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CHANGES IN LIPID PEROXIDATION ACTIVITY IN RATS WITH CONGENITAL HYPERTENSION DURING CANDENSARTAN TREATMENT

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Abstract. The article is devoted to the study of the peculiarities of the state of free radical peroxidation of lipids in rats with congenital arterial hypertension in the treatment of candesartan. In the test, it has been established that candesartan in SHR series rats normalizes the content of peroxide products of free radical reactions in myocardial homogenates and promotes the resistance of cardiomyocyte membranes lipids to reoxidation.

Key words: candesartan, arterial hypertension, free radical lipid peroxidation oxidation, spontaneously hypertensive rats of the SHR line.

Introduction. Candesartan is one of the current high-specific, non-competitive angiotensin II receptor antagonists, which has been successfully prescribed for over 10 years to treat hypertension [7]. Candesartan is rapidly adsorbed from the digestive

canal, its bioavailability is 60-80%, and for effecting the effect does not require metabolic activation. About 96% of the drug is bound to plasma proteins in the blood. Metabolised in the liver by conjugation to form glucuronide and by oxidation. Candesartan and metabolites are excreted from the body with bile and urine [5].

At the Department of pathological physiology of the VDNZ Ukraine "Bukovinian State Medical University", studies have been conducted on the effects of drugs with various mechanisms of antihypertensive pharmacological action in experiments on rats with arterial hypertension (AG). Models of spontaneous and congenital arterial hypertension by the pathogenetic mechanism are most consistent with the development of hypertonic disease in humans. Therefore, it studies the effectiveness of the use of drugs with antihypertensive type of pharmacological action [6, 8, 9, 14]. Morphofunctional, biochemical features were revealed in rats with hypertension, including the activity of non-fermentative peroxide free radical processes in the myocardium and in general in the body [1-4, 11, 12].

In particular, a significant difference in the activity of the system of free radical lipid peroxidation oxidation (VRPOL) in blood plasma, myocardial and liver tissues in control normalized rats and rats with hypertension was shown. The latter leads to the need to study the effectiveness of irbesartan in the processes of LPA in blood plasma, myocardium, liver of rats with hypertension. Such studies on the effects of candesartan on lipid peroxidation processes in rats with hypertension are conducted for the first time.

The purpose of the study was to determine the peculiarities of the effect of candesartan on the activity of the VRPOL system in the blood, myocardium and liver of rats with hypertension.

The Aim Of The Study. to find out the peculiarities of the influence of candesartan on the activity of the VRPOL system in the blood, myocardium and liver of rats with hypertension.

Material and methods. Experiments were carried out on 12 laboratory rats of the SHR series and 6 control normalizing rats of the WKY lineage with an initial weight of 190-210 g, weighing 190-210 g (Biomodelservice kennel of the city of

Kyiv). These rats were divided into two groups of 6 animals in each:

1) control rat SHR;

2) Experimental SHR rats receiving Irbesartan 30 mg / kg body weight for 60 days. In recent years, researchers have put forward specific transgenic lines with spontaneous hypertonic rats (spontaneous hypertonic rats, SHR) that are adequate for human disease. With this disease animals are born, thus increasing the possibility of experimental study of pathogenic mechanisms of hypertension and its possible pharmacokorectification [12]. The line of rats with spontaneous hypertension, SHR, was initiated in 1963 by Japanese scientists L. Okamoto and Aold from Wistar rats, who have high blood pressure. Spontaneous hypertensive rats, the SHR line in the first weeks of life have normal arterial pressure. In these lines of rats, elevated blood pressure is observed at the age of 4-12 weeks. Hypertension occurs without obvious causes in 100% of cases and is transmitted inherited. In the process of aging of animals increased arterial pressure, develops hypertrophy of the myocardium. AG was also accompanied by significant metabolic violations of water-electrolyte exchange [7].

The animals were kept in a clinic for experimental animals on a standard diet with free access to food and water. Rats of the experimental and control groups were withdrawn from the experiment by decapitation under a light etheric inhalation anesthesia, adhering to the rules of humane treatment of laboratory animals. To study, mixed arterial-venous blood was collected with anticoagulant and liver and myocardial tissue on an ice bath.

The activity of the VRPOL system was investigated in a mixed arteriovenous plasma of blood and liver and myocardium tissue homogenates. To this end, the registration of spontaneous (CFL) and Fe2 + -induced superconducting luminescence (chemiluminescence) was used with the help of a chemiluminescenter XLM1C-01 [10].

