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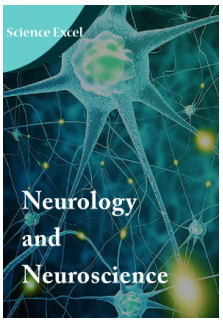


# Stress-sensitive arterial hypertension and tolerance to the salt loading in the ISIAH rats

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## Abstract

The aim of the study is to investigate the ability of ISIAH rats with stress-sensitive arterial hypertension to cope with the salt loading. Hypertensive ISIAH and normotensive WAG rats were kept in metabolic cages for 7 days on three drinking regimes: group 1 – no salt loading (tap water), group 2 – saline solution (0.87% NaCl), and group 3 – 1,5% NaCl solution. After 7 days, no significant changes in the blood pressure in either WAG or ISIAH rats was observed. No differences between hypertensive and normotensive rats were found in the ability to excrete NaCl with urine. Glomerular filtration rates in ISIAH rats receiving both isotonic (saline) and hypertonic salt solutions were significantly higher than in the corresponding groups of WAG rats. In ISIAH, but not in WAG rats, receiving a hypertonic salt solution was accompanied by an increase in the concentrations of norepinephrine and epinephrine in urine. No significant changes in the function of renin-aldosterone system were observed. These and previously obtained results lead to the conclusion that not renal mechanisms but rather sympathetic nervous activity underlies the early development of arterial hypertension in stress-sensitive ISIAH rats, which are well tolerated to the salt loadings at this period of ascending pathology.

## Introduction

Hypertensive disease is diagnosed in about 40% of people over 25 years old, and 10.4 million people die from its complications worldwide every year [1]. Hypertensive disease, or essential hypertension, is diagnosed when the increase in the blood pressure is not secondary, that is, not due to other pathologies, such as kidney disease, Cushing's syndrome, etc. However, it does not mean that primary hypertension has no initial cause: in this case, the clinicians usually talk about various factors of the hypertension development. One of these factors is the increased salt consumption. People are eating much more salt than they were adapted to during million years of evolution. Paleolithic man consumed an average 0.69 g and the modern man consumes 4.9 g sodium per day [2,3]. Changes in the human salt diet occurred over a time of 10,000 years, which is a very short period on the evolutionary timescale [4]. This time is not enough for genetic adaptation to the enhanced salt consumption [5], which leads to a significant strain in the physiological systems maintaining salt balance.

The ideas of the leading role of sodium and kidneys in the development of hypertensive disease were formulated by Arthur Guyton and John Hall [6-8]. The main provisions of their theory are as follows. A high-salt diet leads to an impairment of kidneys' ability to excrete the sodium excess obtained with food, which leads to an increase in extracellular fluid and blood plasma volume, and to the heart preload. This produces a transient increase in cardiac output and the blood pressure. In this case, peripheral vascular resistance may respond differently – it increases, or even decreases. Nevertheless, the ratio of cardiac output and vascular resistance is adjusted so that the blood pressure becomes increased. As a result, pressor diuresis and natriuresis develop, and blood pressure returns to normal. However, in cases when the kidneys ability to sodium excretion is not sufficient, the restoration of sodium balance becomes possible only when the blood pressure is permanently elevated. This, according to Guyton and Hall, is the main condition for hypertension. Thus, the main factor in the pathogenesis of hypertensive disease is inability of kidney to excrete the enhanced amounts of sodium at the normal levels of blood pressure, which requires an increase in blood pressure to restore sodium balance. Hence, the idea of the primacy of the renal factor in hypertension genesis was formulated. Although in this case, it is not clear enough what is the difference between essential (primary) and renal (secondary) hypertension.

Meanwhile, almost 40 years after Guyton et al. had published their theory, which is undoubtedly considered as a classic systematic approach to explain the development of arterial hypertension, other researchers presented an alternative point of view on the effect of excessive salt intake on the

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mechanisms of hypertension development. It postulates that the prime factor in this case is not the kidney mechanisms, but the vascular reactions [9-14]. According to the novel hypothesis, the ability to stop the increase in blood pressure during salt loading is provided mainly by systemic vasodilation. The authors believe that people with salt-sensitive hypertension excrete sodium as good as the salt-resistant people, but with increased salt sensitivity, vasodilation does not develop in response to sodium loading, which leads to an increase in the blood pressure.

