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Efficacy of Flavonoid Apigenin on Hemodynamic indices, Baroreflex Function, Cardiac and Kidney Remodeling and Vasoactive-Inflammatory Biomarkers in Experimental Renal Hypertension

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The hypothesis stated here that, the long-term prevention by natural flavonoid phenolic compound, for example apigenin (Apg), improves baroreflex sensitivity and vascular resistance and occurs beneficial action for attenuation the renal hypertension (RH). One-kidney, 1-clip rats (1K1C) were treated with Apg for 2 weeks after 1 week of surgical intervention. At the end of the study in the control RH group the blood pressure (BP) increased on average by 43.5%, decreased in heart period (HP) by 9.8%, cardiochronotropic (vagal) component of baroreflex sensitivity (BRS) by 50%, and adrenergic component by 34%. Thus, in 1K1C experimental model of hypertension, provides switching to parasympathetic component and accompanied with proportionally nearly two-fold increase in epinephrine (EPN) and norepinephrine (NE) without changes in EPN/NE ratio. Morphometric changes in the kidney and heart confirmed the development of kidney and cardiac hypertrophy and renal functioning disturbances (blood urea nitrogen (BUN) increased in more than two-fold) and markers of sodium reabsorption in proximal tubule, total trans-EETs, decreased in 1.6-fold. The pronounced increased proinflammatory cytokines, interleukin 1β (IL1 β), endothelin -1 (ET-1) and tumor necrosis factor (TNF)-α confirmed the formation of "sterile inflammation" which strengthening by the nearly two-fold decreasing in the level of anti-inflammatory (vasodilatory) mediators, prostaglandin E2 (PGE2). Preventive long-term regime treatment with Apg (5mg/kg i.p./daily) in RH rats significantly decreased BP by 18.6%, increased parasympathetic component of BRS by 38.5% without marked altered its sympathetic component. Such deremodeling in BRS sensitivity associated with significant decreased in heart and kidney hypertrophy and functional activity of kidney, normalization of BUN and total EETs, reducing in circulating plasma level of catecholamines, and markedly attenuated progression of inflammation, decreased of proinflammatory levels of cytokines. Thus, Apg provides preventive beneficial pluripotent action in RH rats by exerting antihypertensive, cardio- and renoprotective effects and attenuation of "sterile inflammation".

Keywords: Baroreflex Sensitivity; Catecholamines; Hypertension; Hemodynamics; Proinflammatory Cytokines, Prostaglandin E2, Apigenin.

The kidneys are a pair of vital important organs that performed multifunctions life supporting role in the body, including regulation of blood pressure (BP) and chemical balance and in turn can affect the health as a whole. Disturbance in renal functioning that coexistent hypertension and human renovascular disease remained a major reason of people morbidity and complications of cardiovascular diseases and stroke. There are several additional drugs in development that target hemodynamic changes under the progression of hypertension, but the prevalence of end-stage renal disease continues high [1-3]. Hypertensive nephropathy in response to low pressure in the renal vessels, sodium and water retention, increased preglomerular resistance and mean arterial pressure (MAP). Increased MAP usually occurs through volume homeostasis mechanisms, damage of mesangial cells, epithelial cells, and podocytes in the glomerulus that initially raise cardiac output and later elevate total peripheral vascular resistance via autoregulatory adjustments. The renal cells damage progression leading to fibrosis development became causes a reduction in renal blood flow, in the permeability of the filtration barrier and, finally in glomerular filtration[4]. Decreased functional nephrons would lead to glomerular hyperfiltration and increased distal tubular flow rate in the remaining nephrons, eventually glomerular damage as strongly implicated of alterations in sympathetic nervous system (SNS)[5]. More validated severe hypertension experimental model associated with high enhancement of sympathetic-mediated contractile responses and pronounced diastolic and endothelial dysfunction is one-kidney, one-clip (1K1C) Goldblatt model of hypertension rats[6]. After 2-week clipping of the renal artery, in a time when the MAP reached a new plateau, increased plasma, cardiac turnover rate of norepinephrine (NE) levels, which indicates on the peripheral sympathetic nervous system hyperactivation.

