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Plasma Content of Glucose, C-reactive Protein, Uric Acid and Cholesterol in Male, Female and Ovariectomized Rats upon Acute and Chronic Stress – a Path for Development of Cardiovascular Diseases

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ABSTRACT

To explore sex differences in cardiovascular function under stress, we analyzed plasma levels of glucose, C-reactive protein (CRP), uric acid and cholesterol in male, female and ovariectomized rats under acute and chronic stress. Glucose tolerance test (GTT) was performed in all rats before any stress was performed, as well as later in the chronic stress experiment. GTT in control animals showed the same trend as in chronically stressed. Male rats showed the highest plasma level of glucose and uric acid upon acute stress in comparison between the other two groups. Ovariectomized rats reached the highest concentration of plasma cholesterol during acute and chronic stress, respectively and also the highest plasma concentration of CRP during acute stress. Stress, as a risk factor of metabolic syndrome, affected biochemical parameters in males upon acute more than upon chronic stress, but the opposite was observed in female rats. Gender differences supported by ovariectomy show that stress managing could be affected by sexual hormones.

Key words: *cardiovascular diseases, chronic stress, acute stress, cholesterol, glucose, uric acid, C- reactive protein, ovariectomy, estrogens, plasma*

Introduction

The relationship between psychological stress and cardiovascular diseases is well established in scientific literature and epidemiological data[1–4]. The mechanism of the negative effect of stress can be indirect, via negative behavioral mechanisms like smoking or an unhealthy diet, or direct via pathological mechanisms involving the autonomous nervous system and the hypothalamic-pituitary-adrenal (HPA) axis[5].

Gender is a very important factor in the development of cardiovascular disease – men with coronary artery disease (CAD) are 7–10 years younger than females[6], while women tend to have more risk factors[7,8], higher mortality after myocardial infarction (MI)[9] and coronary artery bypass grafting (CABG) surgery[10,11] and an atypical clinical presentation[6], especially below 55 years of age[12,13]. Due to the atypical clinical presentation, women with CAD are often under-diagnosed[6,14,15]. The most obvious explanation for the gender-related differences in clinical characteristics is the cardioprotective effect of female sex hormones (estrogens).

Stress is a physiological response to challenges from various stressors and the key element in stress response is the activation of the HPA axis[16,17]. Secretion of corticotropin releasing hormone (CRH) from the hypothalamus

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stimulates the anterior pituitary gland via the CRH-R1 and CRH-R2 receptors to produce corticotropin (ACTH), which in turn stimulates the adrenal cortex to secrete corticosteroids[18,19]. Another important element of the stress response is the sympathoadrenal activation, which results in the release of catecholamines[20]. Glucocorticoids provide a link between the HPA axis and sympathetic activation by acting as transcriptional activators of phenylethanolamine N-methyltransferase (PNMT), which synthesizes epinephrine[21–23].

Stress can be either acute or chronic, and various animal models of stress have been explored (footshock, electric shocks, forced swimming, restraint etc.). Single and repeated exposures to restraint stress induce deregulation of the resting activity of the HPA axis[24], resulting in increased resting corticosterone levels[25–27]. The transcriptome in the adrenal medulla is very different after acute and chronic stress, with the biggest changes happening in transcripts related to growth factors, apoptosis, neurosecretion, structural proteins, cytokines and chemokines[28].

Catecholamines, most importantly epinephrine and norepinephrine, act through various adrenergic receptors on target organs. Gender differences were found in sympathoadrenal activity in rats before and after footshock stress[29] and also in diabetic rat models[30]. Similar experiments on female rats found higher values of corticosterone in females than males and also demonstrated the importance of the estrous cycle on observed adrenergic remodeling, which implies the mediation of sex hormones[31].

Women in menopause experience an increase in total cholesterol, LDL and lipoprotein levels compared to premenopausal women without estrogens deficiencies[32]. Since estrogens are important in controlling food intake, energy expenditure, the regulation of insulin secretion in pancreatic islet ß-cells and the protection from ß-cell failure, estrogens deficiency can contribute to the development of metabolic syndrome, obesity and diabetes[33,34]. Diabetic women also seem to have a higher mortality from cardiovascular diseases than men suffering from diabetes[35,36].

Inflammation has a role in the development of cardiovascular disease, so measurement of C-reactive protein can serve as a marker of inflammation and can be used to improve the prediction of this risk[37].

