DOSE-DEPENDENT INFLUENCE OF TWO-WEEK ADMINISTRATION OF SIMVASTATIN AND METOPROLOL INJECTION ON THE BLOOD PRESSURE IN NORMOCHOLESTEROLEMIC RATS

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Abstract: β-blockers are widely used in clinical practice. It is connected with their multiple cardiac effects: slowing heart rate, decrease of myocardial contractility and lowering of systemic blood pressure. Early use of β-blocker in acute myocardial infarction reduces the risks of reinfarction and ventricular fibrillation. However, the above effects may be associated with the risk of cardiogenic shock. Many patients with cardiovascular diseases receiving β-blockers are recommended to statin therapy, as well. There are several reports indicating that statins have beneficial cardiovascular effects through their broad spectrum of cholesterol-independent action. It has been revealed that statins could decrease blood pressure, as well. The aim of the study was to evaluate the influence of simvastatin in different doses and metoprolol injection on the blood pressure in normocholesterolemic rats. The experiments were performed on Wistar rats, outbred males. Simvastatin at 1, 10 and 20 mg/kg or vehicle (0.2% methylcellulose) were given intragastrically during two-week period. After two week simvastatin administration, rats were injected intraperitoneally with metoprolol at 5 mg/kg b. w. The arterial blood pressure signals were provided by Isotec pressure transducer connected to a direct current bridge amplifier and catheter was implanted into the right carotid artery. Conclusion: Two week administration of simvastatin in different doses to normocholesterolaemic rats does not modify metoprolol impact on the blood pressure.

Keywords: rats, simvastatin, metoprolol, blood pressure

β-Blockers are widely used in clinical practice. It is connected with their multiple cardiac effects: slowing heart rate, decrease of myocardial contractility and lowering of systemic blood pressure. Early use of β-blocker in acute myocardial infarction reduces the risks of reinfarction and ventricular fibrillation. However, the above effects ma be associated with the risk of cardiogenic shock (1). Many patients with cardiovascular diseases receiving β-blockers are recommended to statin therapy, as well. HMG-Co A reductase inhibitors (statins) reduce cardiovascular morbidity and mortality and these benefits have extended their usage in medical practice (2-6). The above positive effects are the result of well-established association between a high cholesterol level and adverse cardiovascular risks and death (7, 8). However, many reports confirmed that these beneficial cardiovascular effects of statins are connected with their broad spectrum of cholesterol-independent action, as well (9-13). These extralipid, so-called pleiotropic, activities include: statin impact on the plaque stabilization and endothelial function; as well as antiproliferative, anti-inflammatory, and antiapoptotic effects. Moreover, animal and clinical studies have reported that statins might influence on the blood pressure (14, 15). Thus, it seems to be important from the practical point to assess the dose dependent effect of co-administration of simvastatin and metoprolol, with their impact on the blood pressure.

The aim of the study was to evaluate the influence of simvastatin at different doses and metoprolol injection on the blood pressure in normocholesterolemic rats.

EXPERIMENTAL

See preceding paper.

RESULTS

The exemplary blood pressure recordings before and after metoprolol administration is shown in Figure1.

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Mean blood pressure (Figure 2.)

Metoprolol or 0.9% NaCl administration did not cause decrease in mean blood pressure in the control group as compared to baseline (99.37 ± 3.89 vs. 96.18 ± 5.67 mmHg or 93.23 ± 5.42 vs. 94.94 ± 8.22 mmHg) (p > 0.05). After administration of sim-vastatin at 1, 10 or 20 mg/kg no changes in the base-line values as compared to the control group were observed. Administration of metoprolol to rats receiving 1 mg/kg of simvastatin statistically insignificantly decreased mean blood pressure as compared to the control group (104.49 ± 6.26 vs. 96.18 ± 5.67 mmHg (p > 0.05). Administration of metoprolol to rats receiving 10 mg/kg of simvastatin statistically insignificantly decreased mean blood pressure as compared to the control group (100.32 ± 12.52 vs 96.18 ± 5.67 mmHg) (p > 0.05) and as compared to rats receiving 1 mg/kg of simvastatin (100.32 ± 12.52 vs. 104.49 ± 6.26 mmHg (p > 0.05). In rats receiving simvastatin at 20 mg/kg adminis-tration of metoprolol caused insignificant changes in mean blood pressure as compared to the control group (102.78 ± 10.46 vs. 96.18 ± 5.67 mmHg) (p > 0.05), as compared to rats receiving 1 mg/kg of sim-vastatin (102.78 ± 10.46 vs 104.49 ± 6.26) (p > 0.05) or 10 mg/kg of simvastatin (102.78 ± 10.46 vs 100.32 ± 12.52) (p > 0.05).

