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Baroreflex Sensitivity, Cardiac and Kidney Remodeling and Deterioration in Vasoactive Substances Content in Blood in Experimental Model of Renovascular Hypertension. Action of Natural Flavone, Luteolin

N.A. Papiashvili[1], M.V. Ghonghadze[2], N.V. Sharikadze[3], M. P. Khutsishvili[4], K.A. Bakuridze[1], A.J. Bakuridze[1], G.V. Sukoyan[5,*], N.V. Gongadze[2]

[1]Department of Pharmaceutical Technology, Tbilisi State Medical University, Tbilisi, Georgia.

[2]Department of Medical Pharmacology, Tbilisi State Medical University, Tbilisi, Georgia.

[3]Department of Biochemistry, Ilia State University, Tbilisi, Georgia.

[4]Laboratory of Biochemistry of Meta Clinic, Tbilisi, Georgia.

[5]International Scientific Center of introduction of New Biomedical Technology, Tbilisi, Georgia.

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Corresponding author:

Galina Sukoyan, PhD, Professor, International Scientific Center of introduction of New Biomedical Technology, 0137, Gr.Lortkipanidze str., 17e, Tbilisi, Georgia; Tel.:+995595418030

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Abstract

This study aimed to analyze pharmacological actions of phenolic compound luteolin on the renal and cardiac hypertrophy, blood pressure (BP), baroreflex sensitivity (BRS), levels of epoxyeicosatrienoic acids (EETs), prostaglandin E-2 (PGE-2) and endothelin-1 (E1) in plasma in the 2 kidney - 1 clip (2K-1C) model of renovascular hypertension (RVH).

All animals, were randomized into 2 groups: control (normal) I - sham-operated, II - RVH male Wistar rats, which after 4 weeks of surgical intervention secondly randomized to control II group, treated 0.1% dimethyl sulphoxide (DMSO) and main group - with luteolin in 15 DMSO, 3 mg/kg body weight, intraperitonially, during 2 weeks. ET-1, EETs and PGE_2 levels investigated in carotid artery blood plasma and analyzed using ELISA kits. All data statistically analyzed using the SPSS-10.0 program.

In RVH rats BP increased by 32%, cardiac and right kidney hypertrophy and reduction in parasympathetic component of BRS by 40% and sympathetic by 39%. The plasma level of total trans-EETs and PGE_2 in RVH rats decreased by 44% and 50% respectively, while the level of ET-1 increased by 67%. Two weeks treatment with luteolin lowered BP, improved parasympathetic, without marked changes in sympathetic component of BRS. Deremodeling of cardiac and renal hypertrophy under prolonged treatment with luteolin accompanied with increasing in the level of EETs by 44%, PGE-2 by 50% and markedly reducing of plasma content of

ET-1 (by 60%).

Inhibition of EET hydrolase using low doses of luteolin provides beneficial cardio and renoprotective action in experimental model of RVH.

Introduction

Renovascular hypertension (RVH) still remains as a major risk factor for heart and renal failure, stroke and different other complications [1-2]. The high morbidity and lethal outcome characteristic for RVH is a large challenge for health professionals [3-4]. A new insight for the successful treatment of this disease is associated with a new targets involving in vascular homeostasis and consequently in the regulation of arterial pressure [5-6]. Endothelial dysfunction considered as a main predisposing factor with prevalence of vasoconstrictors facilitating to the development of cardiovascular disease [7-9]. A number of studies provide an evidence that along with prostacyclin and NO epoxygenase products of arachidonic acid metabolism-epoxyeicosatrienoic acids (EETs) cause vasodilation by activating the smooth muscle large conductance Ca^{2+}-activated K^{+} channels [5, 10]. EETs may function as endothelium-derived hyperpolarizing factors (EDHF) in animal and human vessels providing vasodilatory, natriuretic and anti-inflammatory action [11-17]. In experimental studies EETs showed beneficial effect in hypertensive states, improving vascular endothelium function with reduction of inflammation and increased Na^{+} elimination prevented RVH [5,18-19]. The vasodilatory action of EETs in different vascular beds is decreased by an enzyme soluble epoxide hydrolase (sEH) which converts EETs to less active compounds being their corresponding diols - dihydroxyeicosatrienoic acids (DHET), with a short half-life limiting EETs pharmacological activity [10, 20-25]. Among EETs isomers the 14,15-trans- EET hydrolyzed most rapidly and the rate of EET hydrolysis reduced two-to threefold sequentially from 14,15,11,12-and 8,9-to 5,6, EETs [5-6, 17- 18]. In last years a great interest is directed to compounds providing sEH inhibitory properties to prolong EETs vasodilatory action and enhancing their cardio and renoprotective potential [21, 26-29]. The elevated expression of sEH in SHR and reduction of EETs plasma concentration was shown in subjects with renovascular hypertension [16, 30], while in other findings authors did not established any differences in basal plasma levels of EETs between healthy and hypertensive patients [31]. Such controversial data could indicate about varies role of EDHF depending on the vascular bed and necessity to investigate EETs level in different form of arterial hypertension, as well as elucidate relationship between vasoconstrictive and vasodilation agents.

