Acta Veterinaria (Beograd), Vol. 57, No. 2-3, 123-132, 2007.

DOI: 10.2298/AVB0703123G UDK 619:612.133

ENDOTHELIUM-DEPENDENT RELAXATION OF RAT AORTA INDUCED BY RESVERATROL

GOJKOVIĆ-BUKARICA LJILJANA**, NOVAKOVIĆ ALEKSANDRA*, LEŠIĆ A***
and BUMBAŠIREVIĆ M***

**School of Medicine, Belgrade; **School of Pharmacy, Belgrade,*
****Institute of Orthopedics and Traumatology, Clinical Center of Serbia, Belgrade*

(Received 21. October 2006)

It has been noted that there are a number of biologically active phenolic compounds present in wine, particularly red wine. Such compounds include, for example, catechin, epicatechin, quercetin, rutin, trans-resveratrol and cis-resveratrol. The resveratrol isomers, in particular, have been found to promote vascular relaxation. The mechanisms by which resveratrol causes vasodilatation are uncertain. The aim of this study was to investigate the mechanism(s) of resveratrol-induced vasorelaxation in rat aorta with endothelium present. Rat aortic rings were precontracted with phenylephrine. Resveratrol induced relaxation of the rat aortic rings. L-NAME, an inhibitor of NO synthase, abolished relaxation of rat aorta, but methylene blue, an inhibitor of guanylate cyclase, did not abolish relaxation induced by resveratrol. Highly selective blocker of ATP-sensitive K^+ channels, glibenclamide as well as a nonselective blocker of big Ca-sensitive K^+ channels, charybdotoxin did not block resveratrol-induced relaxation of rat aorta. 4-Aminopiridine, which is a non selective blocker of voltage-gated K^+ (Kv) channels, and margatoxin which inhibits Kv1 channels abolished relaxation of rat aortic rings induced by resveratrol. In conclusion, we have shown that resveratrol potently relaxed rat aortic rings with endothelium present. It seems that NO and smooth muscle K_V channels are included in this relaxation. This finding is of clinical importance in both veterinary and human medicine.

Key words: rat aorta, K^+ channel, NO, resveratrol, vasorelaxation

INTRODUCTION

It has been noted that there are a number of biologically active phenolic compounds present in wine, particularly red wine. Such compounds include, for example, catechin, epicatechin, quercetin, rutin, *trans*-resveratrol and *cis*-resveratrol. The resveratrol isomers, in particular, have been found to promote vascular relaxation (Goldberg, 1995). The mechanisms by which resveratrol causes vasodilatation are uncertain. Today is known, that resveratrol-induced vasorelaxation may either be endothelium-dependent (attenuated by L-NAME) or

endothelium-independent (Naderali *et al*., 2001). Resveratrol might become incorporated into the smooth muscle membrane, where it could either couple with a membrane receptor or interact directly with membrane ion channels, thus inducing endothelium independent vasorelaxation (Jager and Nguyen-Duong, 1999; Andriambeloson *et al*., 1999). Previously, it has been shown that resveratrol produced relaxation of the rat aorta without endothelium and human internal mammary artery by activation of voltage-gated K^+ (K_V) channels located in the smooth muscle (Novakovic *et al*., 2006a; Novakovic *et al*., 2006b; Novakovic *et al*., 2006c). Other authors suggested that resveratrol produces hyperpolarization of the vascular endothelial cells by direct activation of large Ca^{2+}-activated K^+ (BK_{Ca}) channels (Wu, 2003). Orsini *et al*. (2004) suggested that resveratrol derivates inhibit K_V channels in the F-11 neuroblastoma cells. This discrepancy in the results obtained on different experimental models indicates tissue and species selectivity for resveratrol.

Therefore, the present study addressed the question of whether different K^+ channels are involved in the endothelium-dependent mechanism of vasodilatation induced by resveratrol. For that purpose, we tested the action of resveratrol on the rat aorta with endothelium. This could be of value in clinical practice both for animals and humans.