The 1K1C experimental hypertension model observed volume retention shuts off renin secretion, and thus this model providing "angiotensin II-independent" and are not inhibited by heparin[6-8]. In the 1K1C animal renin value are normal or low while volume is high due to the loss of total glomerular filtration rate and so-called "normal-renin essential hypertension"[9]. The important roles as autocrine/paracrine regulators in the kidney to control several renal functions, such as renal blood flow and hemodynamics and transepithelial NaCl transport and mediation of inflammation occurs prostaglandins. It has been universally recognized that major inflammatory mediators in renal pathology, prostaglandin E2 (PGE2), is the most abundant renal arachidonic acid metabolites, thromboxane B2, and leukotriene B4[10-13]. Another product of arachidonic acid metabolism - epoxyeicosatrienoic acids (EETs) cause vasodilation by activating the smooth muscle large conductance Ca^{2+}-activated K^+ channels[11-13] being endothelium derived hyperpolarizing factor, provided natriuretic, anti-inflammatory, vasodilatory action[14], develop cardiovascular hypertrophy[7].

Despite of wide spectrum of antihypertensive drugs sustained satisfactory control of hypertension especially resistant forms[15-17] is not always achievable requiring to investigate a new distinctive target and involving different signaling pathways allowing better control of RH. Currently a great interest is revealed regarding s products – flavonoids with polyphenolic structure possessing's EH inhibitory properties, which prolongs EETs vasodilatory action and elicit beneficial effects on the cardiovascular system throughout vasodilatory, antioxidant and anti-inflammatory action[18-19]. However, it is not fully elucidated their possible preventive cardioprotective and renoprotective effects during remodeling in different forms of RH caused by renal insufficiency, as well as correlation between production of vasoactive-inflammatory agents and alterations in cardiovascular parameters, autonomic nervous system and baroreflex function during development of RH.

The goal of this study was to estimate the modulatory preventive action of flavonoid phenolic compound apigenin (Apg) on cardiovascular indices, baroreflex function, vasoactive-inflammatory biomarkers and cardio-renal remodeling in 1K-1C experimental model of renal hypertension.

MATERIALS AND METHODS

Animals and ethical statement

Experiments were performed in three months aged, male Wistar rats (n=75), weighing

200-250 g, in accordance with the Guide for the Care and Use of Laboratory Animals (NIH Publication No 85-23, revised 1996). The animals were included in the experiments after left to acclimatize (an ambient temperature 22±2°C, under the natural 12-hour day/night cycle) for one week. The experimental protocol of the study was revised and approved by the Interinstitutional Animal Care and Use Committee of the Tbilisi State Medical University, Ilia State University and International Centre of Introduction of New Biomedical Technology, Tbilisi, Georgia (No 12-819021) and is in strict accordance with the Recommendations from the Helsinki Declaration, Guiding principles in the care and use of animals.

Drugs, chemicals and Reagents

Analytical grade chemicals and reagents were used for the study. Dimethyl sulfoxide (DMSO), clear colorless liquid (CarlRoth, Germany); Ketamin ("Zdorovye", Ukraine); Xylazin Bio 2% ("Biovera" Czech); penicillin G sodium (100 000 IU, a vial with lyopylized powder, Antibiotice S.A., Romania); sodium nitroprusside-(SNP, 60 mg/5 ml, Adeka Pharmaceutical Industry, Turkey); heparin sodium 5.000I.U./ml, Ash Road North, Great Britain); phenylephrine (PE, 10 mg/ml, Martindale Pharma, an Ethypharm Group Company, Great Britain)

ELISA Kits EETs plasma level (Eagle Bioscience, USA), PGE-2, Interleukine-1β (IL-1β), Endothelin-1 and Tumor Necrosis factor-alpha by ELISA kits Cusabio (USA), Norepinephrine (NE) and epinephrine (EPN) kits Elabscience (USA), ELISA kits for blood urea nitrogen (BUN) (MyBiosorce, USA); Apigenin (Apg; 42 ,5,7-trihydroxyflavone) light yellow powder with purity obtained from the plant Perilla Nankinensis Decne leaves by the Department of Pharmacognosy and Pharmaceutical Botanic of Tbilisi State Medical University (quality analyzed by high-performance liquid chromatography, purity e"98%).

Experimental design

Animals were randomly allocated into I- control group - sham operated (ShO, n=21) and II –main group with validated 1 kidney -1 clip (1K-1C, n=54) Goldblatt model of renal hypertension (RH). Under sterile condition RH was created in anesthetized (Ketamin-87mg/kg, + Xylazin Bio-13mg/kg, intraperitonially (i.p)) animals by right nephrectomy and partial constriction of left renal artery using silver clip (internal diameter-0.2mm). ShO group animals were submitted to the same procedure, except for the nephrectomy and renal artery occlusion. At the end of surgical procedure penicillin G (100 000 IU) was administered into the cavity and wound was closed with a suture. Rats were observed during 4 weeks after surgical procedure for measuring systolic and diastolic arterial pressure and heart rhythm in unanesthetized animals every week to monitored cardiovascular changes using non-invasive "tail-cuff" sphygmomanometric method after their placing into special chamber and adaptation to experimental condition. For evaluation the parasympathetic (cardiochronotropic) and sympathetic components of baroreflex sensitivity (BRS), phenylephrine (PE)-10mcg/kg and sodium nitroprusside-(SNP)-10mcg/kg i.v., was added respectively as described early[20-21]. All animals from the main group after 1 week from surgical procedure secondly randomized in according with drug administration: positive control group II - RH rats administrated i.p. of sterile 0.1% DMSO in PBS (pH 7.4); III – animals received i.p. 5mg/kg/daily Apg in sterile 0.1% DMSO during 2 weeks after the 1 week of surgical procedures.