The purpose of this study was to evaluate the baroreflex sensitivity and cardiac and kidney remodeling in experimental Goldblatt hypertension model, deterioration in vasodilators and vasoconstrictors substances production/extraction blood and efficacy of pharmacological correction by soluble epoxide hydrolase (sEH) inhibitor, nature phenolic compound, luteolin.

Materials and Methods

Study design, Experimental protocol, hemodynamic and baroreflex sensitivity study

All experimental procedures performed in accordance with the in-house guidelines “Guide for the care and use of laboratory animals” (National Institute of Health publication 86-23, Revised 1996) and occurs with the protocol approved by the Interinstitutional Animal Care and Use Committee of Tbilisi State Medical University, Ilia State University and International Centre of Introduction of New Biomedical Technology, Tbilisi, Georgia (No 11-819021). Experiments were carried out in 52 adult (35-42 days old) male Wistar rats weighing 220-260 g. Rats were kept under controlled conditions (temperature 21 ± 2 °C, humidity 60 ± 10%, 12 h inverted light cycle–light/dark) and fed *ad libitum* on

the standard normal-protein diet and had free access to water. Seven days after acclimatization, animals were randomized in I control group – sham operated (SO, n=21) and II – hypertensive rats reproduced by 2 kidney -1 clip (2K-1C, n=32) model, created with a constricting silver clip (internal diameter – 0.2 mm) on the left renal artery for it's partial occlusion under (87 mg/kg Ketamine ("Zdorovye", Ukraine) + 13 mg/kg Xylazin Bio (Xylazin, 2%, Biovera",Czech), as described early [32-33]. In control, SO rats, the same surgical procedures were performed with only kidney exposure without its removal or renal artery ligation. The rats were involved in experiments after 4 weeks of surgical intervention. Rats that had SBP > 140 mmHg defined as having hypertension. The development of RVH also confirmed by using non-invasive tail-cuff blood pressure methods. Three days before experiments in anesthetized rats, polyethylene catheter inserted in the right carotid artery and connected to a blood pressure transducer for measuring blood pressure (BP) with an electromanometer and heart period (HP) with a cardiotachometer. Catheter placed in the right jugular vein used for drug administration. To evaluate the parasympathetic (cardiochronotropic) and sympathetic components of baroreflex sensitivity (BRS), phenylephrine (PE) – 10 mcg/kg and sodium nitroprusside (SNP) -10 mcg/kg i.v. injections used, respectively. The animals from the II group in according with the received therapeutic treatment were secondly randomized into two group: positive control group – RVH rats received i.p. of 1,0 ml of phosphate buffer solution (PBS) containing 0.1% dimethyl sulphoxide (DMSO, Carl Roth, Germany) and main group – 3 mg/kg body weight of Luteolin, produced from plant Perilla Nankinensis Decne by the Department of Pharmacognosy and Pharmaceutical Botanic of Tbilisi State Medical University (quality analyzed by high-performance liquid chromatography, purity ³98%), during 2 weeks. Based on the literature data and our preliminary study Luteolin (3′,4′,5,7-tetrahydroxyflavone) was dissolved in sterile saline with 0.1% DMSO in PBS, pH 7.4. No adverse effects or toxicity associated with luteolin administration observed in the present study at 24 h after injection. Among the selected compounds, luteolin showed higher inhibitory effect (IC50 μM) on sEH activity, providing vasodilatory action in rat isolated mesenteric resistance vessel preparation using myograph system (unpublished results). Luteolin dose 3 mg/kg i.p. has chosen after doses escalation experiments: 0.1, 0.3, 1.0, 3.0, 5.0 mg/kg. In all animals luteolin was administered i.p. 3 mg/kg during 2 weeks.

