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Human and Animal Physiology

Luteolin Effect on Hemodynamic and Metabolic Alterations in Wistar Rats Submitted to Hyperlipidic Diet

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Abstract. Metabolic syndrome (MS) including dyslipidemia, obesity, arterial hypertension and type-2 diabetes is an important risk factor for cardiovascular complications. The effect of luteolin (L) on hemodynamic indices, endothelium function, glycemic control, lipid spectrum, inflammatory cytokines and adipocytokines production was investigated in Wistar rats submitted to hyperlipidic diet for 6 weeks. It was shown that in hyperlipidic (H) rats vs normolipidic (N) animals significantly increased blood pressure, heart rhythm, insulin, cytokines (IL-1B, TNFα), adipocytokines (leptin, resistin) and vasoconstrictive agent endothelin-1 (E-1) plasma levels, associated with dyslipidemia, marked decreased in baroreflex sensitivity, adinopectin and epoxyeicosatrienoic acids (EETs) plasma concentrations. Preventive long-term treatment with L (3 weeks after the onset of high-fat diet) facilitates the correction of these alterations in hyperlipidic (H) rats indicating its possible favourable therapeutic action in MS. © *2025 Bull. Georg. Natl. Acad. Sci.*

Keywords: metabolic syndrome, endothelium dysfunction, cytokines, adipocytokines, hemodynamic parameters, baroreflex sensitivity

Introduction

Metabolic syndrome (MS) is associated with alterations involving blood lipid profile disturbances, obesity, endothelium dysfunction, arterial hypertension (AH) and diabetes mellitus type-2 (DMT2). These multiple risk factors often result in cardiovascular disorders, sometimes leading to fatal outcomes [1]. Epidemiologic studies over the past 25 years in the USA convincely indicate increasing cases of MS in children and adults suffered with obesity [2] becoming a great problem in public health throughout the world, which necessitates the complex approach for improving treatment outcome of this pathology [3]. A growing number of

evidence suggests that flavonoid origin product luteolin (L) by inhibiting an enzyme epoxide hydrolase facilitates the accumulation of epoxyeicosatrienoic acids (EETs) in the body, that may improve blood lipid spectrum, insulin resistance, endothelial dysfunction and cardiovascular alterations in different cardiovascular diseases [3-5]. However, there is lack of information concerning influence of luteolin on [6-8] lipid profile disorders, disbalance between vasoconstrictive and vasodilative agents production, glycemic control and cytokines and adipocytokines blood level alterations in MS, which can be considered as new insights for early diagnostic and effective treatment outcome of MS.

The objective of this study was to investigate the relationship between changes in lipid spectrum, endothelium dysfunction, hemodynamic indices, glycemic control, plasma cytokines and adipocytokines concentrations in Wistar rats receiving high fat diet and to define luteolin modulatory effect on this alterations.

Materials and Methods

***In vivo* study**. Experiments were carried out on 50 male Wistar rats weighing 250-300 g. The animals were divided into 3 groups: I – Control (C) normolipidics received a standard laboratory chow; II – Hyperlipidic (H) were fed with a hyperlipidic and hypercholesterolemic diet for 6 weeks including 15% cocoa butter fat, 1.25% cholesterol, 0.5% cholic acid, 27.9% protein [9]; III-H rats underwent to Luteolin (3 mg/kg in sterile 0.1% DMSO and PBS, pH-7.4) intraperiotoneal (i.p) administration once daily for 3 weeks after 3 weeks from the onset of (H) rats feeding. In all animals under anesthesia (ketamine – 87 mg/kg + xylazine – 13 mg/kg i.p.) polyethylene catheters were preliminary inserted into the right carotid artery and right jugular vein for measuring afterwards in non-anesthetized rats arterial pressure (AP-mm Hg) by electromanometric method and drugs administration, respectively. Heart period (ms) and heart rhythm (HR) were assessed by cardiotachometer. Baroreflex parasympathetic component sensitivity (BRS) was evaluated by developing bradycardia in response to pressor effect after phenylephrine intravenous injection (10 mcg/kg). Baroreflex regression coefficient was calculated by methods of correlative and regression analysis. The values of hemodynamic parameters in freely moving animals were recorded using radiotelemetric system.