MATERIALS AND METHODS

Vascular rings were prepared from the aortas of male Wistar rats 250 to 300 g, essentially as described elsewhere (Orallo, 1997). The studies reported in this work have been carried out in accordance with the European regulations on the protection of animals, the Declaration of Helsinki and/or the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the United States National Institutes of Health.

Assessment of vascular function

The rat aortic segments were dissected free from connective tissue. They were cut into rings (3 mm) and were mounted between two stainless-steel triangles in an organ bath containing 10 ml Krebs-Ringer-bicarbonate solution (37°C, pH of 7.4), aerated with 95% O_2 and 5% CO_2. One of the triangles has been attached to a displacement unit allowing fine adjustments of tension and the other was connected to an isometric transducer (K30, Hugo Sachs, Freiburg, Germany). The preparations were allowed to equilibrate for 30 min. During this period, the vessels have been washed with a fresh buffer solution every 10 min.

We have examined the effects of resveratrol onto the rings with intact endothelium. After equilibration, the presence of functional endothelium was assessed. Rings were precontracted with phenylephrine (1 μM) and acetylcholine (20 μM) was added into the organ bath. If the maximal relaxant effect was more than 80% of the initial contraction, we considered functional endothelium to be present. Failure of arteries to relax to acetylcholine (20 μM) was considered to indicate a state of endothelial denudation (Naderali *et al*., 2001).

The length-tension characteristics for each vessel were determined as described previously (Gojkovic-Bukarica *et al*., 1997). The resting tension was 2 g (Schoeffter *et al*., 1988). Vascular rings were allowed a further 30 min to equilibrate before being contracted with phenylephrine.

Concentration-response curves were obtained by the cumulative addition of resveratrol (1 - 100 μM) to ring segments contracted to a stable plateau by adding phenylephrine (1 μM). Increasing concentrations of resveratrol have been added only after the previous concentration had produced equilibrium response or after 20 min if no response was obtained. Therefore, the following protocol was used: 1) contraction to phenylephrine and concentration-response curve to resveratrol plotted, followed by three washes, addition of different K^+ channel blocker and a 20 min equilibration period; 2) contraction to phenylephrine and plot of the concentration-response curve to resveratrol.

Treatment of data and statistics

Relaxation produced by each concentration of resveratrol was measured and expressed as a percentage of the maximum possible relaxation (i.e., relaxation back to the baseline tension). The concentration of resveratrol producing 50% of its own maximum response (EC_{50}) was determined for each curve by using a non-linear least square fitting procedure of the individual experimental data, and presented as pD_2 (pD_2 = -log EC_{50}).

The results are expressed as the means ± standard error of the mean (SEM); *n* refers to the number of experiments. All calculations were done by using the computer program Graph Pad Prism (Graph Pad Software Inc., San Diego, U.S.A.).

Drugs

The following drugs were used: trans-resveratrol, phenylephrine, acetylcholine, glibenclamide, charybdotoxin, 4-aminopiridine (4-AP), and margatoxin (Sigma-Aldrich Inc., St. Louis, MO, USA). Resveratrol was dissolved in 70% v/v ethanol with further dilution in distilled water before use. Working concentrations of ethanol in the bath were <0.01 % (v/v). Glibenclamide was dissolved in polyethylene glycol. Previous experiments showed that the solvents used had no effects on preparations at the concentrations applied. All drugs were added directly to the bath in a volume of 50 μL and the given concentrations are the calculated final concentrations in the bath solution.

RESULTS

Effects of resveratrol on precontracted rat aorta

Resveratrol (1 - 100 μM) induced a concentration-dependent relaxation of rings with endothelium with pD_2 values of 4.52 ± 0.11 (maximal response 100±1%, n = 10), (Fig. 1).

Effects of L-NAME and methylene blue on resveratrol-induced relaxation

L-NAME (100 μM) abolished resveratrol-induced relaxation of rat aorta (maximal responses: 100 ± 2 % in the absence vs. 25 ± 2 % in the presence of L-NAME, $p<0.01$, $n = 10$, $p<0.01$, $n = 10$), (Figure 2A).