Systolic blood pressure (Figure 3.)

Systolic blood pressure after metoprolol or 0.9% NaCl administration did not significantly decrease in the control group as compared to baseline (105.96 ± 8.35 vs. 113.41 ± 4.82 mmHg; 104.17 ± 11.13 vs. 103.08 ± 10.72 mmHg) (p > 0.05). No changes after administration of simvastatin at 1, 10 and 20 mg/kg in the baseline as compared to the control group were observed. In rats receiving 1 mg/kg of simvastatin, administration of metopro-lol did not cause any statistically signif-icant changes as compared to the con-trol group (117.24 ± 9.14 vs. 105.96 ± 8.35 mmHg) (p > 0.05). Administration of metoprolol to rats receiving 10 mg/kg of simvastatin caused statistical-ly insignificant changes in SBP as compared to the control group (114.08 ± 15.26 vs 105.96 ± 8.35) (p > 0.05) and compared to rats receiving 1 mg/kg of simvastatin (114.08 ± 15.26 vs. 117.24 ± 9.14) (p > 0.05). In rats receiving simvastatin at 20 mg/kg, metoprolol caused any insignificant changes in systolic blood pressure as compared to the control group (113.48 ± 13.74 vs. 105.96 ± 8.35 mmHg) (p > 0.05), to rats receiving 1 mg/kg of simvastatin (113.48 ± 13.74 vs 117.24 ± 9.14) or 10 mg/kg of simvastatin (113.48 ± 13.74 vs 114.08 ± 15.26).

Diastolic blood pressure (Figure 4.)

Diastolic blood pressure after metoprolol or 0.9% NaCl administration did not significantly decrease in the control group as compared to base-line (87.32 ± 5.30 vs. 87.14 ± 4.95 mmHg; 87.01 ± 6.91 vs. 84.93 ± 4.97 mmHg) (p > 0.05). No changes after administration of simvastatin at 1, 10 and 20 mg/kg in the baseline as compared to the control group were observed. In rats receiving 1 mg/kg of simvastatin, administration of metoprolol did not cause any statistically significant changes in dias-tolic blood pressure as compared to the control group (93.51 ± 4.64 vs. 87.32 ± 5.30 mmHg). Administration of metoprolol to rats receiving 10 mg/kg of simvastatin caused statistically insignifi-cant changes in diastolic blood pressure as com-pared to the control group (89.46 ± 11.37 vs 87.32 ± 5.30) and as compared to rats receiving 1 mg/kg of simvastatin (89.46 ± 11.37 vs. 93.51 ± 4.64). In rats receiving simvastatin at 20 mg/kg, metoprolol caused any insignificant changes in systolic blood pressure as compared to the control group (93.63 ± 10.39 vs. 87.32 ± 5.30 mmHg), as compared to rats receiving 1 mg/kg of simvastatin (93.63 ± 10.39 vs 93.51 ± 4.64) or as compared to rats receiving 10 mg/kg of simvas-tatin (93.63 ± 10.39 vs 89.46 ± 11.37).

No significant changes in plasma total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides levels (the mean ± SD) after two week administra-tion of simvastatin or vehicle [mmol/L] were observed among all groups of the animals.
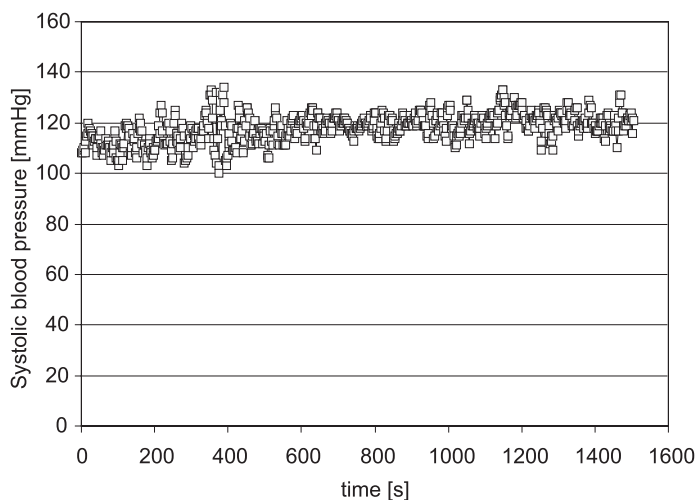