In light of the ongoing discussion in the literature, the aim of our study is to investigate changes in renal function and sodium balance following changes in salt loading, in hypertensive ISIAH rats compared to normotensive WAG rats.

## Materials and methods

3-month-old male hypertensive ISIAH rats (a model of stress-sensitive arterial hypertension) and normotensive WAG rats were studied. Rats were obtained from the vivarium of the Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences (Novosibirsk, Russia), where they were kept under standard conditions and received standard balanced food and tap water ad libitum. The light/dark ratio was 12/12 hours. All experiments were performed in accordance with International rules for research using experimental animals (UFAW Handbook) and were approved by the Biomedical Ethics Committee of Scientific Research Institute of Physiology and Basic Medicine (protocol #7, September 10, 2015).

Animals of both strains were divided into 3 groups of 6 rats in each: group 1 received unsalted tap water as a drink, group 2 – saline solution (0.9% NaCl), group 3 – 1.5% solution of NaCl. Thus, studied were 36 rats in total. The sample size of 6 animals per group was considered sufficient for the purposes of experiment, due to genetic homogeneity of animals in each strain used in the experiment, since both WAG and ISIAH strains are inbred. With housing conditions being the same for all animals, the environmental variation in studied parameters within groups was minimal. Each experimental group was formed from rats of different litters. Criteria for including animals were as follows: normal state of health, mean BP values at the start of experiment should be within interval of 180-200 mmHg for hypertensive ISIAH rats, 120-140 mmHg for normotensive WAG rats. Criterion for excluding animals was observable decline in health during the experiment. There were no exclusions of animals during the experiment. The experimental procedures were carried out in a blinded fashion. Different parts of data analysis were performed by different investigators, with end-to-end numeration of the experimental animals.

All rats were placed for 7 days in individual metabolic cages (Italplast, Italy). They had free access to balanced food and corresponding drink. The volumes of drunk liquid and urine excreted were monitored daily at 10 a.m. At the start and at the end of staying in the metabolic cages, rats' body weight and systolic blood pressure were measured. Systolic blood pressure was measured by tail-cuff method using BIOPAC-MP equipment (USA). The blood pressure measurements were recorded after habituation of the animals to the procedure and was calculated as the average of 10 or more scores. After seven-day experiment, rats were euthanized. Serum and urine samples were stored at -70˚C.

Concentrations of creatinine in urine and blood serum were measured using a biochemical analyzer (BS-200E, China), and the glomerular filtration rate was calculated from creatinine clearance. Sodium ion concentrations were measured by flame photometry (BWB-XP Flame Photometer, UK). Serum concentrations of angiotensin-converting enzyme (ACE), aldosterone and renin were determined using commercial ELISA kits according to manufacturer's instructions: Rat ACE Elisa kit CSB-E04490r, Cusabio; Aldosterone Elisa kit KA1883, ABNOVA; Rat renin Elisa kit MBS 041519, MyBioSource. Using a commercial kit (Elisa Kit EA603/288, DLD Diagnostika GMBH), enzyme immunoassay of catecholamines (epinephrine, norepinephrine, dopamine) in rat urine was carried out.

All data obtained were normally distributed according to Kolmogorov-Smirnov normality test, therefore parametric statistical tests were considered suitable for analysis. Statistical analysis was carried out using STATISTICA 8 software package. The statistical significance of differences in mean values between strains and experimental groups was determined using a two-way ANOVA, in which the factors were strain and salt load. The difference between means was assessed using the post-hoc Tukey-HSD test.

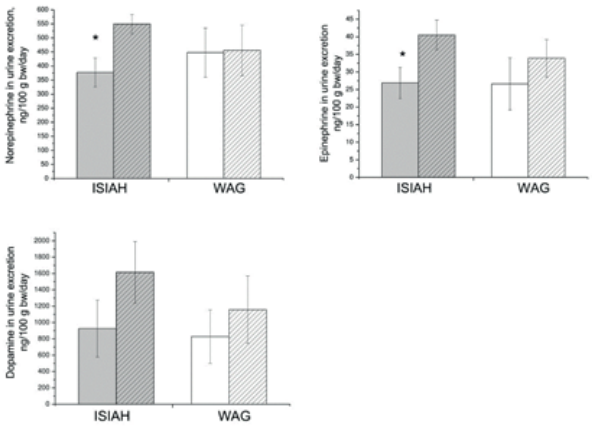


***Figure 1.*** *Catecholamine concentrations in the daily urine (per 100 g of body weight – ng/100 g bw) in ISIAH and WAG rats of the control groups (non-striped columns) and after 7 days salt loading (1.5% NaCl solution) - striped columns. *- intergroup differences, P<0.05..*