***In vitro* experiments. Sample collection and storage**. Blood was obtained from the catheter implanted into carotid artery and fixed between animal shoulders. Plasma was collected in sterile tubes using heparin as anticoagulant and centrifuged for 15 minutes at 1000 xg 2-8ºC within 30 minutes of collection. Samples were stored at -20ºC. The next steps were associated with detection in plasma levels of: glucose, insulin, inflammatory cytokines – TNFα (tumor necrosis factor alfa), interleukine – 1B (IL-1B), adipocytokines (adiponectin, leptin, resistin), vasoactive agents – endothelin-1 (E-1), epoxyeicosatrienoic acids – (EETs) and lipids: LDL (low density lipoproteins), VLDL (very low density lipoproteins), HDL (high density lipoproteins), TG (triglycerids), TC (total cholesterol) which have been done according manufacturer instruction using ELISA kits (Cusabio, USA). The results were calculated on microplate reader at 450 nm, with correction wavelengths set at 540 nm or 570 nm. The atherogenic index (AI) was calculated (3) by the equation: AI = (total cholesterol – HDL/HDL).

Statistical analysis. The SPSS software was used for statistical analysis measurement data to mean ± standard deviation (SD) using **t** test and single factor analysis of variance for group comparison. $P<0.05$ indicates significant difference using Students test.

Results

Study of luteolin influence on alterations of hemodynamic parameters, glycemic control, body weight, cytokines, adipocytokines, lipid profile and vasoactive agents plasma levels in rats submitted to high fat diet for six weeks. The analysis of cardiovascular indices (Table 1) in nonanesthetized hyperlipidic (H) rats revealed significant differences in mean values of systolic (132.4 ± 4.1 mmHg, $p < 0.01$) and diastolic (94.2 ± 3.4 mmHg, $p < 0.01$) arterial pressure (SAP, DAP) vs. the same parameters in normolipidic (N) ones (109.4 ± 3.0 mmHg) and (77.5 ± 2.6 mmHg), respectively. Increased AP in H rats was associated with marked acceleration of heart rhythm (HR)-(380 ± 10 bpm, $p < 0.01$) and reduction in baroreflex sensitivity (BRS) - (0.74 ± 0.04 ms/mmHg, $p < 0.01$) in comparison to identical indices of N animals (338 ± 6 bpm) and (1.1 ± 0.05 ms/mmHg), respectively. Such changes of hemodynamic parameters in H rats vs. N animals were accompanied by significant increase of body weight (BW) with marked rise of adipocytokines: leptin (188.44 ± 7.21 ng/ml, $p < 0.01$), resistin (7.41 ± 0.34 ng/ml, $p < 0.05$), as well as vasocontristor-endothelin-1 (E-1) plasma levels (6.22 ± 0.5 pg/ml, $p < 0.01$) as compared to the same indices in N rats: (92.75 ± 6.62 ng/ml), (3.56 ± 0.18 ng/ml) and (3.11 ± 0.2 pg/ml), respectively with significant reduction in adiponectin (10.52 ± 0.76 ng/ml, $p < 0.01$) and EETs plasma concentration (3.0 ± 0.2 ng/ml, $p < 0.01$) with respect to the same values in N rats (18.32 ± 0.94 ng/m) and (6.8 ± 0.4 ng/ml), respectively. L (3 mg/kg, i.p.) administration in H rats during 3 weeks (III group) was provided marked preventive effect on hemodynamic parameters and BW changes, as well as on plasma level alterations of adipocytokines, vasocontrictive and vasodilatory agents as compared to II group of H animals without L administration (Table 1), facilitated to decrease in SAP (10.1 ± 1.2%, $p < 0.05$), DAP (15.2 ± 1.8%, $p < 0.05$), BW (10.2 ± 2.0%, $p < 0.05$) and increase BRS (24.5 ± 4.2%, $p < 0.01$). This alterations were correlated with significant increase in plasma levels of adiponectin (38.8 ± 5.2%, $p < 0.01$) and EETs (26.7 ± 5.2%, $p < 0.01$), with reduction in leptin (44.2 ± 6.4%, $p < 0.01$), resistin (29.8 ± 5.6%, $p < 0.01$) and E-1 (35.7 ± 6.2%, $p < 0.01$) plasma concentration with respect to II group of animals. In addition to this changes marked alterations were defined concer-