Methylene blue (10 μM) did not abolish resveratrol-induced relaxation of rat aorta ($pD_2 = 4.53 \pm 0.04$ in the absence vs. 4.55 ± 0.03 in the presence of methylene blue, $P>0.05$; maximal response 100 ± 4 % in the absence vs. 100 ± 5 % in the presence of methylene blue, $P>0.05$) (Fig. 2B).

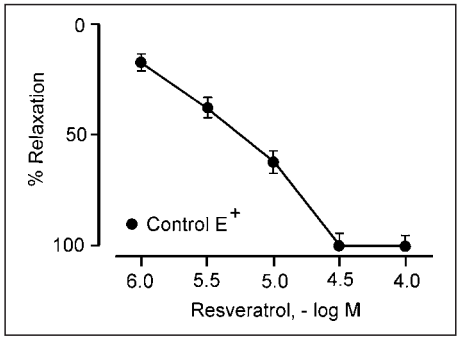

Figure 1. Concentration-response curve for resveratrol in the rat aorta. Rings were precontracted with phenylephrine (1 μM). Responses are expressed as a percentage of the maximum possible relaxation, i.e., the return of tension to the pre-phenylephrine level. Each point represents the mean ± SEM (n = 10)

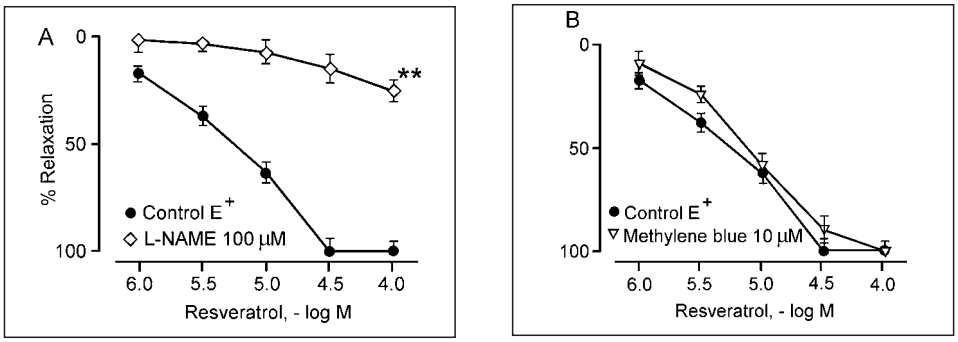

Figure 2. Antagonism of the relaxant effect of resveratrol by a L-NAME and methylene blue in the rat aorta. Concentration-response curves for resveratrol in the absence and presence of L-NAME (A) and methylene blue (B). Responses are expressed as a percentage of the maximum possible relaxation, i.e., the return of tension to the pre-phenylephrine level. Each point represents the mean ± SEM (n = 10). Significance of differences: ** $P<0.01$

Effects of potassium channel antagonists on the resveratrol-induced relaxation of rat aorta with endothelium

Glibenclamide (10 μM), charybdotoxin (10 nM), TEA, 4-AP (3 mM), and margatoxin (10 nM) did not affect basal tension of HIMA (n = 7, each; data not shown).

Glibenclamide (10 μM, n = 10), a selective ATP-sensitive K^+ (K_{ATP}) channels inhibitor did not significantly modify the relaxation of rat aorta induced by resveratrol (pD_2 = 5.28 ± 0.04 in the absence vs. 5.33 ± 0.03 in the presence of glibenclamide, P>0.05; maximal response 100 ± 4 % in the absence vs. 100±5 % in the presence of glibenclamide, P>0.05) (Fig. 3A).

Charybdotoxin (10 nM, n = 10), a potent inhibitor of calcium sensitive K^+ channels did not affect the relaxation of rat aorta produced by resveratrol (pD_2 = 5.29 ± 0.03 in the absence vs. 5.23 ± 0.05 in the presence of charybdotoxin, P>0.05; maximal response 100 ± 5 % in the absence vs. 100 ± 4% in the presence of charybdotoxin, P>0.05) (Fig. 3B).

