ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Resveratrol, Hawthorn Extract, Dihydroquercetinum, Rosuvastatinum: Common Way of Cardioprotective Effect Realization.

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ABSTRACT

The work evaluates the effect of resveratrol (2.5 mg/kg) (I), hawthorn extract (3 mg/kg) (II), dihydroquercetinum (2 mg/kg) (III) and rosuvastatinum (2 mg/kg) (IV) on the area of necrotizing left ventricle myocardium and the level of blood serum troponin in case of acute coronary occlusion (60 min) with consecutive reperfusion (90 min) in anesthetized rabbits. It was evidenced that distant and pharmacological preconditioning, resveratrol, hawthorn extract and rosuvastatinum reduce the area of necrosis by 3, 2.5, 2.5, 2 and 2 times correspondingly. There was discovered that ATP-sensitive potassium channels participate in realization of cytoprotective effect of distant preconditioning, I, II, III and IV which was evidenced by elimination of cardioprotective effects after administration of glibenclamid (4 mg/kg).

Keywords: preconditionong, ischemia/reperfusion, resveratrol, hawthorn extract, dihydroquercetinum, rosuvastatinum.

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ISSN: 0975-8585

INTRODUCTION

There are plenty of works dedicated to examination of cardioprotective effect of phytopreparations based on resveratrol, hawthorn extract, dihydroquercetinum [1, 2, 3]. As a rule the mode of action is considered from the point of view of their antioxidant activity [4, 5]. On the other hand inhibitors of HMG-CoA reductase and rosuvastatinum above all are becoming more frequently used as a baseline therapy for secondary coronary heart disease prevention and the emphasis is being moved towards pleiotropic effects of statins not related to cholesterin [6].

This work was aimed at verification of a hypothesis on participation of the mechanisms forming the basis of ischemic preconditioning in realization of cardioprotective effects of resveratrol, hawthorn extract, dihydroquercetinum and rosuvastatinum.

METHODOLOGY

Study of the survival rate of ischemic myocardium was performed with involvement of 66 rabbits with the weight of 2-2.5 kg. Myocardial infarction was reproduced in anesthetized animals (300 mg/kg of chloral hydrate) under the conditions of controlled respiration by ligation of the descending left coronary artery branch at the level of the bottom edge of the left auricular appendix (60 min) with the subsequent reperfusion (90 min). Transverse myocardium sections were performed at the interval of 0.8 cm starting from the level of 0.8 cm below the applied ligature. The myocardium sections were placed in a container with phosphate buffer (pH 7.4) and 1 mg/ml of triphenyl tetrazolium chloride for formation of red formazan [7, 8]. Computation of the areas of intact and necrotizing left ventricle myocardium was made for each of four sections by means of a pixel-by-pixel analysis in Adobe Photoshop 9.0 program. The level of Troponin I (TnI) was determined by means of an immunofluorescent device Triage MeterPro (Biosite, США).

Ischemic preconditioning was carried out by a 5-minutes long blood flow interruption in the ligated coronary artery 30 minutes prior to total ischemia of the myocardium. Distant ischemic preconditioning was made by applying a tourniquet onto the upper third of the thigh for the period of 10 minutes with the subsequent 20-minutes long reperfusion and reproduction of an infarction model in the course of 60 minutes.

Pharmacological preconditioning was carried out by means of intragastric administration (by gavage) of resveratrol (2.5 mg/kg) (GreensynTM (Guangzhou).,Ltd), hawthorn extract (3 mg/kg) (State Scientific Center for Pharmaceutical Products, Kharkov), dihydroquercetinum (2 mg/kg) (“Capilar”, (Evalar) and rosuvastatinum (2 mg/kg) (“Crestor”, (DSM). In order to justify the theory on realization of cardioprotective effects via ATP-sensitive potassium channels the animals were administered glibenclamid (“Maninil”, Berlin-Chemie (Germany) in a doze of 0.4 mg/kg [9,10].

