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The Role Of NO-System In The Realization Of Ion-Regulating Function Of The Kidneys In The Model Of Chronic Renal Failure.

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ABSTRACT

Nitric oxide (II) plays an important role in the regulation of the excretory system of the kidneys and the water-electrolyte balance of the animal's body. In the kidneys, he controls renal and glomerular hemodynamics, expands the afferent and efferent arterioles, increases the glomerular filtration rate (GFR), inhibits the transport of sodium ions and increases its excretion, participates in the regulation of ion exchange. In chronic renal failure, endothelium is damaged in the capillary system of the renal brain substance, which is the main cause of progressive renal damage, as a result of which the synthesis of nitric oxide (II) decreases, and electrolyte disturbances are observed in the form of lowering the calcium concentration, total protein, increasing the phosphorus concentration and potassium in the blood. The aim of the study was to study the effect of exogenous and endogenous donors of nitric oxide (II) on the ion-regulating function of the kidneys in the model of chronic renal failure. Changes in the concentrations of potassium, sodium and chlorine ions, as well as urea, creatinine and total protein in blood plasma and urine in the course of activation and inhibition of the nitric oxide (II) system in the model of chronic renal failure (CRF) were studied during our studies. On the basis of experimental data, it was found that in the CRF model, the administration of nitric oxide (II) donors restores natriuretic function in white rats. Also, the administration of nitric oxide (II) donors increases the potassium and renal function of the kidneys, restores the excretion of urea, creatinine to baseline values.

Keywords: nitric oxide, chronic renal failure, kidneys, rats, sodium, potassium, chlorides, urea, creatinine, total protein.

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INTRODUCTION

Nitric oxide (II) plays an important role in ensuring the functions of the excretory system [1]. Thus, in the kidneys it controls renal and glomerular hemodynamics, expands afferent and efferent arterioles; it is also able to increase glomerular filtration rate (GFR), inhibit Na+ transport [2] and increase its excretion [3]. The greatest activity of nNOS is observed in macula densa, the smaller-in the accessory artery of the kidney, in the arc and interlobular arteries [4,5]. In chronic renal insufficiency (CKD), endothelial damage occurs in the capillaries of the renal brain matter system for a long time, which is the main cause of progressive kidney damage [6,7]. In chronic renal failure, the endothelium in the renal capillary system is damaged [8], the synthesis of NO by endothelial cells is reduced due to the accumulation of eNOS inhibitors, such as ADMA, this process is a Central link in the progression of kidney diseases [9,10]. At the same time, there is an increase in such indicators as urea and creatinine, electrolyte disorders are observed [11] in the form of lowering the concentration of calcium, total protein, increasing the concentration of phosphorus and potassium in the blood [12]. It is known that in the model of acute renal failure, the introduction of nitric oxide donors restores the secretion of urea, the excretion of chlorine ions, sodium and water reabsorption. At the moment it remains an open question study the effect of nitric oxide donors (II) inorities renal function in a model of chronic renal failure.

MATERIALS AND METHODS

he studies were conducted in KazanGABM in the laboratory of the Department of physiology and pathological physiology in 2017-2018. The experiments used chlofusan, which is an exogenous donor of nitric oxide (II) and n-nitro-L-arginine methyl ether - L–NAME (Sigma-Aldrich), as a no-synthase blocker. The studies were conducted in two stages. A total of 92 laboratory rats participated in the experiment. In the first part of the experiment, 9 groups of 8 laboratory Wistar rats in each (4 males and 4 females) with a body weight of 200-250 grams were organized to study the concentrations of ions in blood plasma and urine during the activation and inhibition of the nitric oxide system, as well as to identify the sexual dependence of the ion-regulating function.

Three (first, fourth, seventh) groups were intact, three (second, fifth, eighth) groups of experimental rats were administered L - NAME at a dose of 20 mg/kg intraperitoneal, three (third, sixth, ninth) groups of rats were administered exogenous donor NO – chlofusan at a dose of 2 mg/kg intragastrically. The blood was taken 2 hours after the introduction of the nitric oxide donor NO (II) and the no-synthase inhibitor. Blood from rats was taken from the tail vein, to collect urine rats were placed in special metabolic cells. The day before the experiments rats were deprived of water and food.n the second part of the experiment studied the effects of nitric oxide donors (II) in a model of chronic renal failure that caused by the introduction of a 50% aqueous solution of glycerol (10 ml/kg) in the muscles of the hind limbs after 2 hours after intragastric administration lopusina (2 mg/kg). Was formed 4 groups of female rats with 5 rats in each: first group – intact rats, the second control rats with induced chronic renal failure; the third group of rats were administered L-arginine intraperitoneally (200 mg/kg) in models of chronic renal failure, the fourth group of rats were injected intraperitoneally gelofusin (2 mg/kg) in models of chronic renal failure.