Body and organ hypertrophy

The body weight, heart and kidney weight were recorded. The cardiac and kidney hypertrophy index were expressed as heart weight/body weight (HW/BW), left kidney and right kidney weight and right kidney weight/body weight (RKW/BW).

Biochemical markers study

Biochemical markers, endothelin -1 (ET-1), epoxyeicosatrienoic acids- EETs and prostaglandin - E_2 (PGE_2), levels were investigated in blood plasma taken from the carotid artery (placed in tubes with 1% heparin) and the animals were euthanized. The blood than immediately centrifuged (10 min at 845 × *g* and 4 ºC temperatures) for plasma sample collection. The serum and plasma samples were stored at -80 ºC until being analyzed. EETs plasma levels were analyzed using Elisa kits (cat. No: MBS9310869, Eagle Biosciences, USA), while PGE-2 (Cat. No: CSB-E07967r, Cusabio, USA) and ET-1 (Cat. No: CSB-E06979r, Cusabio, USA) plasma contents were measured by Elisa Kit (Cusabio, USA) in according with the manufacturer's instruction.

Statistical analysis

SPSS software is used for statistical analysis, measurement data to mean ± standard deviation (average

±SD), using t test and single factor analysis of variance for group comparison, P<0.05 indicates there was a significant difference, using Student's test.

Results

Hemodynamics and baroreflex sensitivity study

In conscious freely moving rats, the analysis of hemodynamic parameters and BRS showed significant differences in baseline values of BP, HP and BRS in RVH and SO rats, however none of the rats died in any of the groups (table 1). In RVH rats BP increased by 32%. Hypertension formation under 2K-1C model correlated with mean values of HP near 140±6 ms and reduction in parasympathetic (cardiochronotropic) component of BRS evaluated with PE vs. observed in SO rats. Assessment of sympathetic component of BRS with SNP in RVH rats significantly did not changes in comparison with hypertensive rats treated with vehicle and SO groups. However, treatment with luteolin reverse the ratio between Sympathetic/parasympathetic component of BRS from 1,12±0,08 ms $mmHg^{-1}$ in chronic RVH to 0,92±0,06 ms $mmHg^{-1}$ (p<0,01), the level observed in control animals. Thus, it will be suggested, that luteolin administration toward to the normal the balance of accentuated antagonism between sympathetic and parasympathetic nervous system

Cardiac and renal hypertrophy formation

The body weights at the beginning of the experiment, 4 weeks after the surgical intervention, and 2 weeks after i.p. administration of the low doses of luteolin of two 2K-1C experimental model of RVH groups were not significantly different (Table 2). The cardiac mass of the RVH group was increased in comparison to the SO group, did not changes under treatment with vehicle and decreased in luteolin treated group up to control level. The mean weight of left clipped kidneys was significantly decreased while the right non-clipped kidneys weight was significantly increased in both 2K-1C groups compared to the SO group. Such alteration of body weights in RVH animals accompanied by marked increase of heart weight/body weight and right kidney weight/body weight ratio in SO rats that indicates for cardiac and renal hypertrophy development. Two weeks treatment with luteolin significantly attenuates cardiac and renal remodeling.

Plasma vasodilators and vasoconstrictors substances alterations in chronic 2K-1C experimental model of renovascular hypertension. Action of low doses of luteolin

Progression of RVH in this experimental model of arterial hypertension characterized with decreasing circulating in plasma vasodilators component such as total trans-EETs up to 4.3±0.1ng/ml from the 7.7±0.2ng/ml in SO group and PGE-2 up to 2.4±0.2 ng/ml from the 4.3±0.1 ng/ml. This accompanied with increased in circulated cytokine, ET-1, levels for about three folds (table 3).

Intraperitonially administration of Luteolin during 2 weeks at the end of treatment associated with improvement of blunted cardiochronotropic component of BRS and increased plasma level of total trans EETs by 58% and did not significantly difference from control (SO) level, PGE-2 increased by 50%, but remained lower than in control group by 27% and markedly reduced ET-1 plasma levels, by 40%, however its exceeds control by 80% (Table 3).

Discussion

Investigation conducted in last decade have provided evidence regarding valuability of epoxyeicosa-trienoic acids (EETs) as a new target for the treatment of cardiovascular diseases [10, 34] being the most frequent causing factor of morbidity and fatal outcome [1-2, 4]. A number of experiments showed EETs beneficial effects in different model of arterial hypertension [5, 11, 14, 18] by improving vascular homeostasis, increased Na^+ elimination and reduction of inflammation. EETs vasodilatory

Table 1. Changes in blood pressure, heart period and bar reflex sensitivity in sham operated and renovacular hypertensive rats. Pharmacological efficacy of low doses of luteolin (3 mg/kg body weight), in prolong regime treatment.