Figure 1. Systolic blood pressure after metoprolol administration in rat.
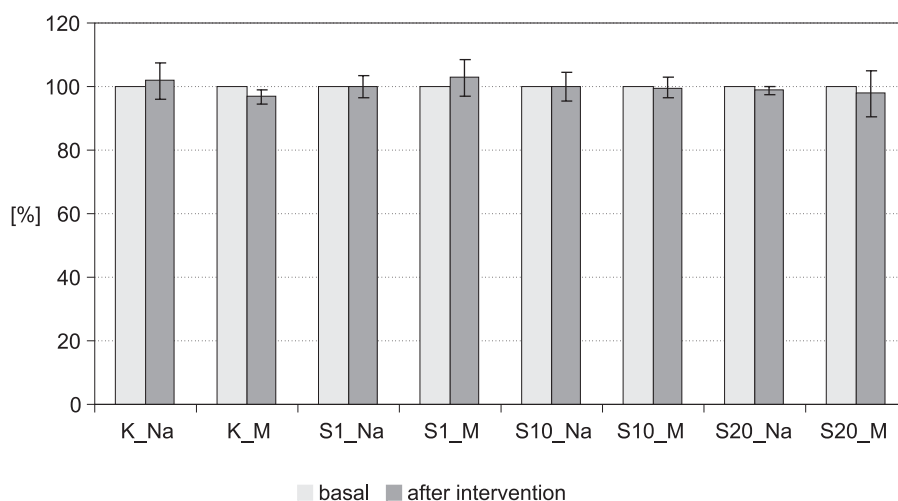
Figure 2. Mean arterial pressure difference[%] before and after metoprolol(M) or 0.9% NaCl (Na) injection to normocholesterolemic rats receiving simvastatin at 1 mg/kg (S1); 10 mg/kg (S10) and 20 mg/kg (S20) during two weeks.
K_Na indicates control group receiving 0.9%NaCl injection, **K_M** indicates control group receiving metoprolol injection, **S1_Na, S1_M** – indicate rats receiving 1 mg/kg simvastatin and 0.9%NaCl or metoprolol injection, **S10_Na, S10_M** – indicate rats receiving 10 mg/kg simvastatin and 0.9%NaCl or metoprolol injection, **S20_Na, S20_M** – indicate rats receiving 20 mg/kg simvastatin and 0.9%NaCl or metoprolol injection.
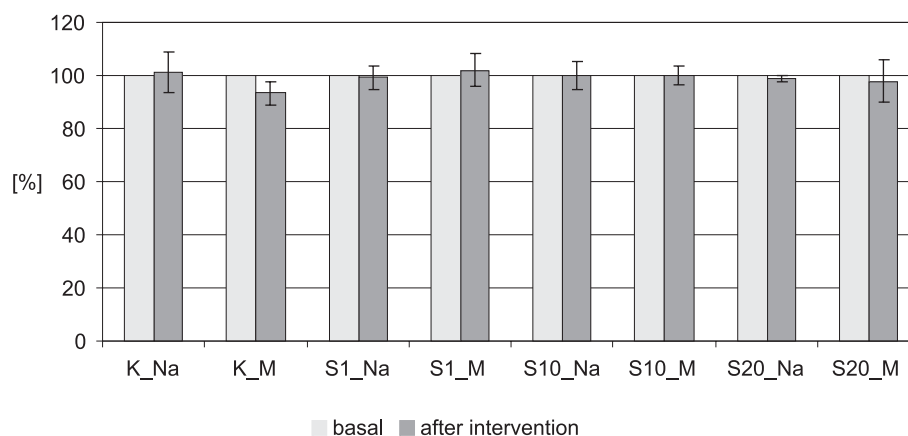

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K_Na indicates control group receiving 0.9%NaCl injection, **K_M** indicates control group receiving metoprolol injection, **S1_Na, S1_M** – indicate rats receiving 1 mg/kg simvastatin and 0.9%NaCl or metoprolol injection, **S10_Na, S10_M** – indicate rats receiving 10 mg/kg simvastatin and 0.9%NaCl or metoprolol injection, **S20_Na, S20_M** – indicate rats receiving 20 mg/kg simvastatin and 0.9%NaCl or metoprolol injection.