Concentration of ions in blood plasma and urine by spectrometric method on "biochemical photometric kinetic Analyzer Bi-An" (Russia) with a set of reagents ("olvex", Russia).

The data were processed by statistical method using student's t-test.

RESULTS AND DISCUSSION

From the data obtained during the experiments it was found out that the amount of sodium in the blood plasma increases, both in males and females with the introduction of the donor of nitric oxide (II) and the inhibitor of NO-synthase.

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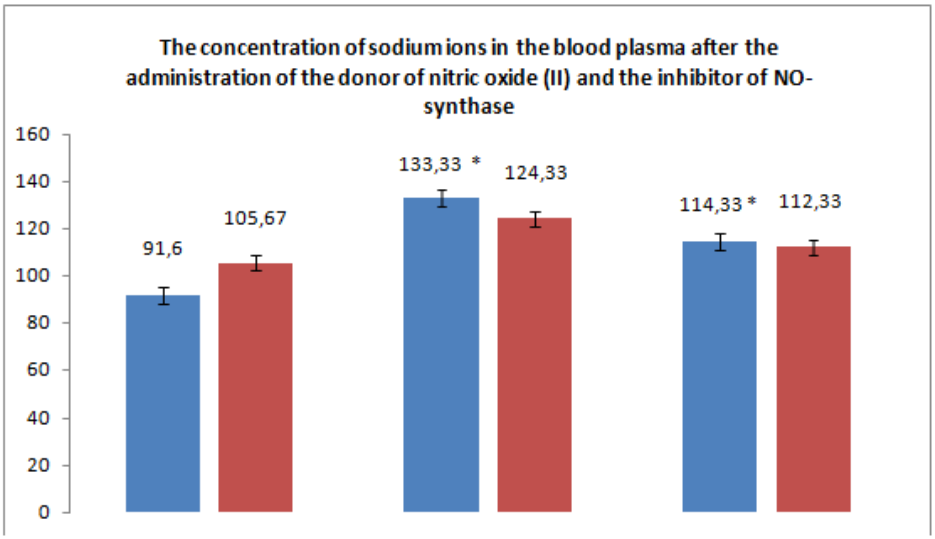

Figure 1: Concentration of sodium ions in blood plasma in white rats after the administration of NO-chlorfuzan and L-NAME, mmol / l.

* - significantly compared to the intact group, (p <0.05)

A significant increase in the amount of sodium in the blood was observed in male white rats when chlorfuzan was administered 1.25 times (p <0.05), and this index increased by 1.45 times when the NO-synthase inhibitor L-NAME was injected (Figure 1). Thus, the introduction of a donor and NO-synthase inhibitor promotes sodium retention in the body.