Parameter/Group	Sham Operated, n=21	Arterial (renal) hypertension	
		Control, n=16	Main, n=16
Blood Pressure, mm Hg	131±8	172±8***	135±8##
Heart period, ms	156±4	139±6*	150±4#
Baroreflex sensitivity, ms mm Hg^{-1}			
Parasympathetic	0.98±0.10	0.58±0.05***	0.75±0.08#
Symphathetic	0.9±0.12	0.65±0.15**	0.69±0.09*

Note: Significance of difference of comparison: *-with SO group, #- with 2K-1C AH group, one symbol - $p<0.05$, two – $p<0.01$, three – $p<0.001$.

Table 2. Cardiac and kidney hypertrophy in chronic 2K-1C experimental model of renovascular hypertension. Action of low doses of luteolin.

Parameters	Sham operated rats (SO) n=21	2K-1C arterial hypertensive rats	
		Control, n=16	2K-1C + luteolin 3mg/kg i.p. n=16
BW*, g	260±10	256±17	264±12
HW, g	1.18±0.07	1.34±0.07*	1.21±0.06#
HW/BW x 10^{-3}	4.54±0.14	5.23±0.12**	4.66±0.10#
Right kidney weight (RKW), g	1.12±0.06	1.32±0.08**	1.19±0.08#
Left kidney weight (LKW), g	1.17±0.08	0.96±0.08	1.03±0.08
RKW/BW x 10^{-3}	4.30±0.13	5.15±0.11**	4.51±0.10#

Note: * - at the beginning of the experiment average body weight in SO group were 238±10 g and in RVH group - 242±12 g; HW/BW- heart weight/body weight ratios, RKW/BW- right kidney weight/body weight ratios, RKW/BW- left kidney weight/body weight ratios. Other symbols the same as in table 1.

Table 3. The effects of luteolin (3mg/kg i.p.) on EETs, PGE-2 and E-1 plasma concentration in sham operated and hypertensive rats.

Parameters	Sham operated rats (SO), n=21	2K-1C arterial hypertensive rats	
		Control, n=16	2K-1C + luteolin 3mg/kg i.p., n=16
14,15 trans-EET	1.5±0.2	1.2±0.15	1.4±0.1
11,12 trans-EET	2.1±0.1	1.0±0.2	1.7±0.4
8,9 trans-EET	1.9±0.3	0.8±0.1	1.6±0.2
5,6 trans-EET	2.2±0.2	1.3±0.1	2.1±0.1
Total trans EETs ng/ml	7.7±0.2	4.3±0.1*	6.8±0.1**
PGE_2 ng/ml	4.9±0.2	2.4±0.15*	3.6±0.12**
ET-1 pg/ml	3.1±1.0	9.4±1.82*	5.6±1.4**