There has been reported a relation between plasma uric acid levels and cardiovascular conditions, such as hypertension, metabolic syndrome, coronary artery disease, cerebrovascular disease, vascular dementia, preeclampsia and kidney disease[38,39].

Estrogens protect against cardiovascular disease in women through effects on the vascular wall and liver. In females, synthesis of estrogens starts in *theca interna* cells in the ovary, by the synthesis of androstenedione from cholesterol[40].

Due to the complex association of glucose regulation, lipid metabolism, uric acid metabolism, inflammatory response and steroid sex hormones, we investigated the major biochemical parameters in this sophisticated biochemical puzzle upon the conditions of acute and chronic stress.

Materials and Methods

Animals

Four-month-old Sprague Dawley rats (N=69) were used. One group of female rats (N=25) were ovariectomized at three months and included in the experiment when they were four months old. Animals were housed in standard cages at room temperature with natural day and night exchange except for the period of chronic stress when lights were on during the night (18:00–09:00). Standard laboratory food and tap water were available at all time except for 24 hours before GTT when food was removed from the cages. Body weights of all rats were measured weekly. During the experiments the animals were handled in accordance with the Croatian law on animal welfare. This study was approved by Ethical Committee of School of Medicine Osijek. Animals were divided into following groups: 19 animals in chronic stress group, 26 animals in acute stress group and 24 animals in a control group.

Glucose tolerance test and biochemical analyses

Glucose tolerance test (GTT) was performed one day before sacrificing, 25% glucose solution was used and 2mg/g glucose per body weight was injected peritoneal. Glucose level was measured at six time points – 0, 15, 30, 45, 60 and 90 minutes in all animals. OneTouch® UltraMini® Glucose Meter (Milpitas, CA) was used for all measurements. Blood was drawn directly from the heart and plasma was separated by centrifugation. Biochemical analyses were performed at the biochemical laboratory of University Hospital Centre Osijek for the plasma concentration of glucose, C-reactive protein (CRP), uric acid and cholesterol for all animals. CRP, glucose and uric acid were measured with SIEMENS Dimension® clinical chemistry system Flex® reagent cartridge (Newark, DE). Cholesterol was measured with Olympus Diagnostic Systems Group (Melville, NY).

Ovariectomy

Female rats (N=25) were ovariectomized according to protocol (Harlan HUS-QREC-PRD-932, Issue: 01, Revision 03). Animals were anesthetized with isoflurane and placed on the operation table in ventral recumbency. Dorsal lumbar area was shaved and the incision was made halfway between caudal edge of the ribcage and the base of the tail. Another incision was made through the muscle bilaterally, after which the ovary and part of the oviduct were extracted and removed with a single incision. Remaining tissue was placed back into the peritoneal cavity. Muscle incision was not sutured, but the skin incision was closed by suturing. Postoperatively animals had food and tap water available at all time and were held in a clean environment under close examination for 72 hours.

Chronic stress protocol

The following animals: 5 male, 4 ovariectomized and 10 female rats, were submitted to chronic stress through 10 days. Chronic stress included stressors in the following daily order: lights on overnight (18:00–09:00), 60 minutes of cage rotation, food and water deprivation overnight (18:00–09:00), 50 minutes of isolation in a cold room at +4ºC, 3 minutes of swim stress, lights on with noise overnight (18:00–09:00; lights on combined with pre-set phone alarms in irregular time intervals from 3–15 minutes), 2 hour exposure to cat´s odor. Some stress sessions were repeated two times during 10 days. GTT was performed in all animals one day before sacrificing. The next day rats were sacrificed and blood was drawn from the heart for the plasma measurements.

Acute stress protocol

The following animals: 5 male, 11 ovariectomized and 10 female rats were submitted to acute stress. On the first day GTT was performed (food was removed 24 hours before). On the second day rats were acutely stressed with 3 hours of isolation in a cold room at +4ºC. Immediately upon acute stress rats were sacrificed and blood was drawn from the heart for plasma measurement. Impact of acute stress on plasma biochemical plasma markers must be measured immediately after acute stress because biochemical processes of recuperation starts immediately after exposure to stress. Therefore, all the animals from acute stress group were sacrificed immediately after the stress was performed.

Control group

The following animals: 4 males, 10 ovariectomized and 10 female rats were in the control group and were not submitted to stress. GTT was performed one day before sacrificing. Next day rats were sacrificed and blood was drawn from the heart for the plasma measurement.