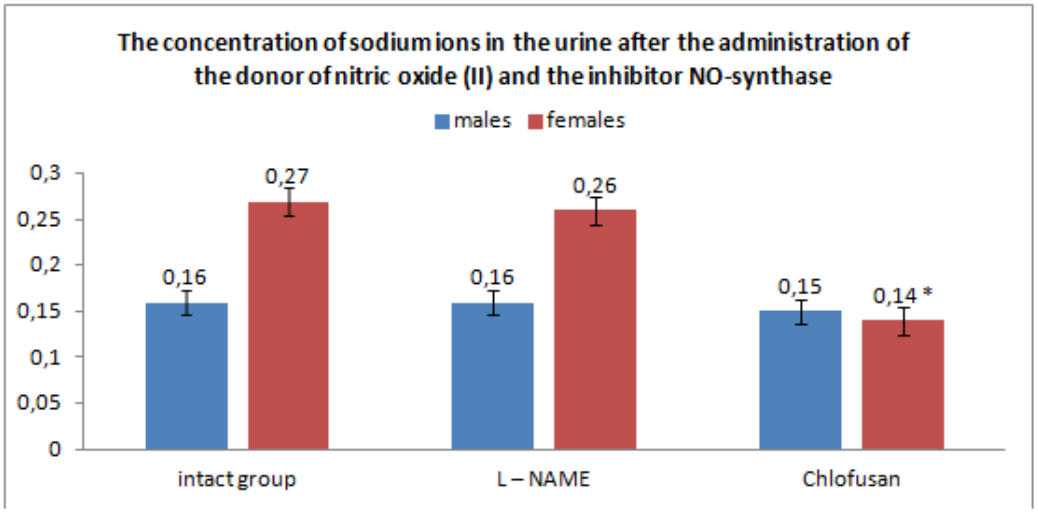

Figure 2: Concentration of sodium ions in urine in white rats after administration of chlorfuzan and L-NAME, mol / 100 g / 24 hours

* - significantly compared to the intact group, (p <0.05)

In the course of the experiment it was found that the amount of sodium in the urine of females is significantly reduced when the administration of chlorfuzan is 0.56 times (p <0.05) (Figure 2).

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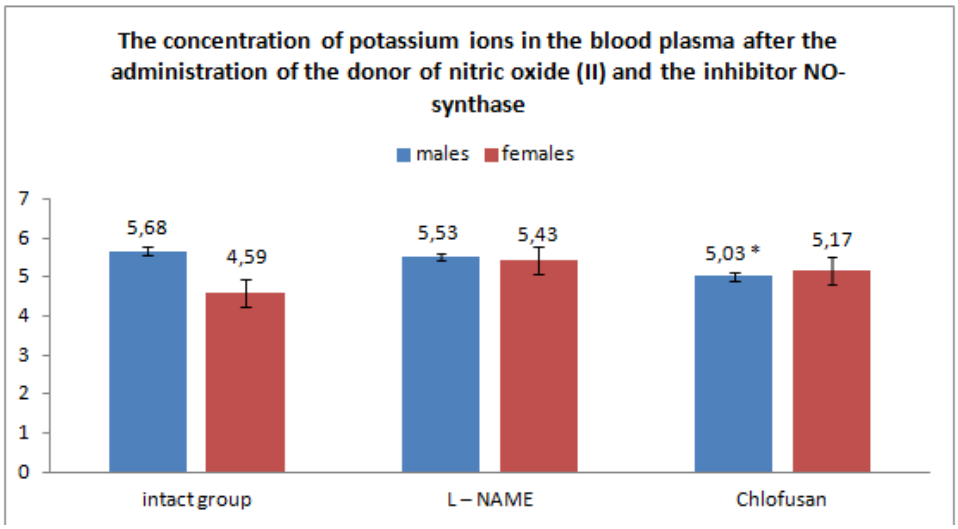

Figure 3: Concentration of potassium ions in blood plasma in white rats after administration of NO-chlorfuzan and L-NAME, mmol / l.

* - significantly compared to the intact group, (p <0.05)

The introduction of chlorfuzan (2 mg / kg) causes a significant decrease in the potassium concentration in males in the blood by 1.13 times (p <0.05) compared with the baseline data. The introduction of L - NAME in the body of rats did not cause a change in the potassium concentration in the blood, its level remained practically unchanged regardless of the sex of the white rats (Figure 3).