Table 1. Luteolin (3mg/kg) influence on the alterations of body weight, hemodynamic parameters, baroreflex sensititvity, adipocytokines and vasoactive agents plasma levels in rats submitted to high fat diet for six weeks

Indices	Control – I group, n=14	H – II group, n=18	H+Luteolin (3mg/kg) III group, n=18
Systolic arterial pressure (SAP), mmHg	109.4±3.0	132.4±4.1$^{▲,**}$	119.0±2.8$^{•,*}$
Diastolic arterial pressure (DAP), mmHg	72.5±2.6	94.2±3.4$^{▲,**}$	80.0±3.5$^{•,*}$
Heart rhythm (HR), bpm	338±6	380±10$^{▲,**}$	350±7$^{•,*}$
Regression coefficient of baroreflex sensititvity (BRS), ms/mmHg	1.1±0.05	0.74±0.04$^{▲,**}$	0.98±0.06$^{•,**}$
Body weight (BW), g	286.1±7.4	320±10.2$^{▲,*}$	291.4±9.0$^{•,*}$
Adiponectin, ng/ml	18.32±0.94	10.52±0.76$^{▲,***}$	14.61±0.84$^{•,**}$
Leptin, ng/ml	92.75±6.62	188.44±7.21$^{▲,**}$	130.65±7.0$^{•,**}$
Resistin, ng/ml	3.56±0.18	7.41±0.34$^{▲,*}$	5.2±0.26$^{•,**}$
Endothelin-1, pg/ml	311±0.2	6.22±0.5$^{▲,**}$	4.0±0.4$^{•,**}$
Epoxyeicosatrienoic acids (EETs) – total trans, ng/ml	6.8±0.4	3.0±0.2$^{▲,**}$	5.2±0.5$^{•,**}$

N – number of animals; H – hyperlipidic and hypercholesterolemic rats; Luteolin (3mg/kg i.p.) during 3 weeks after 3 weeks of onset of high fat diet. Results are given as mean ±SEM; significant differences in comparison with: ▲I group, •II group. *p<0.05, ** p<0.01, ***p<0.001.

Table 2. The preventive effect of luteolin (3mg/kg) in plasma levels alterations of glucose, insulin, lipid spectrum and inflammatory cytokines in rats with high fat diet for six weeks

Parameters	Control – I group, n=14	H – II group, n=18	H+Luteolin (3 mg/kg, i.p.), III group, n=18
Glucose, mmol/L	5.4±0.42	8.2±0.72$^{▲,**}$	6.5±0.36$^{•,**}$
Insulin, mIU/L	10.8±0.35	15.3±0.61$^{▲,**}$	12.7±0.45$^{•,**}$
TNFα, pg/ml	7.5±3.12	22.8±4.0$^{▲,**}$	10.2±3.21$^{•,**}$
IL-1B, pg/ml	2.1±0.14	5.9±0.60$^{▲,***}$	4.0±0.39$^{•,**}$
LDL, mg/dL	26.2±5.74	85.6±8.2$^{▲,**}$	56.7±4.91$^{•,*}$
VLDL, mg/dL	7.6±1.22	11.9±0.71$^{▲,*}$	8.4±0.62$^{•,*}$
HDL, mg/dL	6.8±1.0	7.9±1.52$^{▲}$	7.0±0.94
TG, mg/dL	22.4±1.85	56.2±1.90$^{▲,**}$	41.4±1.61$^{•,*}$
TC, mg/dL	40.5±5.42	105.4±7.51$^{▲,***}$	62.2±6.52$^{•,***}$
AI	4.95±0.64	12.3±1.4$^{▲,**}$	7.8±1.1$^{•,**}$