Plasma collection

Plasma was collected at the time of sacrifice. All animals were cut through the abdominal wall and blood was collected with a syringe from the right ventricle and then transferred to 6 mL EDTA tubes. Plasma was separated by 5 minutes of centrifugation at 3000 x g.

Statistical analysis

Continuous variables are expressed as median and interquartile range. Due to the sample size and data distribution non-parametric methods (Kruskal-Wallis and Mann-Whitney test) were used to compare groups. Statistical significance was defined as $p<0.05$ (two-tailed value). The analyses were performed in IBM SPSS Statistics 20 (SPSS Inc, Chicago, IL).

Results

Table 1 shows median and interquartile range of glucose, CRP, uric acid and cholesterol levels in male, female and ovariectomized animal groups upon no stress, acute stress and chronic stress.

GTT performed in control animals (Figure 1) showed a similar trend as in chronically stressed group (Figure 2). Plasma glucose values upon acute stress were highest in male rats (median 12.5 mmol/L; Table 1 and Figure 3).

Male rats' glucose values upon acute stress were significantly higher than values in female rats ($p=0.02$). Upon chronic stress, the differences in glucose values between male, female and ovariectomized animal group were all non-significant.

CRP plasma levels upon acute stress were highest in ovariectomized rats (median 1.50 mg/L; Table 1 and Figure 4) followed by female and male rats (median 1.41 mg/L and 1.29 mg/L, respectively; Table 1). Upon chronic stress, the CRP levels were higher in male rats and lower in female and ovariectomized rats (Table 1). The differences in CRP levels between male, female and ovariectomized animal group upon acute and chronic stress were all statistically non-significant.

TABLE 1
MEDIAN AND INTERQUARTILE RANGE OF GLUCOSE, C-REACTIVE PROTEIN (CRP), URIC ACID AND CHOLESTEROL VALUES IN MALE, FEMALE AND OVARIECTOMIZED RATS UPON NO STRESS, ACUTE STRESS AND CHRONIC STRESS

Gender	Group	Glucose (mmol/L)	CRP (mg/L)	Uric acid (μmol/L)	Cholesterol (mmol/L)
Males	Control	12.2 (10.7–17.9)	1.57 (1.32–1.65)	351 (288–420)	2.69 (2.38–3.27)
	Acute stress	12.5 (9.5–19.1)	1.29 (1.14–1.40)	220 (165–280)	2.36 (1.96–3.06)
	Chronic stress	9.0 (7.0–9.7)	1.49 (1.44–1.56)	205 (192–218)	1.98 (1.84–2.06)
Females	Control	10.4 (8.6–11.7)	1.43 (0.98–1.57)	259 (221–346)	2.29 (2.05–2.72)
	Acute stress	6.6 (4.4–10.7)	1.41 (0.92–1.49)	150 (102–193)	2.68 (2.19–3.11)
	Chronic stress	7.9 (6.4–11.5)	1.39 (1.25–1.52)	225 (138–277)	2.07 (1.81–2.35)
Ovariectomized	Control	12.9 (9.5–14.6)	1.40 (1.22–1.52)	289 (225–394)	2.32 (1.85–2.80)
	Acute stress	7.9 (3.1–10.6)	1.50 (1.00–1.73)	153 (143–247)	3.15 (3.10–3.66)
	Chronic stress	7.7 (7.3–10.2)	1.47 (1.42–1.57)	214 (202–244)	2.19 (2.08–2.33)

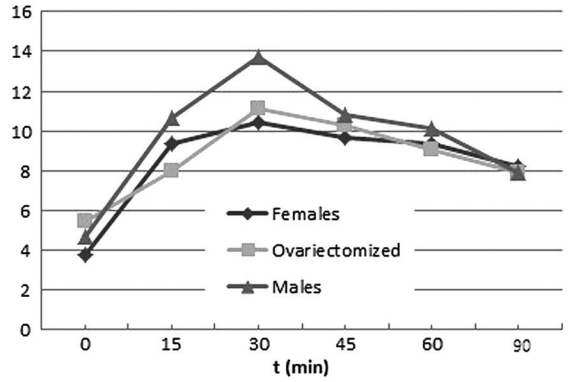

Fig. 1. Glucose tolerance test – control group. Glucose value is expressed in mmol/L.