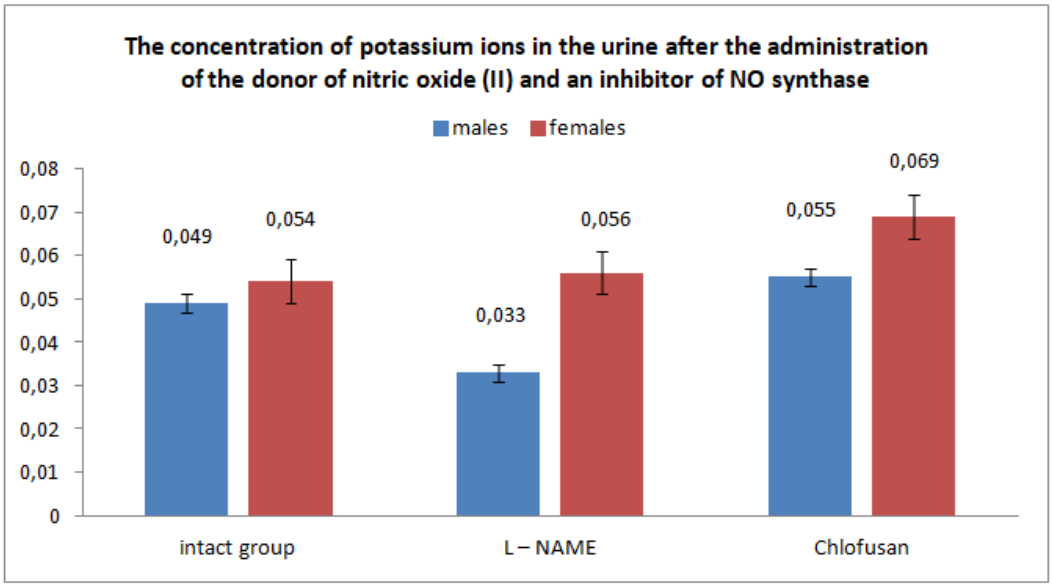

Figure 4: Concentration of potassium ions in urine in white rats after administration of chlorfuzan and L-NAME, mol / 100 g / 24 hours

* - significantly compared to the intact group, (p <0.05)

The content of potassium in the urine did not change significantly when the inhibitor of NO-synthase L-NAME and the donor of nitric oxide (II) of chlorfuzan were administered in both male and female white rats (Figure 4).

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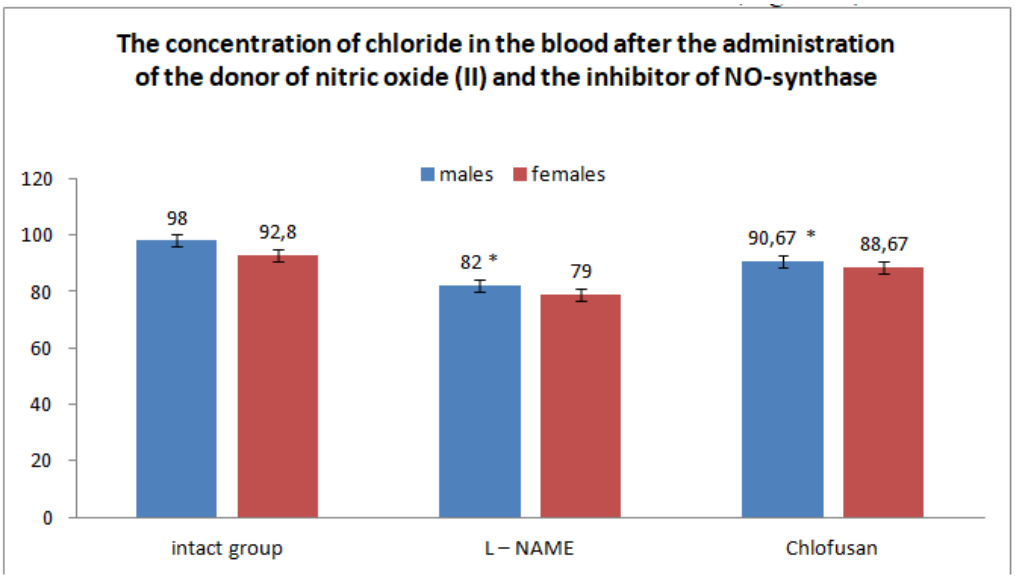

Figure 5: Plasma chloride concentration in white rats after administration of NO-chlorfuzan and L-NAME, mmol / L.

* - significantly in comparison with the intact group (p <0.01)

The introduction of an NO-synthase inhibitor in male rats caused a significant decrease in the concentration of chlorine ions in the blood 1,19 times (p <0,01). When the system of nitric oxide (II) was stimulated with chlorfuzan, the concentration of this index in the blood decreased by 1.08 times (p <0.01) compared to the intact group (Figure 5).