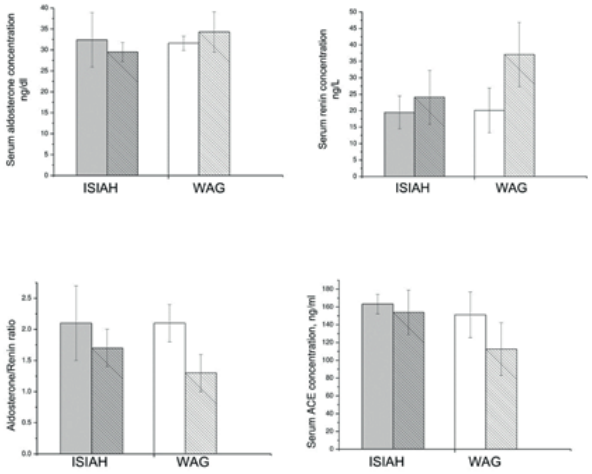


***Figure 2.*** *Serum concentrations of aldosterone, renin and angiotensin converting enzyme (ACE) in ISIAH and WAG rats of the control groups (non-striped columns) and after 7 days salt loading (1.5% NaCl solution) - striped columns.*

***Table 1.*** *Maternal and neonatal variables. *One factor Anova , **Pearson's chi2 .*

| Parameters | Group 1 (tap water) | | Group 2 (NaCl - 0,87%) | | Group 3 (NaCl - 1,5%) | | ANOVA results |
|---|---|---|---|---|---|---|---|
| | ISIAH | WAG | ISIAH | WAG | ISIAH | WAG | |
| Body weight (bw), g | 371,50 ± 11,78 | ***316,00 ± 8,11 | 368,50 ± 7,58 | 333,50 ± 7,58 | 376,83 ± 7,18 | ***297,50 ± 6,83 | Strain – F(1,30)=69,08; P<0,001. Strain x Salt – F(2,30)=3,54; P<0,05 |
| Blood pressure, mmHg | 191,33 ± 7,99 | ***136,67 ± 4,94 | 182,50 ± 6,62 | ***141,83 ± 1,38 | 190,50 ± 9,79 | ***141,67 ± 6,92 | Strain – F(1,30)=335,7; P<0,001 |
| Food consumption, g/day | 27,15 ± 0,91 | **23,24 ± 0,74 | 27,17 ± 0,57 | *24,85 ± 0,44 | 27,95 ± 0,54 | ***22,43 ± 0,62 | Strain – F(1,30)=54,1; P<0,001. |
| Drunk water, ml/100 g bw/day | 7,47 ± 0,68 | 8,79 ± 0,64 | ## 15,13 ± 1,90 | **9,22 ± 0,71 | ### 20,28 ± 1,58 | **12,23 ± 2,52 | Strain – F(1,30)=11,4; P<0,05. Salt – F(2,30)=15,19; P<0,001. |
| Urine, ml/100 g bw/day | 4,23 ± 0,364 | 4,78 ± 0,593 | ## 9,24 ± 1,525 | *5,68 ± 0,402 | ### 13,43 ± 1,375 | ## *9,62 ± 2,055 | Strain – F(1,30)=5,13; P<0,05. Salt – F(2,30)=16,37; P<0,001. |
| (Drunk water) – (Urine) ml/100 g bw/ day | 3,15 ± 0,885 | 3,93 ± 0,377 | # 5,845 ± 0,684 | 3,597 ± 0,419 | ## 6,89 ± 0,559 | *** 2,75 ± 0,644 | Strain – F(1,30)=13,7; P<0,001. Strain x Salt – F(2,30)=8,05; P<0,01. |
| Sodium received with food (Group 1) and with drunk water (Groups 2, 3) mmol/100 g bw/ day | 1,582 ± 0,199 (in food only) | 1,598 ± 0,219 (in food only) | ### 7.292 ± 0,72 | ###* 5.108 ± 0,26 | ### 14.832 ± 1,03 | ### **9.668 ± 1,63 | Strain – F(1,30)=12,71; P<0,001. Salt – F(2,30)=79,89; P<0,001. Strain x Соль – F(2,30)=4,74;P<0,05 |
| Sodium excreted with urine, mmol/100 g bw/ day | 0,404 ± 0,043 | 0,377± 0,039 | 1.704 ± 0,1453 | 1.22 ± 0,0594 | ### 3.775 ± 0,8393 | *2.030 ± 0,3455 | Strain – F(1,30)=5,70; P<0,05. Salt – F(2,30)=16,52; P<0,001. |
| (Sodium received) – (Sodium excreted) mmol/100 g bw/ day | 1,178 ± 0,056 | 1,221 ± 0,107 | ## 5.588 ± 0,592 | 3.888 ± 0,203 | ### 11.057 ± 1,233 | ## *7.638 ± 1,292 | Strain – F(1,30)=7,49; P<0,05. Salt – F(2,30)=61,12; P<0,001. |
| Sodium received-excreted difference as percentage from sodium received, % | 24,9 ± 2,202 | 23,1 ± 1,292 | 23.4 ± 1,200 | 23.9 ± 1,372 | 25.4 ± 2,266 | 21.0 ± 1,393 | NS |
| Glomerular filtration rate, ml/100 g bw/h | 30,16 ± 4,22 | 23,455 ± 2,534 | 206,796 ± 0,5928 | ** 14,9604 ± 0,474 | 39,1368 ± 10,6272 | ** 20,1522 ± 1,6614 | Strain – F(1,30)=7,02; P<0,01. |