Note: the symbol the same as in table 1

action is decreased by an enzyme soluble epoxide hydrolase (sEH) converting EETs to less active dihydroxyeicosatrienoic acids (DHETs) limiting EETS pharmacological activity [10, 23]. Currently a great interest is directed to compounds revealing sEH inhibitory properties with ability to prolong and enhance EETs cardioprotective potential [21, 23, 26]. According our experiments performed in 2K-1C 4 weeks hypertensive rats (HR) phenolic compound flavonoid luteolin with sEH inhibitory properties during 2 weeks of treatment significantly reduced blood pressure (BP), cardiac rhythm and improved blunted baroreflex cardiochronotropic component sensitivity without marked changes in baroreflex sympathetic component sensitivity. Our results are consistent with findings of other authors [3, 35] demonstrated in SHR hypotensive effect of flavonoid quercetin with improving sensitivity of vagal component of baroreflex without marked influence on it's sympathetic component. Reduction in BP regarding luteolin and quercetin may be associated with induces NO production and arterial relaxation [35-36], including reduction in blood pressure by endothelium dependent and independent mechanisms. Positive influence of abovementioned antioxidants in hypertensive states on baroreflex function by authors opinion is caused by improved autonomic function, endothelin dysfunction and baroreflex impulses from the carotid artery [35]. Luteolin in our experiments significantly increased EETs plasma level in HR vs. SO animals resulting in it's vasodilatory effect which is in agreement with data obtained by other authors showing reduction in blood pressure of SHR in increased level of trans-EETs [18]. Diminished endothelial function characterized with reduction in release of vasodilatory agents and increased production of vasoconstrictive substances [7, 35, 37-40]. Thus, observed increased of ET-1 plasma levels in RVH vs. SO rats consistent with elevation plasma level of ET-1 in experimental and clinical hypertension [8, 39-42], which can be considered as a marker and predisposing factor for the development of RVH. Luteolin significantly decreased ET-1 plasma concentration in RVH which confirm the suggestion that luteolin directly inhibits the secretion and gene expression of ET-1, for example, in porcine aortic endothelial cells. Its ED50 was about 10 microM. In addition, the inhibition of ET-1 by a glycoside compound of luteolin (luteolin-6-C-glucoside) was weak [39]. Not less important, that luteolin increase endothelium-dependent relaxation in rat aortic rings, which may be mediated by reducing reactive oxygen production, enhancing activity in the NOS-NO pathway and reducing levels of tumor necrosis factor -α and thus occurs anti-inflammatory action and reduced vascular inflammation in endothelial cells via preventing the activation of nuclear factor (NF)-kappa B [42]. Regarding PGE-2 there are controversial data concerning PGE-2 plasma content in hypertensive states. Our results showed that plasma level of PGE-2 in RVH elevated after treatment with luteolin. This data are in agreement with results of other authors considering this potent lipid mediator as a vasodepressor and modulator of blood pressure homeostasis [9]. In contrast to this and our data a group of authors suggest about increased activity of prostanoid system maintaining the hypertension [43]. Such differences in obtained data can be explained by fact that PGE-2 reveals multiple actions throughout 4 distinct E-prostanoid (EP) receptor isoforms: EP-1 to EP-4. Among them EP-4 receptor facilitates to PGE-2-dependent vasodilation, but its role in the development of arterial hypertension is not fully elucidated. Multiple functioning role of EP4R in regulation of BP and in arterial hypertension based on the possible implication of the EP4R in different tissues beyond vascular smooth muscle cells [38]. Epoxyeicosatrienoic acids provide improved myocardial and other tissues remodeling by revealing antioxidant, antiinflammatory and antifibrotic action [34, 43-46]. Increased right kidney weight/body weight ratio simultaneously with diminished the same ratio in the left kidney of hypertensive rats in comparison with SO animals, indicate on the renal remodeling. 2 weeks treatment with luteolin significantly decreased such alteration in kidney weight. The same directions in alteration in heart and kidney weight/body weight ratio early found in 2K-1C hypertensive rats under influence of

flavonoid nobiletin [47], which gave ground to suggested that this is intrinsic pathophysiological molecular mechanism of natural flavonoids.

Conclusion

Present results suggested about beneficial potential positive effect of luteolin in the treatment of renovascular hypertension, decreasing blood pressure, deremodeling baroreflex sensitivity (in part of parasympathetic component) and renal and cardiac hypertrophy. In the basis of intrinsic mechanism of pharmacological action of prolonged treatment of lower doses of luteolin leads restoration of the sympathetic/parasympathetic component in BRS. One of the key link of positive pharmacological effects of prolong administration of low doses of luteolin is the improving circulated vasodilators component in the blood, endothelial function in several circulatory disorders related to venous insufficiency.

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Conflict of interest

The authors declare that the research conducted in the absence of any commercial or financial relationships that could construed as a potential conflict of interest.

Affiliations

The original contributions presented in the study are included in the article/supplementary material further inquiries directed to the corresponding authors. The data are not publicly available due to privacy or ethical restrictions.

Author contributions

Participated in research design and conception: Gongadze, Sukoyan.

Conducted experiments: Bakuridze K., Papiashvili, Ghonghadze, Sharikadze

Provision of study materials, *contributed new reagents or analytic tools*: Bakuridze A., Bakuridze K., Papiashvili, Khutsishvili

Data analysis performed and interpretation: Sukoyan, Gongadze, Papiashvili

Wrote or contributed to the writing of the manuscript: Gongadze, Sukoyan, and Papishvili.

Final approval of manuscript:

All authors.

Ethics statement

All experimental procedures in this study approved by The Animal Care & Welfare Committee of Tbilisi State Medical University, Ilia State University and International Research Center of introduction of New Biomedical Technology, Tbilisi, Georgia and implemented in accordance with the guidelines for the ethical review of laboratory animal welfare.

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