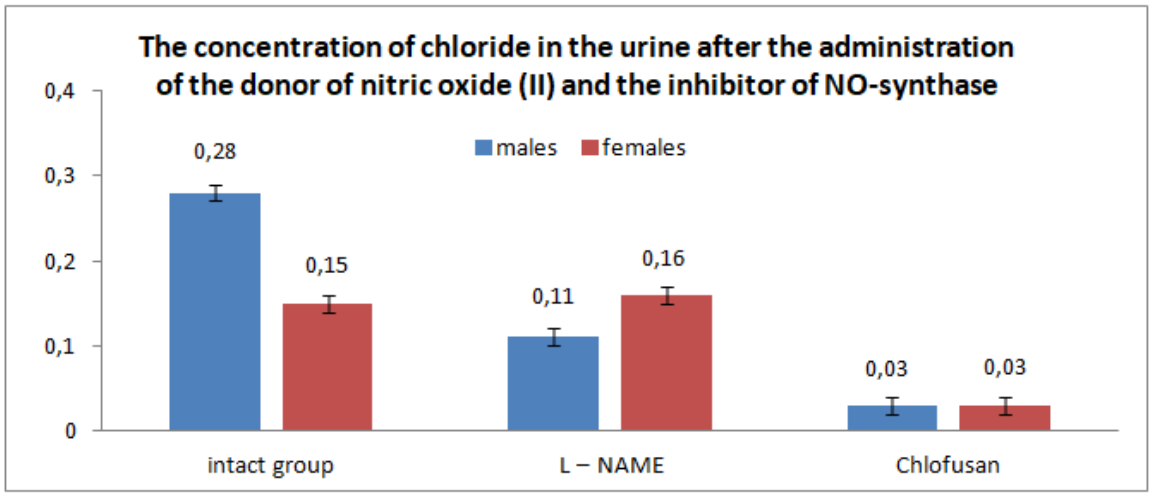

Figure 6: Concentration of urinary chloride in white rats after administration of chlorfuzan and L-NAME, mol / 100 g / 24 hours

* - significantly compared with the intact group (p <0.05)

These studies show that the administration of an exogenous NO-chlorfuzan donor (2 mg / kg) significantly reduces the chloride content in urine in male and female white rats by 9.3 times (p <0.05) and 5.0 times (p < 0.05), respectively. After the introduction of the NO synthase-L-NAME inhibitor (20 mg / kg) in males, the excretion of chlorine significantly decreased by 2.5 times (p <0.05) (Fig. 6). The main criteria for diagnosing chronic renal failure are indicators of biochemical analysis of blood and urine. At the initial stages of chronic renal failure, the concentration of potassium in the blood decreases, which is usually reduced because of polyuria. The sodium level also decreases, as the kidney tubules are affected in the body. When

changes in the work of the kidneys become irreversible, the concentration of urea and creatinine in the blood sharply increases. After administration of L-arginine and chlorfuzan nitric oxide donors, the concentration of sodium in urine decreased 2.4 times and 4.9 times (p <0.01) (Table 2), and in the blood this index increased by 1.06 times and in 1,13 times (p <0,01) in comparison with the control group by the group. The concentration of potassium in the blood increases with the introduction of L-arginine and chlorfuzan 1.16 times and 1.8 times (p <0.05), respectively, compared with the control group (Table 1). The tendency to increase in blood has chlorine anions (Table 1), in the urine there is a significant decrease by 1.4 times (p <0.05) and 2.8 times (p<0.01) in comparison with the control group (Table 2).

Table 1: Biochemical blood indices in the model of chronic renal failure with the introduction of donors of nitric oxide (NO)

Index	Groups			
	Intactrats (n=5)	Rats with a CRF model (Control) (n=5)	L-arginine (n=5)	Chlofusan (n=5)
Concentration sodium, mmol / l	103,80±9,84	107,00±0,79	113,60±3,13 *	121,4±1,53 *
Concentration potassium, mmol / l	4,34±0,24	4,84±0,47	5,6±0,19 *	8,7±1,09*
Concentration chlorine, mmol / l	87,80±1,29	83,60±1,96	86,20±1,56	85,40±1,35
Concentration total protein, mmol / l	69,80±2,58	66,40±0,91	70,40±5,79	72,20±1,92
Concentration urea, mmol / l	5,71±0,236	74,91±1,453 *	52,53±4,551 *	70,53±6,350 *
Concentration creatinine, mkmol / l	65,60±0,91	929,60 ±30,55 *	344,60 ±71,32 *	661,20±68,09 *

* - significantly compared to the intact group, (p <0.05)