Blood plasma samples were obtained by mixing 0.2 ml of arteriovenous blood from 9.0 ml of potassium phosphate buffered chemiluminescence solution (dilution 1:46) in glass tubes to prevent its coagulation. Buffer solution composition: 100

mmol KCl, 20 mmol KH2PO4 • 7H2O. The pH 7.4 was corrected by 0.1 N solution of KOH or by 0.1 N HCl solution, respectively. The tubes were centrifuged for 15 minutes at 3000 rpm to separate the formed blood elements from the plasma, after which the blood plasma in full volume was transferred to a plastic cuvette of the chemiluminescope.

Swabs of myocardium and liver tissue were homogenized in a glass homogenizer in an ice bath in a potassium phosphate buffer for chemiluminescence, filtered through four layers of gauze, and then diluted with a buffer solution to a final concentration of 3.7 mg / ml and 5.6 mg / ml, respectively. Before chemiluminescence registration samples of blood plasma and tissue homogenates were stored in an ice bath in a shaded room no longer than 3 hours.

Before recording chemiluminogram, plasma samples of blood and liver and myocardial tissue homogenates (biological substrates) were kept in full darkness in the Biostatic unit of the chemiluminescope for 10 minutes at +37,0 ± 0,1 ° C. After that, the level of CFL of the biological substrate was determined on the basis of chemiluminescence readings for 1 min (imp / min). Then 1.0 ml of FeSO4 · 7H2O solution (1.7 mg / ml of bistilled water) was added to it and the Fe2 + -initiated chemiluminogram (ICHL) was recorded for 6 minutes. The following indicators were determined on it: 1) the amplitude of a fast flash of light (h, imp / s), which reflects the content in the biological substrate of lipids hydroperoxides; 2) the maximum amplitude of the slow flash of ultra-weak glow (N, imp / s) and its amplitude for 6 minutes of registration of ICHL (I6, imp / s), which characterize the intensity of the flow in the biological substrate of the VRPOL process; 3) the magnitude ∠α of the slope of the slow flare of the XLL of the biological substrate, which indicates the rate of lipid peroxidation in it; 4) latency of the reaction after the initiation of CL - time from the moment of introduction of the standard concentration of Fe2 + to the biological substrate prior to the development of a slow flash of IHL (t1, c) and the time of release of the ICHL curve on the plateau (t2, c), characterizing the ratio in the biological substrate of the prooxidants and antioxidants. On the testimony of the chemiluminometer, ICHL was obtained for 6 minutes of registration (S1, IMP /

6 min), which reflects the content of peroxide products of free radical reactions in the biological substrate accumulated in it as a result of the initiation of VRPOL by Fe2 + ions. The index of lipid resistance of the biological substrate to reoxidation (S2, IMP / 6 min) was calculated as the difference between S1 and the sum of the level of CFL for 6 minutes of ICHL registration. The evaluation of the functional state of the VRPOL system in the investigated biological substrates was carried out in accordance with [10]. Blood pressure (AT) in rats was measured on the caudal artery using a plethysmograph.

The results of the surveys are statistically calculated using Student's t-criterion.

Results And Discussion. It has been established that candesartan lowers blood pressure in rats with hypertension by 17% (rats with AG of 156.0 ± 2.0 mm Hg, under the influence of candesartan 139.0 ± 5.0 mm Hg). When comparing the activity of the VRPOL system in the biological substrates of the control WKY and SHR rats examined (Table 1-3), it was found that in the group of rats with hypertension:

- in the integrative environment of the organism, blood plasma was almost twice as prolonged by the latent period of the development of a slow IHL outbreak (110.0 ± 14.0 s versus 57.5 ± 6.2 s, p <0.01) with unchanged other indicators of ultra-weak luminosity, which indicated an increase in the antioxidant defense of the organism;

- in liver tissue homogenates there was a tendency to increase the level of CFL (868 ± 38 imp / min vs. 655 ± 90 imp / min, p <0,1), which indirectly confirmed the activation of VRPOL;

- in the homogenates of the myocardium tissue, more significant violations of the activity of the VRPOL system were revealed, indicating a decrease in the content of the primary products of the lipid peroxidation process (44.0 ± 5.2 imp / s versus 52.7 ± 2.1 imp / s, p < 0,2) and peroxide products of free radical reactions (6325 ± 2447 imp / 6 min vs. 11756 ± 1612 imp / 6 min, p <0,1), as well as increased lipid resistance of membranes of cardiomyocytes to the process of reoxidation (2635 ± 1654 imp / 6 min versus 8314 ± 2305 imp / 6 min, p <0,1), which was also combined with a significant extension of the latent period of slow spa development

Laha Ihl (115.0 ± 20.5 s versus 49.2 ± 3.5 s, p <0.02).