Experimental protocol

At the end of the experiment's rats were weighed and fasted overnight. The following day, blood samples were withdrawn from the carotid artery in heparinized tubes for sample of plasma preparation, which stored at -80°C until the time of biochemical analysis. Afterward, the rats were euthanized under i.p. lethal dose (60mg/kg i.p.) of pentobarbital and left kidney and heart were excised, cleaned from the surrounding fat and connective tissue and weighting.

No adverse or toxic-effects associated with Apg administration observed in the present study at 24 h after injection. Apigenin produced a high inhibitory effect (IC 50μM) on soluble epoxide hydrolase activity (unpublished results). Apigenin dose 5 mg/kg i.p. has chosen after dose escalation experiments: 0.1, 0.3, 1.0, 3.0, 5.0 mg/kg.

Body and organ hypertrophy

For investigation of apigenin (5mg/kg) preventive action on the morphometric changes during development of RH the body and organs

mass were investigated. The heart and kidney hypertrophy index were expressed as heart weight/ body weight (HW/BW) and kidney weight/body weight (KW/BW) ratio.

Biomarkers study

Biomarkers: epoxyeicosatrienoic acids-EETs, endothelin -1 (E-1) and prostaglandin -E_2 (PGE_2), Interleukin 1b, tumor necrosis factor (TNF)-a, blood urea nitrogen (BUN), norepinephrine (NE) and epinephrine (EPN) levels were determined using ELISA kits in according with manufacturer instruction. After plasma extraction the samples were stored at -80°C until being analyzed by ELISA kits.

Statistical analysis

Data analysis were done in SPSS 22 software. Results were expressed as mean± standard deviation (SD), using t test and single factor analyses of variance for group comparison, P value less than 0.05 was set as the level of significant difference using Student's test.

RESULTS

Modulatory effect of apigenin on cardiovascular parameters and baroreflex sensitivity in hypertensive and sham operated rats.

The analysis of hemodynamic indices and BRS in conscious freely moving rats revealed marked differences between baseline values of BP, HP and BRS in ShO and hypertensive rats (Table1). In animals with RH elevation of BP by 43.5%, was associated with decreased mean values of HP by 9.8%, and reduction in parasympathetic by 50%, and sympathetic by 33.7%, components of BRS, respectively vs. ShO rats. Assessment of sympathetic component of BRS with SNP in RH rats did not changes significantly in comparison with hypertensive rats that administered vehicle.

Preventive treatment with Apg (5mg/kg i.p.) during 2 weeks significantly reduced in RH rats BP by 18.6%, correlated with increased HP by 7.4±1.2%, and parasympathetic component of BRS by 38.5% ($p<0.05$), without marked changes in sympathetic component of BRS possibly indicated that Apg could improve the dysbalance between sympathetic and parasympathetic nervous system.

Cardiac and renal hypertrophy formation

Morphometric variable were estimated according organ weight/body weight ratios in untreated ShO and RH rats and after their pretreatment with apigenin (5mg/kg i.p./ daily) during 2 weeks after 1 week of RH creation. It was revealed that body weight in ShO, untreated and treated with Apg animals' groups were not significantly differ (Table 2). The cardiac mass of the RH group was increased in comparison to the ShO group, did not changes under treatment with vehicle and decreased in Apg treated animals up to control level. The remaining kidney weight was markedly increased in RH group non treated with Apg animals in comparison to ShO rats. Heart weight/body weight ratio in RH was significantly increased as compared to ShO rats that confirmed the cardiac and renal hypertrophy development.