STUDY RESULTS

Modeling of the coronary artery ischemia/reperfusion resulted in progression of the myocardium necrosis which size made 27.3±1.2 % of the left ventricle weight (Table 1).

Ischemic preconditioning (5 min) 30 minutes prior to the coronary artery occlusion resulted in reduction of the area of the necrotizing myocardium by 3 times up to 11.8±0.8% (Table 1).

Distant preconditioning, intragastric administration of resveratrol (2.5 mg/kg), hawthorn extract (3 mg/kg), dihydroquercetinum (2 mg/kg) and rosuvastatinum (2 mg/kg) 30 minutes prior to modeling of infarction due to coronary occlusion resulted in positive decrease of the area of necrotizing myocardium which made 9.05±0.6, 10.8±1.0, 13.5±0.5, 14.1±0.9 and 13.9±1.1% correspondingly. The similar tendency could be observed in relation to TnI serum level dynamics (Table 1).

Blocking of the ATP-sensitive potassium channels by glibenclamid at time of the myocardium ischemia/reperfusion modeling resulted in complete removal of the cardioprotective effects of resveratrol (2.5 mg/kg), hawthorn extract (3 mg/kg), dihydroquercetinum (2 mg/kg) and rosuvastatinum (2 mg/kg) and distant ischemic preconditioning with regard to the area of necrosis and the level of TnI (Table 1).

Therefore in the course of the carried out study the investigators discovered that IP, DIP and 3-(2,2,2-trimethylhydrazinium) propionate had comparable cardioprotective effect on the ischemia/reperfusion models in the anasthesized rabbits.

Table 1: The effect of resveratrol, hawthorn extract, dihydroquercetinum rosuvastatinum and distant ischemic preconditioning on the size of necrosis areas and the level of troponin I at time of acute coronary occlusion (60 min) with the subsequent reperfusion (90 min) in the anesthesized rabbits (M±m; in % of the left ventricle weight; n=6).

Item No.	Experimental group	% of necrosis	Serum level of TnI (ng/ml)
1.	Ischemia/reperfusion (control)	27.3±1.2	16.3 ±1.2
2.	Ischemia/reperfusion + IP	11.8±0.8*	5.4±1.4*
3.	Ischemia/reperfusion + DIP	9.05±0.6*	4.6±0.8*
4.	Ischemia/reperfusion + resveratrol (2.5 mg/kg)	10.8±1.0*	5.2±1.0*
5.	Ischemia/reperfusion + hawthorn extract (3 mg/kg)	13.5±0.5*	6.4 ±2.9*
6.	Ischemia/reperfusion + dihydroquercetinum (2 mg/kg)	14.1±0.9*	8.7±0.8*
7.	Ischemia/reperfusion + rosuvastatinum (2 mg/kg)	13.9±1.1*	9.3 ±1.7*
8.	Ischemia/reperfusion + resveratrol (2.5 mg/kg) + glibenclamid (4 mg/kg)	25.7±2.1#	15.4 ±1.9#
9.	Ischemia/reperfusion + hawthorn extract (3 mg/kg) + glibenclamid (4 mg/kg)	26.3±2.1#	17.1 ±1.8#
10.	Ischemia/reperfusion + dihydroquercetinum (2 mg/kg) + glibenclamid (4 mg/kg)	27.2±1.9#	16.4±1.5#
11.	Ischemia/reperfusion + rosuvastatinum (2 mg/kg) + glibenclamid (4 mg/kg)	30.6±2.8#	17.9 ±2.9#
12.	Ischemia/reperfusion + DIP+ glibenclamid (4 mg/kg)	39.4±2.3#	18.1 ±2.4#

Remark: Ischemia/reperfusion – coronary occlusion of the descending left coronary artery branch at the level of auricula (60 min) with the following reperfusion (90 min); IP – ischemic preconditioning (5 min); DIP – distant ischemic preconditioning (10 min) of the upper thigh third; *$p < 0.05$ – as compared to control; # $p < 0.05$- as compared to the series without pharmacological analyzer.