TNFα (Tumor necrosis factor alfa), IL – 1B (Interleukin-1B), LDL – Low density lipoproteins, VLDL (very low density lipoproteins), HDL (high density lipoproteins), TG (Triglycerids), TC (Total cholesterol), AI (Atherogenic index); other symbols are the same as in Table 1.

ning glycemic control, lipid spectrum and inflammatory cytokines production in studying groups of animals (Table 2).

In H rats (group II) as compared to control group of animals was revealed significant increase in plasma levels of glucose (8.2 ± 0.72 mmol/L, $p < 0.01$) and insulin (15.3 ± 0.61 mIU/L, $p < 0.01$) vs. (5.4 ± 0.42 mmol) and (10.8 ± 0.35 mIU/L), respectively associated with marked elevation in plasma TNFα (22.8 ± 4.0 pg/ml, $p < 0.01$) and IL-1B (5.9 ± 0.6 pg/ml, $p < 0.01$) in H rats vs control group of animals (7.5 ± 3.12 pg/ml) and (2.1 ± 0.14 pg/ml), respectively.

Such alterations were accompanied by significant increase in lipids plasma concentration in H rats manifested by pronounced elevation of LDL (85.6±8.2 mg/dL, $p<0.01$), VLDL (11.9±0.71 mg/dL, $p<0.05$), TG (56.2±1.90 mg/dL, $p<0.01$) and TC (105.4±7.51 mg/dL, $p<0.001$), respectively, resulting in rised AI (12.3±1.4, $p<0.05$) vs. the same values of control group of N animals: LDL (26.2±5.74 mg/dL), VLDL (7.6±1.22 mg/dL), TG (22.4±1.85 mg/dL), TC (40.5±5.42 mg/dL) and AI (4.95±0.64 mg/dL) respectively. L (3mg/kg i.p.) administration (III group) was provided significant reduction in plasma concentrations of glucose (20.3±3.2%, mmol/L, $p<0.05$), insulin (17.2±2.8% mIU/L, $p<0.05$), TNFα (11.4±1.6% pg/ml, $p<0.05$), IL-1B (22.2±4.0% pg/ml, $p<0.01$), LDL (33.8±5.2% mg/dL, $p<0.01$), VLDL (29.4±3% mg/dL, $p<0.01$), TG (26.7±4.1% mg/dL, $p<0.01$), TC (41.0±5.8% mg/dL, $p<0.01$) and AI (26.6± 2.5%, $p<0.05$) in comparison to II group of rats, indicating about approximation of plasma levels of this values to control I group of animals after L administration.

Discussion

This study evaluates the preventive effects of flavonoid origin product luteolin (L) on the development of metabolic syndrome (MS) determinants: obesity, arterial hypertension (AH), dyslipidemia and glycemic control impairment in Wistar rats submitted to hyperlipidic diet for six weeks. It was shown that in hyperlipidic (H) rats vs control (normolipidic) animals the alterations of hemodynamic parameters were manifested in elevation of systolic (S) and diastolic (D) arterial pressure (AP), tachycardia and decreased baroreflex sensitivity associated with increased body weight (BW). Such changes in H animals vs. N rats were correlated with hyperglycemia, hyperinsulinemia and dyslipidemia associated with increased production of inflammatory cytokines (IL-1B) and (TNFα), as well as vasoconstrictor agent E-1 and reduction in

vasodilative agents EETs. Such changes in hemodynamic indices, glycemic control and BW in H rats may indicate about increased activity of sympathetic nervous system (SNS) also expressing in blunted parasympathetic component of BRS. Our data are in consistent to result of other authors that showed in rats with high fat or fructose diet a close link between increased BW, SNS overactivity, hemodynamic changes, impaired glycemic control and insulin resistance [9-11]. Hyperinsulinemia plays significant role in peripheral vascular resistance via prolong activation of SNS resulting in arterial hypertension [9] and dyslipidemia which are in agreement with our results, additionally showing increased plasma level of vasoconstrictor – E-1 and diminution of vasodilative EETs.