Table 1. Alteration in blood pressure (BP), heart period (HP) and baroreflex sensitivity (BRS) in renal hypertensive rats (RH) after preventive therapy with Apigenin

Parameters/group	Control I group, ShO, n=21	Control II group, RH,n=26	Main group RH + Apg, n=28
Blood pressure, mmHg	124±7	178±8**	145±6$^{\#\#}$
Heart period, ms	153±5	138±4*	149±5$^{\#}$
Components of Baroreflex sensitivity (BRS), ms $mmHg^{-1}$			
Sympathetic (S) component	0.92±0.15	0.61±0.10**	0.66±0.08*
Parasympathetic (PS) component	0.96±0.12	0.48±0.12***	0.78±0.06$^{\#\#\#*}$
PS/S	1.04±0.09	0.79±0.07**	1.18±0.12$^{\#\#\#}$

Note: RH - 1kidney 1 clip (1K-1C) model of renal hypertension; significance of difference in comparison:
*- with sham operated (ShO) group, # - with 1K-1C RH; one symbol- $p<0.05$, two - $p<0.01$, three - $p<0.001$.

Influence of Apigenin on alterations in plasma levels of vasoactive agents and inflammatory biomarkers in 1K-1C renal hypertension (RH)

Development of RH characterized by functional renal indices disturbances: BUN increased by 58.2% ($p<0.001$), accompanied with hemodynamic changes, decreased baroreflex sensitivity and increased plasma biomarkers levels of circulating vasoactive compounds ET-1 by 75% ($p<0,01$), EPN by 44.3% ($p<0,01$) and inflammatory compounds (Table 3), which expressed in decreased total level of vasodilatory trans-EETs by 37.2% ($p<0.05$) and PGE-2 by 47.6% ($p<0,01$). Obtained increasing levels of proinflammatory cytokines of IL-1b by 78.7% ($p<0.001$), TNFá by 54.3% ($p<0.01$) indicates that "sterile" inflammation developed.

Preventive administration of Apg (5mg/kg i.p./daily) during 2 weeks after one week of creation of RH provided marked influence on renal functioning: the level of BUN decreased by 49.3%, EETs by 25.0% associated with the reduction in EPN by 32%, NE by 28.4%, proinflammatory cytokines IL-1b by 57.5%, TNFá by 60,0% and vasoconstrictor ET-1 by 35.4%.

DISCUSSION

Cardiovascular diseases being most common causing factor of morbidity and lethal outcome requires a new target for effective treatment[22-25]. Among them a proper control of arterial hypertension especially its resistant forms

Table 2. Apigenin influence on cardiac and kidney hypertrophy in 1K-1C model of renal hypertension in rats

Parameters	Control-1 group, Sham operated rats (ShO) n=21	Control II group, 1K-1C RH n=26	Main group, 1K-1C RH + Apg n=28
Body weight (BW), g	264±22	242±14	256±16
Heart weight (HW), g	1.30±0.04	1.44±0.05*	1.26±0.04##
HW/BWx10^{-3}	4.90±0.12	5.95±0.15**	4.92±0.10#
Kidney weight (KW), g	1.18±0.05	1.39±0.04**	1.24±02#
Kidney weight/100g body weight (g/100g)	0.44±0.04	0.57±0.05**	0.48±0.03#

Note: at the beginning of the experiments average body weight in ShO group of rats were 245±6 g and in 1K-1C RH group - 240.0±8 g; n - animal amount in each group. Other symbol the same as in table 1.

Table 3. The preventive effects of apigenin 5mg/kg on alterations of plasma vasoactive-inflammatory biomarkers in renal hypertension, caused by 1K1C model in rats

Parameters/group	Control - I group, ShO, n=21	Control II group, 1K-1C +vehicle, n=26	Main Group, 1K-1C RH + Apg, n=28
BUN, mg/dL	16.9±1.2	40.4±6.2***	20.5±3.4#
Total trans EETs ng/ml	8.6±0.4	5.4±0.8*	7.2±1.0#
EPN, pg/ml	49±7	88±8**	60±8#
NE, pg/ml	210±36	438±43*	315.0±28.5#
EPN/NE	0.23±0.03	0.20±0.02	0.19±0.04
ET-1, pg/ml	3.2±0.6	12.7±2.5*	8.2±2.0#
PGE-2, ng/ml	4.2±0.1	2.2±0.2**	3.8±0.15#
IL-1b, pg/ml	2.01±0.02	9.4±1.8***	4.0±1.5#
TNFá, pg/ml	17.6±3.8	38.5±5.2*	15.4±4.6#

Note: EETs - epoxyeicosatrienoic acids, ET-1-Endothelin-1, NE-norepinephrine, EPN-epinephrine, BUN-blood urea nitrogen, PGE-2- Prostaglandin E2, IL-1β-Interleukin-1β, TNFα – Tumor necrosis factor. Other symbols the same as in table 1

not so rarely remain unachievable problem in modern cardiology and nephrology[16].