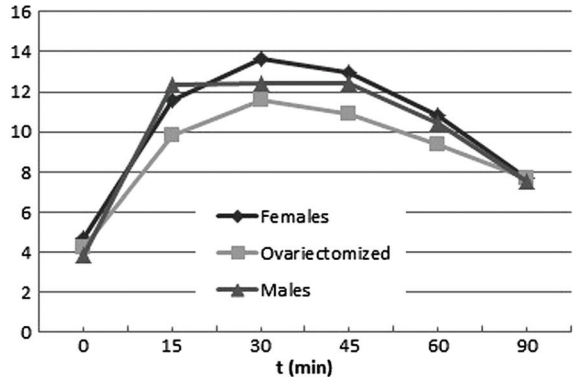

Fig. 2. Glucose tolerance test upon chronic stress. Glucose value is expressed in mmol/L.

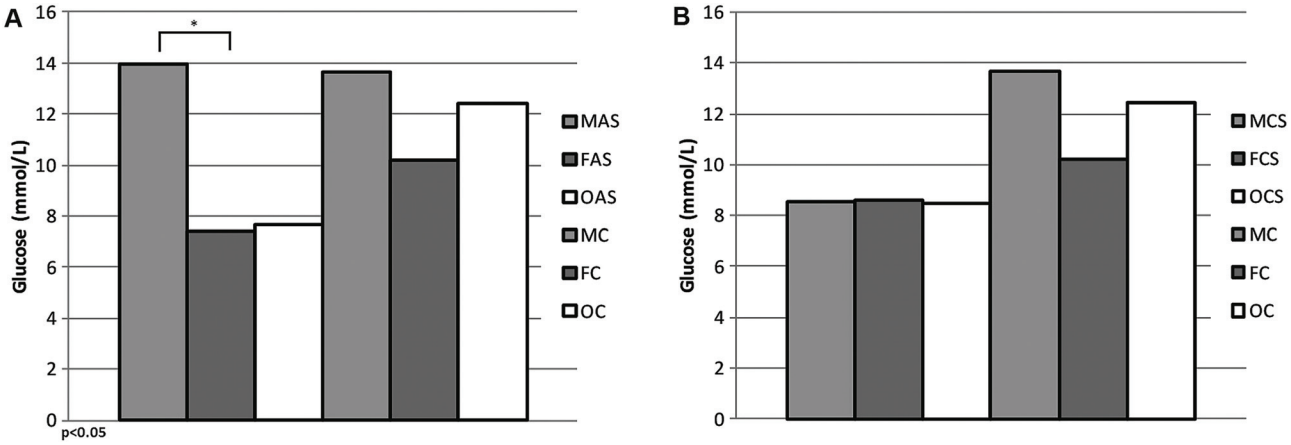

Fig. 3. Plasma glucose values compared in all animal groups upon acute (A) and chronic stress (B). MAS – males acutely stressed, FAS – females acutely stressed, OAS – ovariectomized acutely stressed, MC – male controls, FC – female controls, OC – ovariectomized controls, MCS – males chronically stressed, FCS – females chronically stressed, OC – ovariectomized chronically stressed.

