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EVALUATION OF THE CORTICOSTEROID RECEPTORS' LEVEL IN THE KIDNEYS OF RATS AFTER SYSTEMIC ISCHEMIA-REPERFUSION

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ABSTRACT — Background: With disturbance of the systemic blood supply, the body experiences hypoxia and stress. Under stress of any etiology, there is a non-specific rearrangement of physiological and biochemical processes. These processes occur under the influence of corticosteroid hormones. Aim: To determine the level of corticosteroid receptors in the kidneys of rats at different times after systemic ischemia-reperfusion. Methods: The study included 80 male white rats. All the animals were divided into 2 groups. A model of systemic ischemia-reperfusion was created in the main group (n=70). Further, on 1, 3, 5, 7, 14, 21 and for 35 days, we determined the level of gluco - and mineralocorticoid receptors in the kidneys. Results: In the animals of the main group, we observed a short-term period (during the first 3 days) of a decrease in the content of both glucorticoid ($p<0.05$) and mineralocorticoid ($p<0.01$) receptors. The dynamics of recovery of the level of corticosteroid receptors was 3 times faster than that of mineralocorticoid receptors. Conclusions: The dynamics of corticosteroid receptors' level in the kidneys of rats after ischemia caused by an arrest of systemic circulation show the recovery time after ischemia-reperfusion injury, which ensures the stability of an individual to hypoxia.

KEYWORDS — glucocorticoid receptors, mineralocorticoid receptors, resistance to hypoxia, ischemia-reperfusion injury.

INTRODUCTION

The complex of protective and compensatory reactions that occur under the influence of extreme hypoxia primarily involves the activation of the hypothalamic-pituitary-adrenal system. It is known that under the influence of corticosteroid hormones (CSH) under stress of any etiology, a nonspecific rearrangement of physiological and metabolic processes occurs, which is necessary to ensure the coordinated functioning of all body systems and adaptation to the pathogenic factor [1].

In case of disruption of the systemic blood supply, the effects of corticosteroid hormones can be significantly distorted due to changes in the sensitivity of target tissue receptors and disorders in the processes of hormone biotransformation, which can cause serious maladaptive consequences [2].

The kidney is an organ that is very sensitive to hemodynamic disorders and ischemia [3]. Therefore, the study of the reaction of resistance to hypoxia after ischemia-reperfusion disorders is an urgent issue.

Aim:

To determine the level of corticosteroid receptors in the kidneys of rats at different times after systemic ischemia-reperfusion.

METHODS

The study was experimental in type and included 80 mature male white rats. The study was carried out in accordance with the ethical standards for the treatment of animals adopted by the European Convention for the Protection of Vertebrate Animals for Research and Other Scientific Purposes, the Federation of European Associations for the Laboratory Animal Science and the International Council for the Laboratory Animal Science.

All animals were divided into two groups:

— main group (n=70; 10 rats for each stage of observation). In this group, we created a model of systemic ischemia-reperfusion.

— control group (n=10).

At first, we gave ether anesthesia to all the animals of both groups. Then, we simulated a 5-minute stop of systemic circulation by clamping the vascular bundle of the heart intrathoracically under ether anesthesia to the rats of the main group. Further, we carried out resuscitation measures in these animals: external heart massage and artificial lung ventilation. In the control group of rats after ether anesthesia, the circulatory arrest was not reproduced.

We evaluated the response of resistance to hypoxia after systemic ischemia-reperfusion based on

the level of gluco- and mineralocorticoid receptors in the kidney tissue homogenates. The level of receptors was determined on the analyzer "StatFox 2100" by the method of enzyme immunoassay, using standard test kits ELISA Kit (China) from Cloud-Clone Corp (USA). We studied the level of corticosteroid receptors on 1, 3, 5, 7, 14, 21 and 35 days.

Statistical processing of the material was carried out using the program "STATISTICA 7.0". The confidence of differences between quantitative indicators was evaluated using the Mann-Whitney test. The differences were considered significant at $p<0.05$.

RESULTS

In the animals of the main group, we observed a short-term period (during the first 3 days) of a decrease in the content of both glucorticoid ($p<0.05$) and mineralocorticoid ($p<0.01$) receptors (Fig.1, 2). This fact can be explained by the possible structural and functional rearrangement of physiological/biochemical systems for the implementation of a complex of adaptation reactions to the changed internal conditions. Starting from the 5th day of the post-resuscitation period, we observed a gradual increase in the activity of glucocorticoid and reduced activity of mineralocorticoid receptors. Moreover, the level of glucocorticoid receptors gradually increased, and by the end of the follow-up period was significantly higher by 23% ($p<0.05$) (Fig. 1).

The dynamics of the increase in the level of mineralocorticoid receptors were recorded 2 weeks after ischemia-reperfusion injury (Fig. 2). By the end of the follow-up period, the level of mineralocorticoid receptors did not significantly differ from those in the control group of animals.