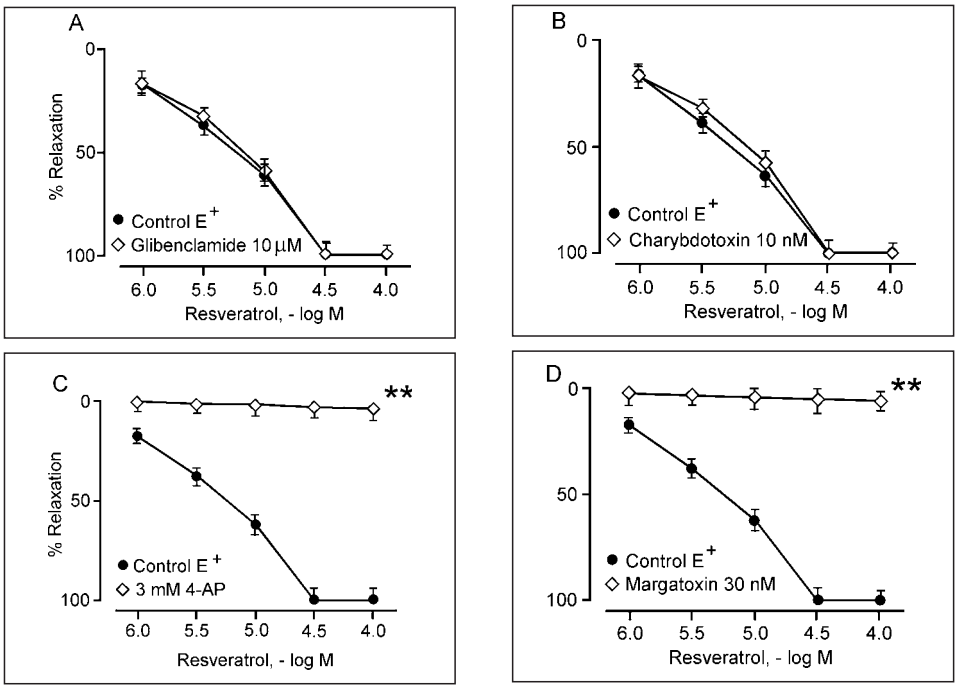

Figure 3. Antagonism of the relaxant effect of resveratrol by a K^+ channel inhibitors in the rat aorta. Concentration-response curves for resveratrol in the absence and presence of: glibenclamide (A), charybdotoxin (B), 4-amynopiridine (C) and margatoxin (D). Rat aortic rings were contracted with phenylephrine (1 μM). Responses are expressed as a percentage of the maximum possible relaxation, i.e., the return of tension to the pre-phenylephrine level. Each point represents the mean ± SEM (n = 10). Significance of differences: ** P<0.01

4-AP (3 mM, n = 10), a predominant blocker of K_V channels abolished resveratrol-induced relaxation of rat aorta (maximal response: 100 ± 2 % in the absence vs. 4 ± 2 % in the presence of 4-AP, $P<0.01$) (Fig. 3C).

Margatoxin (10 nM, n = 10), a potent inhibitor of Kv1 channels abolished the resveratrol-induced relaxation of the rat aorta (maximal responses: 100 ± 4 % in the absence vs. 6 ± 3 % in the presence of margatoxin, $P<0.01$) (Fig. 3D).

Glibenclamide (10 μM), charybdotoxin (10 nM), 4-AP (3 mM), and margatoxin (10 nM) did not affect the basal tension of the rat aorta with endothelium nor the contraction induced by phenylephrine (data not shown, n = 6 - 7).

DISCUSSION

Several studies suggested vasorelaxant effects of polyphenolic compounds (Andriambeloson *et al*., 1997; Fitzpatrick *et al*., 1995). Resveratrol is thought to be a prime compound of the polyphenols, causing the relaxation of human internal mammary artery, rat aorta, mesenteric and uterine artery of guinea pig, prior contracted by phenylephrine, noradrenaline or KCl (Chen and Pace-Asciak, 1996; Orallo *et al*., 1997; Naderali *et al*., 2000; Naderali *et al*. 2001; Rakici *et al*., 2005; Novakovic *et al*., 2006a; Novakovic *et al*., 2006b). In the present study, we have shown that resveratrol induces concentration-dependent relaxation of rat aorta with endothelium.