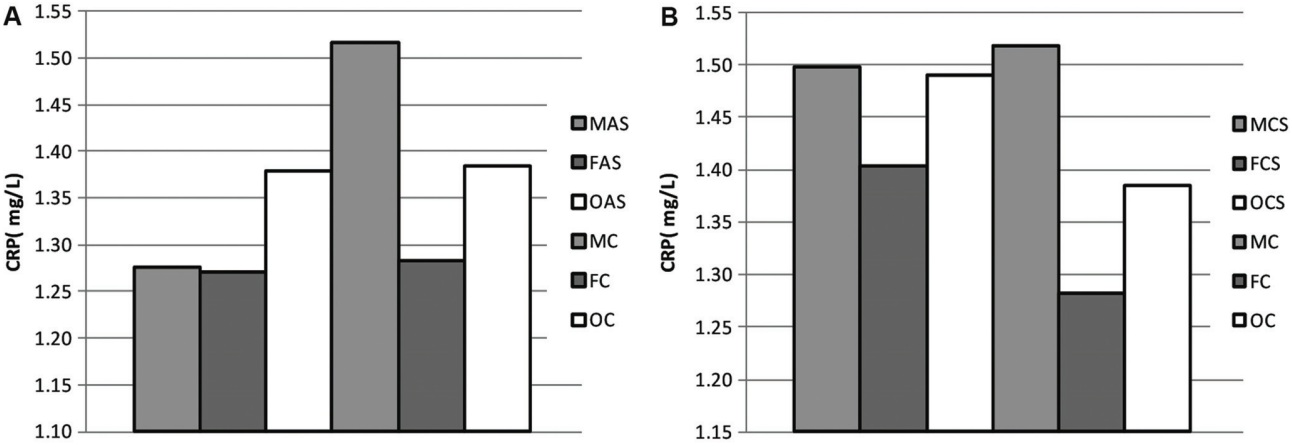

Fig. 4. Plasma CRP (C-reactive protein) values in all animal groups upon acute (A) and chronic stress (B). MAS – males acutely stressed, FAS – females acutely stressed, OAS – ovariectomized acutely stressed, MC – male controls, FC – female controls, OC – ovariectomized controls, MCS – males chronically stressed, FCS – females chronically stressed, OC – ovariectomized chronically stressed.

Uric acid plasma levels were lower upon acute stress in all three groups when compared to the control group (Table 1 and Figure 5). Uric acid levels in male rats upon acute stress were significantly higher than the female rats values (p=0.04), while the difference between male and ovariectomized rats remained non-significant. Uric acid values decreased in male rats upon chronic stress and increased in female and ovariectomized rats (Table 1). The differences in uric acid levels between male, female and ovariectomized animal group upon chronic stress were all non-significant.

Cholesterol plasma levels upon acute stress decreased in male rats and increased in female and ovariectomized rats (Table 1 and Figure 6). Cholesterol levels were highest in ovariectomized rats (median 3.15 mmol/L), followed by female (median 2.68 mmol/L) and male rats (median 2.36 mmol/L; Table 1) upon acute stress. The difference in cholesterol levels upon acute stress between male and female rats was not significant. However, the differences between male and ovariectomized and then female and ovariectomized rats upon acute stress were both statistically significant (p=0.036 and p=0.018, respectively) with ovariectomized group having the highest values. The differences in cholesterol levels between male, female and ovariectomized animal group upon chronic stress were all non-significant.

Discussion

The results of this study demonstrate a significant difference between tested groups in plasma glucose, uric acid and cholesterol levels upon acute stress. It is important to note that these differences were statistically significant only upon acute stress; in chronic stress groups the differences were non-significant for all measured parameters.

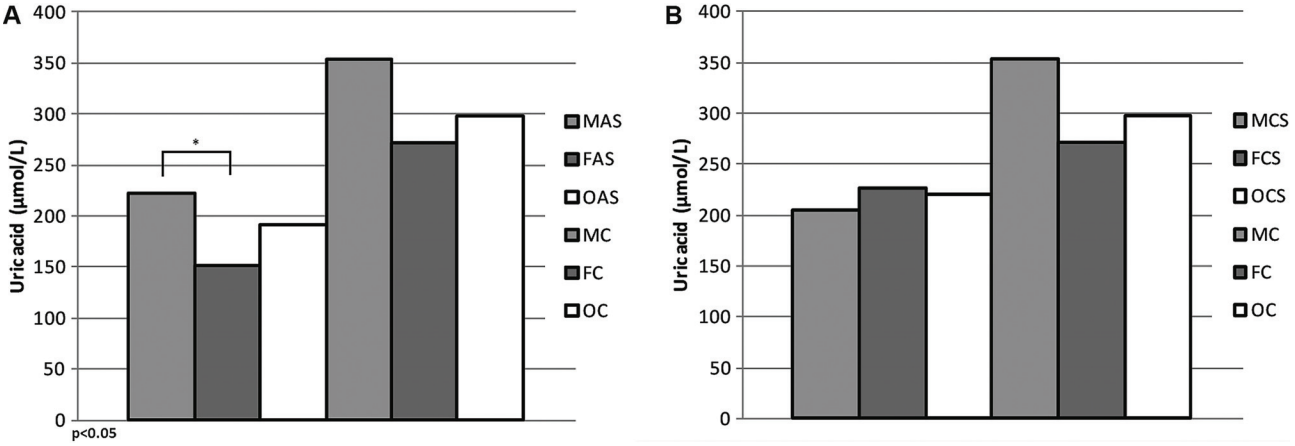

Fig 5. Plasma uric acid values in all animal groups upon acute (A) and chronic stress (B). MAS – males acutely stressed, FAS – females acutely stressed, OAS – ovariectomized acutely stressed, MC – male controls, FC – female controls, OC – ovariectomized controls, MCS – males chronically stressed, FCS – females chronically stressed, OC – ovariectomized chronically stressed.