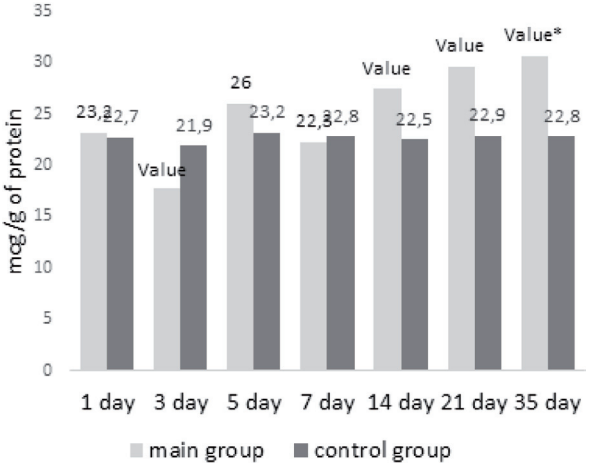

Fig. 1. *Dynamics of the content of glucocorticoid receptors in the kidneys of rats in the post-resuscitation period (*p<0.05)*

DISCUSSION

Adaptation to hypoxia is a reaction aimed at maintaining the vital activity of the body in conditions of oxygen deficiency. It is controlled by central, intercellular, and intracellular regulatory mechanisms. During the period of an urgent generalized response to hypoxia, there is a simultaneous activation of various signaling systems of regulation and an increase in the urgent resistance of the body to oxygen deficiency [4]. The leading role in this process is played by the hypothalamus—pituitary—adrenal system and its main mediators-catecholamines and corticosteroids. During this period, multiple subordinate signaling systems are also activated, which ensure the formation of an urgent compensatory protective reaction of the body in response to hypoxia [1].

The kidney is one of the main target organs for systemic circulatory disorders. Studies of various scientists have shown that aldosterone, through mineralocorticoid signaling, plays a key role in the pathogenesis of ischemia-reperfusion kidney damage, manifested in the development of progressive renal dysfunction, proteinuria, glomerulosclerosis, tubulointerstitial fibrosis, etc. [2, 3, 5]. According to Barba-Navarro R. I. blockage of mineralocorticoid receptors with spironolactone before or even after ischemia prevents acute functional and structural damage caused by ischemia-reperfusion [6].

CONCLUSION

After ischemia-reperfusion injury, a dynamic increase in the level of glucocorticoid receptors in the kidney is observed from day 5. Recovery of the level of mineralocorticoid receptors is observed from the 14th day. Consequently, in the early post-resuscitation period, the kidney is most vulnerable to the effects of remodeling factors and fibrosis.

REFERENCES

1. **Bayburina G.A., Nurgaleeva E.A., Agletdinov E.F., Samigullina A.F.** Effect of hypoxia tolerance on the relation between indicators of free radical oxidation of lipides and proteins in murine kidneys during the post-resuscitation period // Kazan medical journal. – 2017. – Vol. 98. – No 6. – P. 949–954. doi: 10.17750/KMJ2017-949
2. **Jaisser F., Farman N.** Emerging roles of the mineralocorticoid receptor in pathology: toward new paradigms in clinical pharmacology. Pharmacol. Rev. 2016; 68(1): 49–75. DOI: 10.1124/pr.115.011106
3. **Zheng HF, Zhang YN, He JN, Yang Z, Zhang R, Li L, Luo ZH, Ye YR, Sun QQ.** Hydroxychloroquine Inhibits Macrophage Activation and Attenuates Renal Fibrosis After Ischemia-Reperfusion Injury. Frontiers in immunology. 2021;12: 645100. DOI: 10.3389/fimmu.2021.645100

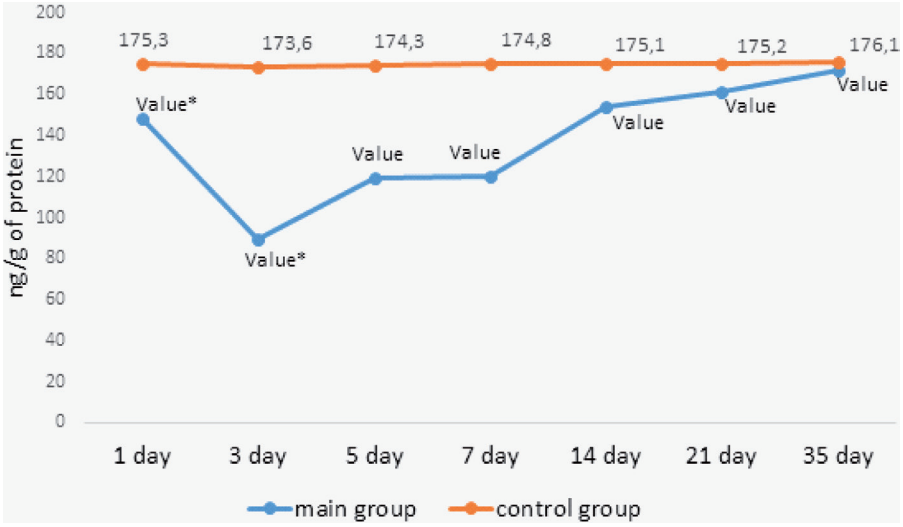

Fig. 2. Dynamics of mineralocorticoid receptor content in rat kidneys in the post-resuscitation period

4. **dos Santos MS, Canale D, Bernardo DRD, Shimizu MHM, Seguro AC, Volpini RA, de Braganca AC.** The Restoration of Vitamin D Levels Slows the Progression of Renal Ischemic Injury in Rats Previously Deficient in Vitamin D. Frontiers in medicine. 2021; 8: 625647. DOI: 10.3389/fmed.2021.625647

5. **Blankenburg M., Fett A.-K., Eisenring S., Haas G., Gay A.** Patient characteristics and initiation of mineralocorticoid receptor antagonists in patients with chronic kidney disease in routine clinical practice in the US: a retrospective cohort study. BMC Nephrol. 2019; 20(1): 171. doi: 10.1186/s12882-019-1348-4.

6. **Barba-Navarro R., Tapia-Silva M., Garza-Garcia C., López-Giacoman S., Melgoza-Toral I., Vázquez-Rangel A., Bazúa-Valenti S., Bobadilla N., Wasung de Lay M., Baranda F., Chawla L.S., Gamba G., Madero M.** The effect of spironolactone on acute kidney injury after cardiac surgery: a randomized, placebo-controlled trial. Am. J. Kidney Dis. 2017; 69(2): 192–199. DOI: 10.1053/j.ajkd.2016.06.013.