Thus, it was found that in rats of the control group SHR with arterial hypertension, in comparison with normalizing WKY rats, violations of the activity of the VRPOL system in blood plasma, liver tissue and, especially, myocardial tissue, were characteristic of prolonged activation of the lipoperoxidation process. In blood plasma of hypertensive rats receiving candesartan, accumulation of the primary products of the lipid peroxidation process (60.6 ± 3.0 imp / s against 44.0 ± 3.6 imp / s, p <0) was shown in comparison with the standardized WKY rats , 01), acceleration of the rate of oxidation of lipids (12,8 ± 1,8 ° against 8,0 ± 0,7 °, p <0,05), the tendency to accumulation of peroxide products of free radical reactions (13690 ± 2509 imp / 6 min against 9004 ± 1025 imp / 6 min, p <0,2) and to decrease the resistance of its lipids to the reoxidation process (10888 ± 2204 imp / 6 minutes versus 6631 ± 1352 imp / 6 min, p <0,2). At the same time, the latent period of the slow flash development and the time of the output of the ICH curve on the plateau were prolonged (Table 1). Then, as compared to the control group of SHR rats after candesartan administration, only the increase in the content of plasma lipid hydroperoxide blood (p <0.1) was observed and the lipid oxidation rate significantly increased (p <0.05) (Table 1).

Table 1

The activity of the system of free radical peroxidation of lipids in blood plasma of rats with arterial hypertension under the influence of candesartan, M ± m

Group of animals	CFL, IMP / min	Fe^{2+}- induced chemiluminescence							
		h, imp / m	H, imp / m	I6 min, imp / m	∠α, °	t_1, c	t_2, c	S_1, imp/ 6 m	S_2, imp/ 6 m
1.Control WKY	479 ± 129	44,0 ± 3,6	29,3 ± 4,2	28,0 ± 4,2	8,0 ± 0,7	57,5 ± 6,2	348,6 ± 8,3	9004 ± 1025	6631 ± 1352
2. Control SHR	654 ± 133	47,0 ± 6,7	37,0 ± 15,7	38,0 ± 14,6	6,5 ± 1,7	110,0 ± 14,0	352,5 ± 8,4	13199 ± 3906	9269 ± 4467
3.SHR + candesartan	464 ± 103	60,6 ± 3,0	42,0 ± 10,1	32,0 ± 10,1	12,8 ± 1,8	109,0 ± 12,9	360,0 ± 0,0	13690 ± 2509	10888 ± 2204
P_{1-2}	< 0,5	> 0,5	> 0,5	> 0,5	< 0,5	< 0,01	> 0,5	< 0,5	> 0,5
P_{1-3}	> 0,5	< 0,01	< 0,05	> 0,5	< 0,05	< 0,01	< 0,2	< 0,2	< 0,2
P_{2-3}	> 0,5	< 0,1	> 0,5	> 0,5	< 0,05	>0,5	> 0,5	> 0,5	> 0,5

The use of candesartan in rats led to the activation of the system of VRPOL in

plasma, which may be due to its ability to bind to its proteins [6].

In contrast, in the liver tissue homogenates of the rats group used candesartan, no significant violations of the activity of the VRPOL system were detected in comparison with control normotensive and control hypertensive rats (Table 2). The latter, probably, is due to the fact that for the realization of its pharmacological effect, candesartan does not require metabolic activation with the participation of hepatocytes [7].

Table 2

The activity of the system of free radical peroxidation of lipids in the liver tissue of rats with arterial hypertension for the influence of candesartan, M ± m

Group of animals	CFL, IMP / min	Fe^{2+}- induced chemiluminescence							
		h, imp / m	H, imp / m	I6 min, imp / m	∠α, °	t_1, c	t_2, c	S_1, imp/ 6 m	S_2, imp/ 6 m
1.Control WKY	65 ± 90	76,6 ± 4,8	252,6 ± 15,7	93,1 ± 7,9	76,1 ± 2,4	25,0 ± 2,3	160,7 ± 9,8	65758 ± 3073	60546 ± 3222
2. Control SHR	868 ± 38	71,2 ± 5,2	236,0 ± 4,5	111,2 ± 11,2	78,6 ± 1,7	25,0 ± 3,2	163,0 ± 17,2	70006 ± 6904	65749 ± 5471
3.SHR + candesartan	830 ± 170	73,1 ± 4,8	244,0 ± 13,9	95,4 ±10,3	79,1 ± 1,7	22,1 ± 1,5	161,4 ± 11,3	65960 ± 1924	60079 ± 2751
P_{1-2}	< 0,01	< 0,5	< 0,5	< 0,5	< 0,5	> 0,5	> 0,5	> 0,5	< 0,5
P_{1-3}	< 0,5	> 0,5	> 0,5	> 0,5	< 0,5	< 0,5	> 0,5	>0,5	> 0,5
P_{2-3}	> 0,5	> 0,5	> 0,5	> 0,5	> 0,5	> 0,5	> 0,5	> 0,5	> 0,5