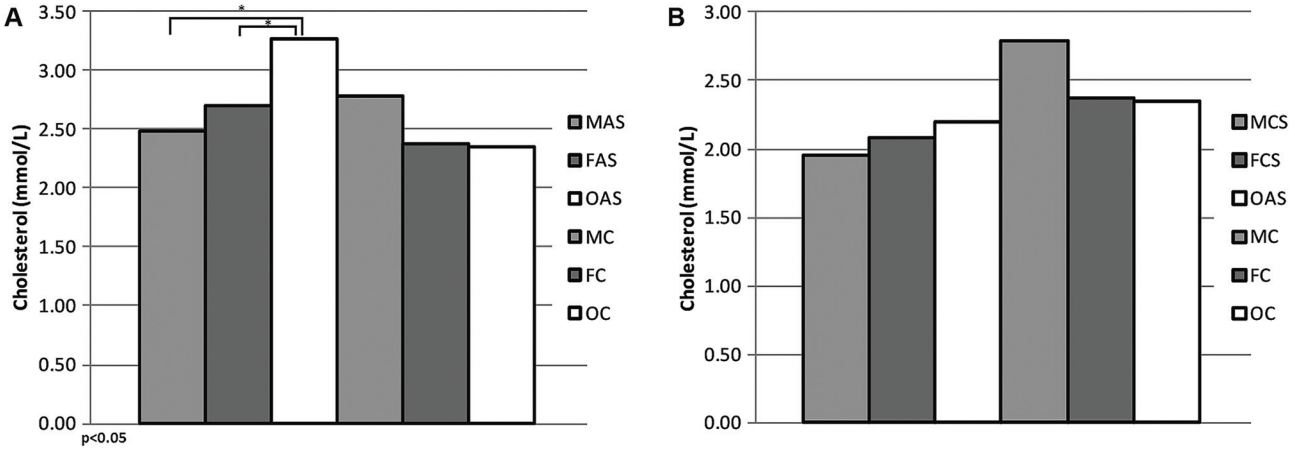

Fig. 6. Plasma cholesterol values in all animal groups upon acute (A) and chronic stress (B). MAS – males acutely stressed, FAS – females acutely stressed, OAS – ovariectomized acutely stressed, MC – male controls, FC – female controls, OC – ovariectomized controls, MCS – males chronically stressed, FCS – females chronically stressed, OC – ovariectomized chronically stressed.

Glucose plasma levels were higher in all groups at acute and chronic stress when compared to the first measurement during the GTT and can be explained as additional stress during the collection of the blood from the heart. Glucose plasma levels were lower in all chronic stress groups compared to the control group and upon acute stress the levels were highest in male rats, followed by ovariectomized and female rats. We found a significant difference in glucose plasma levels between male and female rats upon acute stress, but no significant difference was found between male and ovariectomized rats. These differences could be the consequence of mediation of acute stress response by sex hormones, since ovariectomized rats with lower estrogens levels respond more similarly to male than female rats. Estrogens play an important role in numerous physiological functions[41], including lipid metabolism and inflammatory response, which are both crucial for the development of atherosclerosis[6]. With this in mind, it is not surprising that estrogens deficiency, whether in menopause[42] or in premenopausal women[43,44], has a deleterious effect on the development of cardiovascular disease.

Since inflammation is believed to have a role in the development of cardiovascular disease, measurement of CRP as a marker of inflammation has been used as a method to improve the prediction of this risk[37]. CRP plasma levels were lower in males upon acute stress when compared to control group. Also, CRP values were highest in males, with ovariectomized females a close second, particularly upon chronic stress. Similarly to the plasma glucose concentrations, this might imply a connection between acute-phase proteins (such as CRP) and estrogens levels. In our study we did not find statistically significant differences in CRP values among groups, which could also imply that a longer, more intensive chronic stress protocol and perhaps a bigger sample size is needed to obtain expected results.