Today is known that endothelium-dependent effect of resveratrol is apparent at low concentrations (10 - 30 μM) and is blocked by inhibitors of NO synthase. In our study, pretreatment with L-NAME, an inhibitor NO synthesis, completly abolished endothelium-dependent relaxation of rat aortic rings produced by resveratrol. This finding is in agreement with previous reports where resveratrol-induced vasodilatation was attenuated with inhibitors of NO synthesis (Chen and Pace-Asciak, 1996; Fitzpatrick *et al*., 1995; Naderali *et al*., 2001; Novakovic *et al*., 2006c). Oppositely, the relaxation induced by resveratrol was not blocked by methylene blue, an inhibitor of soluble guanylate cyclase. According to this, it seems that endothelium-dependent vasorelaxation of rat aorta caused by resveratrol could be mediated by endothelial generation and release of NO. The mechanism underlying the NO-induced vasodilatation has been intensively investigated. Current knowledge suggests a central role for cGMP-dependent activation PKGI which can phosphorylate different membrane proteins. NO can also activate K_{Ca} channels and increase the outward potassium current. It has been shown that this action of NO can be both independent and dependent on activation PKGI (Gewalting and Kojda, 2002). The relative contribution of each of these PKGI and K^+ channel dependent vasodilating mechanism of NO remains to be determined (Gewalting and Kojda, 2002).

To determine whether the K^+ channels mediated relaxation of rat aorta with endothelium induced by resveratrol, we used different potassium channel blockers.

To analyze the contribution of K_{ATP} channels to the endothelium-dependent resveratrol-induced relaxation of the HIMA, we used glibenclamide (10 μM).

Glibenclamide is known as one of the most selective blockers of K_{ATP} channels, although when used at high concentrations (>30 μM), it may block some other types of K^+ channels (Sturgess *et al*., 1985; Schmid-Antomarchi *et al*., 1987; Cook and Quast, 1990). In the present study, glibenclamide did not inhibit the relaxation of rat aorta induced by resveratrol. Accordingly, it seems that K_{ATP} channels are not involved in the pathway by which resveratrol produces a relaxation of the rat aorta. This result is in agreement with the view that glibenclamide does not antagonize antinociceptive effect of resveratrol (Granados-Soto *et al*., 2002; Novakovic *et al*., 2006b).

To analize the possibility that the endothelium-dependent relaxation of the rat aorta, evoked by resveratrol, is mediated via BK_{Ca} channels, charybdotoxin was tested. Originally described as a selective inhibitor of BK_{Ca} channels (Miller *et al*., 1995), charybdotoxin was later found to inhibit small conductance Ca^{2+}-activated K^+ channels and Kv channels (Alexander *et al*., 2006). In each case, channel inhibition occurs with similar potency in the low nanomolar range (K_d~ 0.3 and 10 nM) (Wallner *et al*., 1999). The concentration of charybdotoxin used in our study was sufficient to block BK_{Ca} channels, but did not alter relaxation of the rat aorta induced by resveratrol. Accordingly, it seems that charybdotoxin-sensitive channels are not involved in the mechanism of resveratrol-induced relaxation of the rat aorta.

To study the contribution of K_V channels to the resveratrol-induced relaxation in the rat aorta, we used 4-AP. This compound is the most widely used blocker in the identification of potassium channel types. With very few exceptions, 4-AP have been shown to be without effect on BK_{Ca} (Ritchie, 1987). Using low milimolar concentration, 4-AP achieved some selectivity for K_V channels (Beech and Bolton, 1989). This feature complies with the results given by our experiments i.e. 4-AP (3 mM) antagonized resveratrol-induced relaxation of HIMA rings with comparable potency. Thus, our finding supports a relevant participation of K_V channels in the relaxation of HIMA produced by resveratrol. Consistent with this idea is the result obtained by Granados-Soto *et al*., (2002) that suggests that activation of K_V channels participates in the peripheral nociceptive effect of resveratrol.

