensin receptor blockers and calcium channel blockers soared [16–18]. Moreover, in patients with hipercholesterolaemia rise in angiotensin II receptors AT1 density was observed and statin therapy reversed this process, and a subsequent drop in aldosterone concentrations was noted [19, 20]. Among effects of HMG-CoA reductase inhibitors that can lead to fall in blood pressure an influence on autonomic nervous system should also be taken into account. Statins significantly reduced sympathetic activity, increased parasympathetic activity and improved baroreflex sensitivity [21–23].

EMERGING BIOLOGICAL CRUCIAL ROLE OF HYDROGEN SULFIDE

The cell and organ function in mammals is modulated by a variety of signal molecules including lipids, peptides, small and inorganic molecules with ions and amino acids, and numerous metabolism intermediates. Among these signal carriers a special place has a family of gaseous compounds with NO and carbon monoxide (CO) at the forefront. These so-called ‘gasotransmitters’ have been proven to play a crucial role in cardiovascular biology, blood pressure and flow regulation. NO i.a. stimulates guanylate cyclases and degradative enzymes like phosphodiesterases. CO resembles this action but with much lower potency [24, 25]. Studies from recent years have been revealing that a third gaseous molecule hydrogen sulfide (H₂S) is deeply implicated in the regulation of many physiological and pathological processes including neurotransmission, insulin secretion, immune and inflammatory processes, gastric mucosal integrity, intestinal motility, perception and vascular tone control [7, 26].

H₂S is endogenously formed from L-cysteine in several enzymatic reactions, catalyzed by cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE) and 3-mercaptopyruvate sulfurtransferase (3MST). CBS is mainly expressed in nervous system, liver and kidney, while CSE is mostly found in vascular and non-vascular smooth cells and in the liver. H₂S is also formed in non-enzymatic pathways in many tissues and in erythrocytes. Intestinal flora is also a source

of the gas in the organism. H_2S participates in the relaxation of vessels by opening of adenosine triphosphate (ATP)-sensitive potassium channels and increasing $\text{Cl}^-/\text{HCO}_3^-$ exchanger activity and metabolic inhibition (cytochrome c inhibition) in the vascular smooth muscle cells [27–30]. H_2S interacts with carbon monoxide (CO) and nitric oxide (NO) systems in a complex manner including affecting each other's synthesis and biological responses within target tissues and organs. Moreover, all these three gases bind to haemoglobin and inhibit mitochondrial oxidative phosphorylation by impeding cytochrome c oxidase [24].

HYDROGEN SULFIDE, BLOOD PRESSURE AND KIDNEY FUNCTION

The role of H_2S in the regulation of blood pressure was explored by Yang and al. in the group of CSE lacking mice (CSE KO) [31]. The main observations showed 50–80% reduction of H_2S tissue concentration in arteries, liver and kidney and 50% decrease of H_2S serum level. As soon as seven weeks after birth the mice developed arterial hypertension with systolic blood pressure around 20 mm Hg higher than the control group. Infusion of H_2S reduced blood pressure in healthy mice and CSE KO individuals, but the response in the latter was much more pronounced. In the other part of the experiment, when isolated mesenteric arteries were examined, arteries of CSE KO showed reduced by 50–60% vasorelaxative effect of acetylcholine, what points that vasorelaxation is influenced by H_2S generated by endothelial CSE. These data prompt to consider H_2S as a part of endothelium-derived relaxing factors (EDRFs). H_2S shares other features of EDRFs with NO such as the acute regulation by vasorelaxative hormones through calmodulin and inositol-1,4,5-triphosphate (IP_3)-dependent pathways [25].

In the kidney both CBS and CSE were identified to produce hydrogen sulfide. H_2S has been recognized as a participant of the control of renal function which involves both vascular and tubular actions. In the study on rats of Xia et al. induction of endogenous H_2S production with L-cysteine (L-Cys) infusion into renal artery increased glomerular filtration rate (GFR), urinary sodium and potassium excretion. The inhibitory effect of H_2S on tubular reabsorption has been shown to involve $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter (NKCC) and Na^+/K^+ -ATPase (NKA). Exogenous H_2S produced dose-related increases renal blood flow, GFR and urinary excretion [32]. H_2S has been also identified to inhibit angiotensin-converting enzyme (ACE) by complexing with the zinc atom at its active site [33].

STATINS AND HYDROGEN SULFIDE

Recently the influence of two doses of atorvastatin on H₂S tissue concentration in different organs of mice was examined. The effect of the drug on brain, liver and heart did not exceed 10.6% of H₂S tissue level. In the kidney lower dose of atorvastatin induced 9.7% rise in H₂S concentration (control group: 5.26 ± 0.09 µg/g, atorvastatin dose 5 mg/kg b.w./d group: 5.77 ± 0.11 µg/g, p = 0.0003); while higher dose increased H₂S level by 42.2% (atorvastatin 20 mg/kg b.w./d group: 7.48 ± 0.09 µg/g, p < 0.0001) [34]. This experiment outcome and previously discussed data show that endogenous H₂S may have contribution to the effect of atorvastatin on blood pressure. Subgroup analyses of major clinical studies and meta-analyses of smaller trials indicate that statin therapy slows the decline of the glomerular filtration rate and reduce proteinuria in patients with chronic kidney disease. In researchers' opinion statins have been appearing to protect the kidneys through complex unclear non-cholesterol-mediated mechanisms apart from effects of lipid lowering [35, 36]. These observations encourage to explore the role of H₂S in physiology and pathology of kidney.

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DZIAŁANIE HIPOTENSYJNE STATYN. CZY JEST MIEJSCE DLA SIARKOWODORU
W TEJ UKŁADANCE?

Streszczenie

Obniżające poziom cholesterolu we krwi statyny (inhibitory reduktazy 3-hydroksy-3-metyloglutarylo-koenzymu A) zmniejszają ryzyko chorobowości i śmiertelności sercowo-naczyniowej u osób z chorobami układu krążenia. Wyniki niektórych badań wskazują ponadto, że ta grupa leków obniża ciśnienie tętnicze. W prezentowanym artykule dyskutowane są pleiotropowe efekty działania statyn, które mogą mieć wpływ na ciśnienie tętnicze. Przedstawione są wyniki badań na temat roli siarkowodoru (H₂S) w układzie sercowo-naczyniowym oraz fizjologii nerek z uwzględnieniem najnowszych eksperymentalnych danych wskazujących, że atorwastatyna zwiększa tkankowe stężenie H₂S w nerkach.

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