Our data demonstrate increased plasma level of adipocytokines leptin and resistin associated with dyslipidemia and reduction in adiponectin concentration in H rats vs. N ones. These results are in consistent with findings of other authors that were revealed the same changes in H Wistar rats [12-17]. Such alterations in H rats can be ascribed to more leptin production, producing from increased body fat, facilitating positive correlation between leptin and resistin concentration and body mass index in contrast to adiponectin negative correlation with decreased its plasma level [2, 18-20]. Glycemic control disorders and obesity facilitates to insulin resistance and diabetes mellitus type 2 accompanied by chronic inflammation [7], which was proved in our experiments by increased level of inflammatory cytokines IL-1B and TNF. L was provided anti-inflammatory, hypoglycemic and vasodilatory action reducing BW, AP, tachycardia and increased BRS correlated with improved glycemic control, lipid spectrum profile, diminished IL-1 and TNF plasma levels. These changes are in agreement with results indicated the possibilities of flavonoid origin products to exert the identical alterations [2].

It is suggested that luteolin in near future can be considered as promising pharmaceutical product against MS with potential antihypertensive, anti-inflammatory and antiatherosclerotic effects.

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(წარმოდგენილია აკადემიის წევრის დ. მიქელაძის მიერ)

მეტაბოლური სინდრომი, რომელიც მოიცავს დისლიპიდემიას, სიმსუქნეს, არტერიულ ჰიპერტენზიას და დიაბეტს-ტიპი 2, კარდიოვასკულური გართულებების მნიშვნელოვან რისკ-ფაქტორს წარმოადგენს. ლუტეოლინის ეფექტი ჰემოდინამიკურ მაჩვენებლებზე, ენდოთელიუმის ფუნქციაზე, გლიკემიურ კონტროლზე, ლიპიდურ სპექტრზე, ანთებითი ციტოკინებისა და ადიპოციტოკინების პროდუქციაზე გამოკვლეულ იქნა ვისტარის ჯიშის ვირთაგვებში, რომლებიც იმყოფებოდნენ ჰიპერლიპიდურ დიეტაზე 6 კვირის განმავლობაში. ნაჩვენები იქნა, რომ ჰიპერლიპიდურ ვირთაგვებში ნორმოლიპიდურისგან განსხვავებით მნიშვნელოვნად იზრდებოდა სისხლის არტერიული წნევა, გულის რითმი, ინსულინის, ციტოკინების (IL-1B, TNFα), ადიპოციტოკინების (ლეპტინი, რეზისტინი) და ვაზოკონსტრიქციული აგენტის ენდოთელინი-1 (E-1) პლაზმური დონე, რაც ასოცირდებოდა დისლიპიდემიასთან, ბარორეფლექსის მგრძნობელობის, ადინოპექტინისა და ეპოქსიეიკოზატრიენოის მჟავების (EETs) პლაზმური კონცენტრაციების მნიშვნელოვან დაქვეითებასთან. ლუტეოლინით პრევენციული ხანგრძლივი მკურნალობა (ცხიმების მაღალი შემცველობის დიეტის დაწყებიდან 3 კვირის შემდეგ 3 კვირის განმავლობაში) ხელს უწყობდა ამ ცვლილებების კორექციას ჰიპერლიპიდურ ვირთაგვებში, რაც მიუთითებდა მეტაბოლური სინდრომის დროს ლუტეოლინის შესაძლო სასურველი თერაპიული მოქმედების შესახებ.

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