Margatoxin, a potent and selective blockers of the Shaker-type (Kv1) voltage-gated K^+ channels was used to determine the role of these channels in the resveratrol-induced relaxation of rat aorta. This peptide is highly selective inhibitor of the Kv1.1, Kv1.2, and especially Kv1.3 channels, but displays no affinity for the mammalian BK_{Ca} channel (Garcia Calvo *et al*., 1993, Suarez-Kurtz *et al*., 1999, Alexander *et al*., 2006). Kv1.2 channels are primarily expressed in endothelial cells, whereas Kv1.3 channels were identified in arteriolar smooth muscle cells (Xu *et al*., 1999; Cheong *et al*., 2001). Here, margatoxin used in a concentration sufficient to block Kv1 channels (10 nM), abolished resveratrol-induced relaxation, suggesting that those channels might be included in the mechanism of resveratrol-induced endothelium-dependent vasodilatation of rat aorta.

The data presented here corresponds well with the results obtained on human internal mammary artery and rat aorta without endothelium (Novakovic *et*

al., 2006a; Novakovic *et al*., 2006b). This observation needs to be evaluated in cardiovascular and orthopaedic practice.

In conclusion, we have shown that resveratrol induces relaxation of the rat aorta rings with endothelium. It seems that NO, 4-AP and margatoxin-sensitive K^+ channels located in vascular smooth muscle mediated the relaxation of rat aorta produced by resveratrol. Further investigations will be necessary to explain the nature of interaction between NO and K^+ channel in rat aorta.

ACKNOWLEDGEMENT:
We thank Mrs. Milena Zabunovic for technical support during this study. The study was supported by a Scientific Research Grant from Ministry of Science and Technology Serbia.

Address for correspondence:
Ass. Prof. Dr. Ljiljana Gojković-Bukarica
Department of Clinical Pharmacology,
Pharmacology and Toxicology,
School of Medicine,
P.O. Box 840,
11129 Belgrade, Serbia
E-mail: bukarica@rcub.bg.ac.yu

REFERENCES

1. *Alexander S, Mathie PA, Peters JA*, 2006, Guide to receptors and channels, 2nd edition, *Br J Pharmacol,* 147, S1-168.
2. *Andriambeloson E, Stoclet JC, Andriantsitohaina R*, 1999, Mechanism of endothelial nitric oxide-dependent vasorelaxation induced by wine polyphenols in rat thoracic aorta, *J Cardiovasc Pharmacol,* 33, 248-54.
3. *Beech DJ, Bolton TB*, 1989, Properties of the cromakalim induced potassium condutance in smooth muscle cells isolated from the rabbit portal vein, *Br J Pharmacol*, 98, 851-64.
4. *Chen CK, Pace-Asciak CR*, 1996, Vasorelaxing activity of resveratrol and quercetin in isolated rat aorta, *Gen Pharmacol*, 27, 363-6.
5. *Cheong A, Dedman AM, Xu SZ, Beech DJ*, 2001, Kvα1 channels in murine arterioles: differential cellular expression and regulation of diameter, *Am J Physiol Heart Circ Physiol*, 281, H1057-H65.
6. *Cook NS, Quast U*, 1990, Potassium channel pharmacology, In: Cook, NS, editor. *Potassium channels: Structure, classification, function, and therapeutic potential*, New York: John Wiley and Sons, 181-258.
7. *Fitzpatrick DF, Hirschfield SL, Ricci T, Jantzen P, Coffey RG*, 1995, Endothelium-dependent vasorelaxation caused by various plant extracts, *J Cardiovasc Pharmacol*, 26, 90-5.
8. *Garcia-Calvo M, Leonard RJ, Novick J, Stevens SP, Schmalhofer W, Kaczorowski GJ, et al.,* 1993, Purification, characterization, and biosynthesis of margatoxin, a component of centruroides margaritatus venom that selectively inhibits voltage-dependent potassium channels, *J Biol Chem*, 268, 18866-74.
9. *Gewalting MT, Kojda G,* 2002, Vasoprotection by nitric oxide: mechanisms and therapeutic potential (Review), *Cardiovascular Research*, 55, 250-60.
10. *Gojkovic-Bukarica Lj, Kazic T, Sajic Z, Djukanovic B, Panic, Peric M*, 1997, The effects of levcromakalim and pinacidil on the human internal mammary artery, *Fundam Clin Pharmacol*, 11, 550-60.
11. *Goldberg MD,* 1995, "Does wine work?", *Clin Chem*, 41, 14-6.
12. *Granados-Soto V, Arguelles CF, Ortiz MI*, 2002, The peripheral antinociceptive effect of resveratrol is associated with activation of potassium channels, *Neuropharmacol*, 43, 917-23.