DISCUSSION AND CONCLUSION

A lot of studies showed that pleiotropic activities of statins might contribute to β-adrenergic stimulation (16). It was demonstrated that treatment of cardiac myocytes with statin, reduces the cAMP, and force-increasing effect of β-adrenergic stimulation in a concentration-dependent manner. The above effect was accompanied by cytosolic accumulation of a fraction of G-protein γ-subunits with an apparently smaller molecular weight, cytosolic accumulation of G protein β-subunits and a decrease in Gαs total protein. Statin effect on Gαs was fully reversed by mevalonate and GGPP, but not by FPP or squalene (17). Biochemical evaluations showed that isoprenylation of Gγ has been found to be essential for membrane attachment of Gγ and Gβ which forms a tight complex with Gγ (18, 19). Thus, by interfering with Gγ isoprenylation, statins could influence membrane association and function of heterotrimeric G-proteins (18, 20).
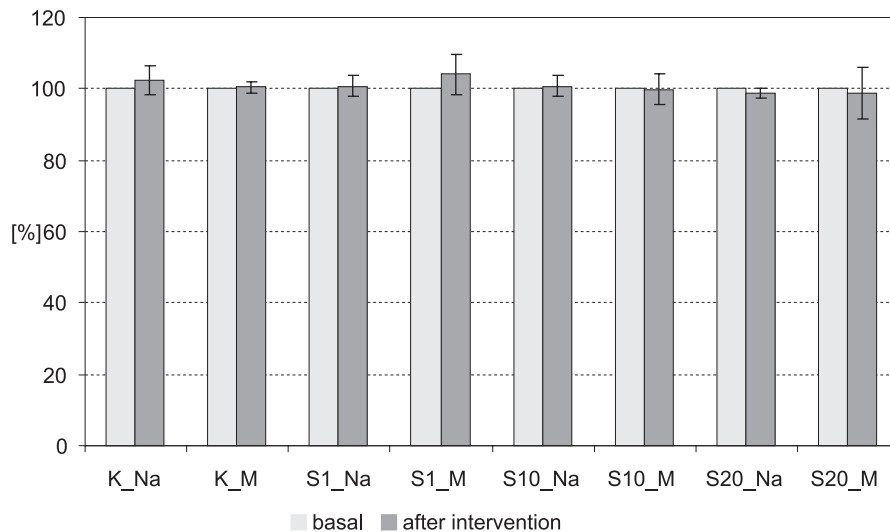
Figure 4. Diastolic arterial pressure difference before and after metoprolol (M) or 0.9% NaCl (Na) injection in normocholesterolemic rats receiving simvastatin at 1 mg/kg (S1); 10 mg/kg (S10) and 20 mg/kg (S20) during two weeks.
K_Na indicates control group receiving 0.9%NaCl injection, **K_M** indicates control group receiving metoprolol injection, **S1_Na, S1_M** – indicate rats receiving 1 mg/kg simvastatin and 0.9%NaCl or metoprolol injection, **S10_Na, S10_M** – indicate rats receiving 10 mg/kg simvastatin and 0.9%NaCl or metoprolol injection, **S20_Na, S20_M** – indicate rats receiving 20 mg/kg simvastatin and 0.9%NaCl or metoprolol injection.

Another point is that β-adrenergic stimulation is connected in Rho kinase pathway. Statins can decrease intracellular pathway across small GTPases Rho, Ras, Rac (21) and β-blockers were shown to modulate small GTPases, as well (22). Some reports indicate the possible statin impact on the blood pressure (23-25). In CARE study it was revealed that statins had no significant effects on blood pressure (24) but in ASCOT-LLA study, atorvastatin (10 mg) administration resulted in significant decrease in blood pressure (25). It was suggested that the above differences in the obtained results could be connected with the degree of LDL-C reduction achieved in these trials (26). In our study no changes in LDL-C level after simvastatin administration in all used doses were observed, too. A lack of statin anti-hypertensive activity observed in our study seems to explain conclusion from clinical trials. In our study short term administration of simvastatin did not influence the blood pressure after metoprolol injection. The above observation in normocholesterolemic rats was independent of the drug dose used in the experiment. It did not reveal apparent "anti-adrenergic effects" of statins (27, 28). The possible statin influence on beta-receptor activity and blood pressure in normocholesterolemic rats after two-week statin administration was confirmed by biochemical examinations only. Further evaluation of interaction after long simvastatin treatment in normocholestrolemic i hipercholesterolemic models is needed.

Acknowledgments

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