Based on the data of the table, it can be noted that the urea level in the control group increased 13-fold (p <0.05) compared to the intact group, which indicates a violation of the filtration function of the kidneys (Table 1). The introduction of L-arginine and chlorfuzan reduces the urea concentration by 1.4 times and by 1.1 times (p <0.05), respectively (Table 1). The obtained data indicate a significant increase in the excretion of urea in the urine under a load of L-arginine 2.8 times (p <0.05) and chlorfuzan 2.6 times (p <0.05) compared to the intact group (Table 2) . The introduction of an exogenous donor leads to a 2.7-fold decrease in sodium excretion (p <0.01) in comparison with the intact group (Table 2), in the blood the concentration of sodium increases 1.17 times (p <0.01) as compared with intact group and 1.13 times (p <0.01) compared with the control group (Table 1). The content of potassium in the blood with the introduction of the donor of nitric oxide of chlorfuzan increases by a factor of 2 (p <0.05) (Table 1), and the urinary excretion of urine 2.5 times (p <0.05) as compared with the intact group (table 2). The concentration of chloride in the blood tends to increase with the introduction of donors of nitric oxide (II) (Table 1), whereas in the urine there is a significant increase in 2.8 times (p <0.05) with the administration of chlorfuzan and 5.6 times p <0.05) with L-arginine compared to the intact group (Table 2).

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Table 2: Biochemical indicators of urine in the model of chronic renal failure with the introduction of donors of nitric oxide (NO)

Index	Groups			
	Intactrats(n=5)	Rats with a CRF model (Control)(n=5)	L-arginine(n=5)	Chlofusan(n=5)
Excretion of sodium, mmol / 100 g / 24 h	0,29±0,02	0,52±0,07 *	0,22±0,01 *	0,11±0,01 *
Excretion potassium, mmol / 100 g / 24 h	0,06±0,01	0,09±0,01 *	0,13±0,01 *	0,14±0,01 *
Excretion chlorine, mmol / 100 g / 24 h	0,10±0,01	0,77±0,07 *	0,56±0,04 *	0,28±0,01 *
Excretion of total protein, mmol / 100 g / 24 h	0,06±0,01	0,02±0,01 *	0,04±0,01 *	0,03±0,002 *
Urea excretion, mmol / 100 g / 24 h	1,68±0,22	0,46±0,17 *	4,72±0,51 *	4,40±0,24 *
Excretion of creatinine, mkmol / 100 g / 24 h	41,491±5,17	15,923±2,15 *	20,008±0,96 *	12,172±0,86 *

* - significantly compared to the intact group, ($p < 0.05$)

The level of creatinine in the blood increased by 14.2 times ($p < 0.05$) with respect to the intact group (Table 1), which proves a violation of the glomerular function, since the kidney is responsible for excretion of this substance. The introduction of nitric oxide (II) donors is accompanied by a 2.7-fold decrease in creatinine ($p < 0.1$) and 1.4 times ($p < 0.1$) (Table 1) and an increase in urinary excretion of 1.3 ($p < 0.05$) with L-arginine, and the introduction of 2 mg / kg of chlorfuzan reduces the excretion by a factor of 1.3 (Table 2) relative to the control group, which is explained by the fact that, with an excess of the substance, the donor starts to act, as an inhibitor. The total protein in the urine significantly decreases with activation of the L-arginine NO system by a factor of 1.7 ($p < 0.1$) and chlorfuzan by 1.97 times ($p < 0.05$) compared to the intact group (Table 2), in the blood there is a tendency to increase the amount of total protein in comparison with the intact group (Table 1). Protein excretion increases 2.1 times and 1.8 times ($p < 0.05$) with the introduction of L-arginine and chlorfuzan, respectively, relative to the control group (Table 2). Blood also increases the concentration of total protein in rats fed nitric oxide donors compared to the control group (Table 1).

CONCLUSION

On the basis of experimental data, it has been established that in the model of chronic renal failure, the administration of nitric oxide (II) donors restores natriuretic function in white rats. Also, the administration of nitric oxide (II) donors increases the potassium and renal function of the kidneys compared to both the intact group and the group of rats in whom CRF was caused. The established facts require additional chronic experiments, since at the moment it is not known whether the effect from the action of donors of nitric oxide (II) will remain for a long time or this temporary phenomenon, as a result of which the compensatory mechanisms of the organism are triggered.

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