The ATP-sensitive potassium channels are an effector mechanism in realization of anti-ischemic effect both of distant ischemic preconditioning and resveratrol, hawthorn extract, dihydroquercetinum and rosuvastatinum. It can be assumed that NO acts as an ischemic preconditioning trigger, in the both cases its synthesis occurs due to activation of iNOS and eNOS [11, 12].

CONCLUSION

- Resveratrol (2,5 mg/kg), hawthorn extract (3 mg/kg), dihydroquercetinum (2 mg/kg) and rosuvastatinum (2 mg/kg) take intense protective effect on the ischemia/reperfusion models in the anasthesized rabbits by reducing the area of necrosis and the level of TnI in blood serum by 2-2.5 times.
- The ATP-sensitive potassium channels participate in realization of the cardioprotective effects of resveratrol (2.5 mg/kg), hawthorn extract (3 mg/kg), dihydroquercetinum (2 mg/kg) and rosuvastatinum (2 mg/kg).

REFERENCES

[1] Hattori R, Otani H, Maulik N, Das DK, 2002. Pharmacological preconditioning with resveratrol: role of nitric oxide. Am J Physiol Heart Circ Physiol. 282(6):1988-1995.

[2] Swaminathan JK1, Khan M, Mohan IK, et al. 2010. Cardioprotective properties of Crataegus oxycantha extract against ischemia-reperfusion injury. Phytomedicine. 17(10):744-752.

[3] Gumanova NG, Artyushkova EB, Metel'skaya VA, et all. 2007. Effect of antioxidants pQ510 and resveratrol on regulatory function of the endothelium in rats with modeled arterial hypertension. Bull Exp Biol Med. 143(6):678-681.

[4] Liang L, Gao C, Luo M, et all. 2013. Dihydroquercetin (DHQ) induced HO-1 and NQO1 expression against oxidative stress through the Nrf2-dependent antioxidant pathway.J Agric Food Chem. 20; 61:2755-2761.

[5] Mikhin V.P., Pokrovskiy M.V., Gureev V.V. et al., 2011. Efficiency of a home-produced myocardial cytoprotector and its pharmacodynamics in case of acute myocardial ischemia: clinical results and experimental models. Russian Journal of Cardiology, 2: 37-42.

[6] Vale N1, Nordmann AJ, Schwartz GG, et all. 2011. Statins for acute coronary syndrome. Cochrane Database Syst Rev. 15;(6): 1002-1014.

[7] Ragulina V.A., Korokin M.V., Pokrovskiy M.V. et al. 2011. Study of cardioprotective activity of 3-oxipiridine derivative. International Journal of Applied and Fundamental Research, 3:118.

[8] Chernomortseva Y.S., Pokrovskiy M.V., Pokrovskaya T.G. et al. 2009. Experimental study of cardioprotective and endothelioprotective effect of macrolides and azalides. Eksperimentalnaya y klinicheskaya pharmakologiya Journal, 2: 29-31.

[9] Downey J.M., Davis A.M., Cohen M.V., 2007. Signaling pathways in ischemic preconditioning. Heart Fail Rev., 12(3-4): 181-188.

[10] Skyschally A., Schulz R., Heusch G., 2008. Pathophysiology of myocardial infarction: protection by ischemic pre- and postconditioning. Heart Fail Rev., 33: 88-100.

[11] Matsumura K., Jeremy R.W., Schaperet J. al. 2008. Progression of myocardial necrosis during reperfusion of ischemic myocardium. Circulation, 97(8): 795-804.

[12] Kolesnik I.M., Pokrovskiy M.V., Danilenko L.M. et al. 2010. Distant and pharmacological preconditioning – new possibilities of neovasculogenesis stimulation. Kubanskii nauchnyi meditsinskii vestnik, 6:56-58.