In plasma measurements of uric acid levels – values were highest in male rats, followed by ovariectomized and female rats. We found a significant difference between male and female rats upon acute stress, but the difference between male and ovariectomized rats remained non-significant, which also suggests sex hormone mediation of acute stress response. Uric acid is known as an oxidative stress biomarker. Low levels of uric acid are less common than high levels and could be linked with neurodegenerative diseases. It has been postulated that a low uric acid level could translate into greater oxidative stress, since uric acid is a known antioxidant[45]. Hyperuricemia is also associated with risk for cardiovascular disease[46]. In our study we observed a significant decrease in uric acid values upon acute stress in all groups (Table 1). Compared to acute stress groups' values, uric acid values increased after chronic stress in female and ovariectomized rats, but decreased slightly in male rats. The differences in uric acid levels between acute stress groups were not significant in male and ovariectomized rats, but we found a significant difference between male and female rats. These results indicate that females react more promptly to acute stress and that a longer period of chronic stress is needed to produce the expected elevation in uric acid levels in male and ovariectomized rats. Since most cardiovascular diseases are chronic by nature, it is essential to determine the adequate time needed to yield results in future experiments. Gender-related differences in uric acid levels were previously documented in rat models[47], but not after acute and chronic stress exposure. Gender-related changes in uric acid levels might be another factor modulated by the circulating sex hormone levels.

Sexual dimorphism is also well documented in various mouse models of diabetes, but the exact mechanisms of pathogenesis remain elusive[48–50]. Elevated serum uric acid (hyperuricaemia) is also observed more frequently with the occurring epidemic of metabolic syndrome, diabetes and cardiovascular disease, and it is postulated that it might play a causal role in the pathogenesis of these ailments[51–53].

Cholesterol levels increased upon acute stress in both female and ovariectomized rats, while we observed a decrease in male rats. Ovariectomized rats had the highest cholesterol levels upon acute stress, significantly higher than both female and male rats. After chronic stress the differences were all non-significant. These findings suggest that the metabolic response to acute stress is affected by the estrogens deficiency following ovariectomy. Basal levels of cholesterol were, as expected, higher in male rats.

Conclusion

We observed statistically significant differences in plasma levels of glucose, uric acid and cholesterol in male, female and ovariectomized rats upon acute stress. We can conclude that female rats' acute stress response in this experimental setting is different from the response of male rats and ovariectomized female rats, which suggests a role for sex hormone mediation. Gender-related differences were present in chronic stress response as well, but they were not substantial enough to achieve statistical significance. Findings from this introductory study warrant further investigation, which is why we are currently working on involving other biochemical markers for oxidative stress in cardiovascular pathology (malondialdehyde, glutathione peroxidase, super oxide dismutase, nitric oxide synthase) in acute and chronic stress protocols.

There are two limitations to our study – the first is a relatively small sample size, and the second is the time needed to produce biological changes in chronic stress protocol. While it is often difficult to increase sample size due to technical and ethical reasons, we see much room for improvement in the chronic stress protocol. In particular, the duration of stress exposure and the type of stressor could be improved to obtain maximal effect from the chronic stress protocol in the future.

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SADRŽAJ GLUKOZE, C-REAKTIVNOG PROTEINA, MOKRAĆNE KISELINE I KOLESTEROLA U PLAZMI MUŽJAKA, ŽENKI, TE OVARIEKTOMIZIRANIH ŠTAKORA POD UTJECAJEM AKUTNOG I KRONIČNOG STRESA – PUT ZA RAZVOJ KARDIOVASKULARNIH BOLESTI

S A Ž E T A K

Kako bismo istražili razlike kardiovaskularne funkcije pod utjecajem stresa između spolova, analizirali smo razine glukoze, C-reaktivnog proteina (CRP), mokraćne kiseline, te kolesterola u plazmi mužjaka, ženki i ovariektomiziranih štakora pod utjecajem akutnog i kroničnog stresa. Također smo izveli test tolerancije na glukozu (GTT) na svim štakorima prije stresnog tretmana, te nakon kroničnog stresa. GTT kontrolnih životinja pokazuje isti obrazac kao i životinje koje su podvrgnute kroničnom stresu. U usporedbi s ostale dvije grupe mužjaci pokazuju najviše vrijednosti glukoze i mokraćne kiseline u plazmi nakon akutnog stresa. Ovariektomizirana grupa pokazuje najviše vrijednosti kolesterola u plazmi pod utjecajem akutnog i kroničnog stresa, te također najviše vrijednosti CRP-a pri akutnom stresu. Stres kao rizični faktor metaboličkog sindroma, utječe na biokemijske parametre u mužjaka više pod akutnim, nego kroničnim stresom, no suprotno vrijedi za grupu ženki. Razlike između spolova, a posebno pri ovariektomiji pokazuju kako bi podnošenje stresa moglo biti pod utjecajem spolnih hormona.