13. *Jager U, Nguyen-Duong H*, 1999, Relaxant effect of trans-resveratrol on isolated porcine coronary arteries, Arzneim Forsch, 49, 207-11.
14. *Miller C*, 1995, The charybdotoxin family of K^+ channel-blocking peptide, Neuron, 15, 5-10.
15. *Naderali KE, Doyle JP, Williams G,* 2000, Resveratrol induces vasorelaxation of mesenteric and uterine arteries from female guinea-pigs, *Clin Sci,* 98, 537-43.
16. *Naderali KE, Smith LH, Doyle JP, Williams G*, 2001, The mechanism of resveratrol-induced vasorelaxation differs in the mesenteric resistance arteries of lean and obese rats, *Clin Sci,* 100, 55-60.
17. *Novakovic A, Bukarica Gojkovic Lj, Peric M, Nezic D, Djukanovic B, Lipkovski Markovic J, Heinle H,* 2006a, The Mechanism of Endothelium-Independent Relaxation Induced by the Wine Polyphenol Resveratrol in Human Internal Mammary Artery, *J Pharm Sci,* 101, 85-90.
18. *Novakovic A, Bukarica Gojkovic Lj, Kanjuh V, Heinle H,* 2006b,Potassium Channels Mediated Vasorelaxation of Rat Aorta Induced by Resveratrol, *Basic & Clinical Pharmacology & Toxicology, (In Press).*
19. *Novakovic A, Bukarica Gojkovic Lj, Peric M, Nezic D, Djukanovic B, Lesic A, et al.,* 2006c, Endothelium-Dependent Relaxation of Internal Mammary Artery Produced by Resveratrol, *Acta Veterinaria*, 56, 203-13.
20. *Orallo F, Alvarez E, Camina M, Leiro J, Gomez E, Fernandez P*, 2002, The possible implication of trans-resveratrol in the cardioprotective effects of long-term moderate wine consumption, *Mol Pharmacol*, 61, 294-302.
21. *Orallo F,* Study of the in vivo and in vitro cardiovascular effects of a hydralazine-like vasodilator agent (HPS-10) in normotensive rats, 1997*, Br J Pharmacol*, 121, 1627-36.
22. *Orsini F, Verotta L, Lecchi M, Restano R, Curia G, Redaelli E, Wankedl E*, 2004, Resveratrol derivates and their role as potassium channels modulators, *J Nat Prod*, 67, 421-42.
23. *Rakici O, Kiziltepe U, Coskun B, Aslamaci S, Akar F*, 2005, Effects of resveratrol on vascular tone and endothelial function of human saphenous vein and internal mammary artery*, Int J Cardiol*, 105, 209-15.
24. *Ritchie AK*, 1987, Two distinct calcium-activated potassium currents in a rat anterior pituitary cell line, *J Physiol*, 385, 591-609.
25. *Schmid-Antomarchi, H DeWelle J, Fosset M, Lazdunski M*, 1987, The receptor for antidiabetic sulfonylureas controls the activity of the ATP-modulated K+ channel in insulin-secreting cells, *J Biol Chem*, 262, 15840-4.
26. *Schoeffter P, Dion R, Godfraind T,* 1988, Modulatory role of the vascular endothelium in the contractility of human isolated internal mammary artery, *Br J Pharmacol*, 95, 531-43.
27. *Sturgess NC, Ashford ML, Cook DL, Hales CN*, 1985, The sulfonylurea receptor may be an ATP-sensitive potassium channel, *Lancet,* 2, 474-5.
28. *Suarez-Kurtz G, Vianna-Jorge R, Pereira BF, Luisa Garcia M, Kaczorowski J*, 1999, Peptidyl inhibitors of Shaker-Type KV1 channels elict twitches in guinea pig ileum by blocking KV1.1 at enteric nervous system and enhancing acetylcholine release, *J Pharm Exp Ther*, 289, 1517-22.
29. *Wallner M, Meera P, Toro L*, 1999, Calcium-activated potassium channels in muscle and brain, In: Kurachi Y, Jan LY, Lazdunski M, editors, *Current Topics in Membrane*, Volume 46: *Potassium ion channels, Molecular structure, function, and diseases*, San Diego: Academic Press, 117-35.
30. *Wu SN*, 2003, Large-conductance Ca2+- activated K+ channels: physiological role and pharmacology, *Curr Med Chem*, 10, 649-61.
31. *Xu C, Lu Y, Tang G, Wang R*, 1999, Expression of voltage-dependent K+ channel genes in mesenteric artery smooth muscle cells, *Am J Gastrointest Liver Physiol*, 277, G1055-G63.