In the homozygous tissue of the HSIAH group of myocardial tissues, which was used as candesartan, the intensity of the flow of the LPO process (21.3 ± 6.4 imp / s versus 38.0 ± 9.0 IU / s, $p < 0.2$) and the content of peroxide products of free radical reactions (9206 ± 2100 mg / min 6 min versus 11756 ± 1612 mg / min, $p < 0.5$) and the lipid resistance of the cardiomyocyte membranes to reoxidation (4575 ± 2103 imp / 6 min against 8314 ± 2305 imp / 6 min, $p < 0.5$). At the same time there was an extended latent period of development of a slow flash of IHL.

At the same time, in the homogenates of the myocardial tissue of the group of rats with AG, which were used candesartan, compared with the rats of the control group, the activity of the system of VRPOL remained unchanged (Table 3).

Table 3

The activity of the system of free radical lipid peroxidation oxidation in myocardial tissue of rats with arterial hypertension due to candesartan, M ± m

Group of animals	CFL, IMP / min	Fe^{2+}- induced chemiluminescence							
		h, imp / m	H, imp / m	I6 min, imp / m	∠α, °	t_1, c	t_2, c	S_1, imp/ 6 m	S_2, imp/ 6 m
1.Control WKY	559 ± 106	52,7 ± 2,1	38,0 ± 9,0	38,0 ± 9,0	9,0 ± 1,7	49,2 ± 3,5	360,0 ± 0,0	11756 ± 1612	8314 ± 2305
2. Control SHR	574 ± 111	44,0 ± 5,2	24,0 ± 9,0	24,0 ± 9,0	8,6 ± 1,7	115,0 ± 20,5	360,0 ± 0,0	6325 ± 2447	2635 ± 1654
3.SHR + candesartan	712 ± 128	50,9 ± 1,2	21,3 ± 6,4	21,3 ± 6,4	6,7 ± 1,6	85,0 ± 9,8	360,0 ± 0,0	9206 ± 2100	4575 ± 2103
P_{1-2}	< 0,5	< 0,2	< 0,5	< 0,5	> 0,5	< 0,02	> 0,5	< 0,01	< 0,01
P_{1-3}	< 0,5	< 0,5	< 0,2	< 0,2	< 0,5	< 0,01	> 0,5	< 0,5	< 0,1
P_{2-3}	< 0,5	< 0,5	< 0,5	< 0,5	< 0,5	< 0,5	< 0,5	< 0,5	< 0,5

Irbesartan in hypertensive rats contributes to the normalization of such important indicators of chemiluminescence of myocardial homogenates as the content of peroxide products of free radical reactions and lipid resistance of membranes of cardiomyocytes prior to reoxidation, which testified to the positive changes in the activity of the VRPOL system in the cardiac muscle. One of the mechanisms of the normalizing effect of candesartan on VRPOL processes is a decrease in blood pressure in rats with hypertension. Possible mechanisms are also inhibition of the biological effects of angiotensin II and its vasoconstrictive effect. Contributes to the regulation of VRPOL processes under the influence of candesartan, reduction of pre- and post-loading on the myocardium, normalization of carbohydrate and lipid metabolism [5, 13, 15-17], as well as renal function [18]. Further research is needed to establish the molecular mechanisms of the action of irbesartan on the processes of VRPOL in rats with hypertension.

Conclusions: 1. In rats of the HSIAH control group with congenital stress-induced arterial hypertension, in comparison with control WKY normotensive rats, violations of the activity of the VRPOL system in blood plasma, liver tissue, and especially myocardial tissue, are characteristic of prolonged activation of the lipoperoxidation process.

2. Candesartan, which was injected intragastrically in SHR series 60 days at a dose of 30 mg / kg body weight, caused a slight functional activation of the system of

VRPOL in plasma, which probably is due to its ability to bind to its proteins. At the same time, its application did not lead to a violation of the activity of the VRPOL system in the liver tissue, probably due to the fact that for the realization of the pharmacological effect candesartan does not require metabolic activation with the participation of hepatocytes.

3. Candesartan in the SHR series of rats normalizes the content of peroxide products of free radical reactions in myocardial homogenates and promotes lipid resistance of membranes of cardiomyocytes to reoxidation, which is typical for control normotensive rats of the WKY line, and indicates the presence of a positive effect of the drug on the activity of the VRPOL system in the cardiac muscle.

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