Early, it was shown, that in validated experimental models of kidney's disease which induced abnormalities of sympathetic activation, increasing of blood pressure, could be taken in preclinical studying as good protype of clinical renal injury. Clinically it related to the normal or low-renin, renin-independence essential hypertension which characterized by failure in renin production and EET's deficiency in response to sodium depletion.

According our data, preventive administration of Apg (5mg/kg i.p.) during 2 weeks after 1 week of surgical intervention in rats with RH significantly decreased elevated blood pressure, increased heart period and cardiochronotropic component of BRS without marked influence on its sympathetic tone. Present results coupled with dates[24-25] that hypotensive effect of flavonoid quercetin in spontaneously hypertensive rats (SHR) associated with increasing of vagal component of BRS without significant changes in its sympathetic component sensitivity. In our experiments apigenin markedly reduced NE, EPN and ET-1 plasma level in RH which is in agreement with results of other authors showing elevation of ET-1 sympathetic tone and catecholamines[26] as well as to result of some investigators demonstrated that Apg enhanced endothelium-dependent relaxation in rat aortic rings, possible inducing by reduction in reactive oxygen production, leading to increase activity in NOS-NO pathway in experimental renovascular hypertension[27]. The decreased of plasma level of NE in the 1K1C RH at the end of experiment secondary confirmed for the reducing the sympathetic nervous system activity at this stage of pathological process or/and increased the amounts of NE at postsynaptic receptor sites.

Diminution in arterial pressure associated with Apg and quercetin shall be due with releases of NO and hence arterial dilation[28-32]. Favorable action of various traditionally using drugs on baroreflex sensitivity in hypertension leads to attenuation of autonomic function, endothelial dysfunction and baroreflex impulses from the carotid artery[25, 33]. Apg markedly increased total trans-EETs plasma level in RH rats in comparison with ShO animals, producing vasodilatory action which is in agreement with results received by other authors demonstrating increased plasma concentration of total EETs correlated with declined blood pressure in SHR[34]. Because 1K-1C models characterized by severe vascular hypertrophy and as a result, vasoconstrictor component, endothelin-1 overexpression in 4-fold[20]. Endothelial dysfunction is associated with reduction in production of vasodilatory agents and raised the release of vasoconstrictive compounds[14, 35-36]. Elevation of plasma level of ET-1 in RH in comparison with ShO rats consistent with dates in patients with chronic arterial hypertension, and suggested to recommended degree of plasma ET1 increasing as a biomarker of delayed diagnosis of renal disease [35-36]. As a result, there is an urgent need to identify and develop novel biomarkers to diagnose renal injury at the earliest stages. Our results demonstrate increased plasma level of vasodilatory PGE-2 caused by Apg in RH. This data comparable with results of other authors considering this potent lipid mediator as a vasodilatory prostaglandin involving in modulation of blood pressure homeostasis[36], while other investigators in contrast to this and our data postulated about increase activity of prostanoid system maintaining the hypertension caused to PGE-2 dependent vasodilation, but its role in the formation of arterial hypertension is not fully established[37]. In our results preventive treatment with Apg in RH rats significantly reduced plasma content of dramatically upregulated compared with normal control rats proinflammatory cytokines: IL-1b and TNF-á and thus providing anti-inflammatory effect with decreased "sterile inflammation".

CONCLUSION

According our results we can postulate that natural flavonoid phenolic compound apigenin exerts preventive pluripotent favorable effect on cardiovascular parameters in experimental 1K-1C model of renal hypertension markedly reducing blood pressure and heart rhythm with significant increased parasympathetic component of baroreflex sensitivity (BRS). Assumingly such hemodynamic and BRS changes may associated with reduction of sympathetic nervous system activity and decreasing of circulating levels of EPN and NE. Alterations in hemodynamic indices and BRS were correlated with cardio- and renoprotective action

of Apg, manifested in diminution of morphometric changes in these organs. Apigenin in RH rats significantly decreased elevated plasma levels of BUN and facilitates to increase plasma level of vasodilatory agents EETs which indicates with the normalization of heart and kidney morphometric parameters to improving of renal and cardiac functioning. As a results attenuation of "sterile inflammation" is occurs and increasing in PGE2 and decreasing in proinflammatory cytokines developed. The main mechanism potentially implicated in antihypertensive preventive effect of Apg is associated with cardiorenal deremodeling and anti-inflammatory activity resulting in improving endothelial dysfunction and vascular homeostasis. Hence, Apg can be considered as a promising compound with beneficial preventive antihypertensive action during development of arterial hypertension.

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Conflict of interest

No potential conflict interest was reported by the authors.

Finding source

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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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