Acta Veterinaria (Beograd), Vol. 57, No. 2-3, 123-132, 2007.
Gojković-Bukarica Ljiljana *et al.*: Endothelium-dependent relaxation of rat aorta induced by resveratroll

ENDOTEL-ZAVISNA RELAKSACIJA AORTE PACOVA PROUZROKOVANA REZVERATROLOM

GOJKOVIĆ-BUKARICA LJILJANA, NOVAKOVIĆ ALEKSANDRA, LEŠIĆ A i BUMBAŠIREVIĆ M

SADRŽAJ

Zapaženo je da je veliki broj biološki aktivnih, fenolnih jedinjenja prisutan u crnom vinu. Takva jedinjenja uključuju katehin, epikatehin, kvercetin, rutin, kao i *trans* i *cis* rezveratrol. Smatra se da polimeri rezveratrola poseduju značajno vazodilatatorno dejstvo, ali mehanizam vazodilatacije još uvek nije poznat. Cilj ovog rada bio da se ispitaju efekti i mehanizam vazorelaksantnog delovanja rezveratrola na aorti pacova sa endotelom. Aorta pacova je prekontrahovana fenilefrinom, a rezveratrol je koncentracijski-zavisno relaksirao aortu pacova. L-NAME, inhibitor NO sintaze, je antagonizovao relaksaciju aorte pacova, ali metilensko plavo, inhibitor solubilne gvanilat ciklaze, nije antagonizovao relaksaciju, prouzrokovanu rezveratrolom. Visoko selektivni blokator ATP-senzitivnih K^+ kanala, glibenklamid, kao i neselektivni blokator velikih Ca-senzitivnih K^+ kanala, karibdotoksin nisu antagonizovali rezveratrolom indukovanu relaksaciju aorte pacova. 4-Aminopiridin, neselektivni blokator volatazno-zavisnih K^+ (Kv) kanala, i margatoksin, blokator Kv1 kanala, su antagonizovali relaksaciju aorte pacova prouzrokovanu rezveratrolom. Može se zaključiti da je endotel-zavisna relaksacija aorte pacova, prouzrokovana rezveratrolom, verovatno posredovana NO. Izgleda da su, 4-aminopiridin- i margatoksin-senzitivni K-kanali smešteni u membrani vaskularnih glatko-mišićnih ćelija aorte pacova, uključeni u mehanizam endotel-zavisne relaksacije prouzrokovane rezveratrolom.