## Results

A one-week salt loading (0.9% or 1.5% NaCl) did not lead to an increase in blood pressure in either normotensive WAG or hypertensive ISIAH rats as compared to the blood pressure levels of these rats receiving tap water (Table 1). At the same time, in all groups, the blood pressure in ISIAH rats was significantly higher than in WAG rats: by 58 mm Hg in the group without salt loading, and by 57 and 46 mm Hg respectively in groups with isotonic and hypertonic salt loading. Nevertheless, the absence of a blood pressure response to the sodium increase in the drinking water was accompanied by changes in a number of other parameters. At the start of the experiment three-month-old ISIAH rats had a greater body weight than WAG rats of the same age. In the absence of salt loading, the difference is 50 g (362 ± 12.8 versus 312 ± 11.9; P <0.05). At the end of the experiment, in the groups with saline, the difference in body weight between WAG and ISIAH rats became insignificant due to an increase in the weight of WAG rats. However, in the group of rats receiving 1.5% NaCl solution, the endpoint interstrain differences became more pronounced (378 ± 7.6 versus 308 ± 11.1; P <0.001), both due to an increase in the body weight in ISIAH rats and its slight decrease in WAG rats. This forms an impression of a reduced tolerance of WAG rats to salt loading as compared to hypertensive ISIAH rats, which seems paradoxical at a first glance. Indeed, based on general concepts, it should be hypertensive individuals, who as it supposed may experience greater discomfort from increased salt intake.

The daily intake of tap water per unit of body weight in WAG and ISIAH rats does not differ. However, when drinking salt water, there was a significant increase in fluid intake by ISIAH, but not by WAG, rats, although the latter also showed a small, statistically insignificant, increase in 1.5% salt solution intake. Diuresis changed similarly, a significant increase in daily diuresis was noticed only in ISIAH rats receiving 1.5% salt solution. The difference between the volumes of drunk fluid and urine, indicating possible fluid retention in the body, is increased as compared to the tap water drinking rats, only in ISIAH rats receiving both isotonic and hypertonic sodium solutions. On the contrary, the difference between the drunk and excreted fluids in WAG rats being on the hypertonic salt regime is decreased compared to control, which made the differences in this parameter between ISIAH and WAG rats highly significant.

Due to the fact that ISIAH rats drank more salt water than WAG rats, the sodium intake in hypertensive rats was also significantly higher when drinking both the isotonic and hypertonic solutions. Accordingly, ISIAH rats also excreted more sodium with urine, however the difference between entered and excreted sodium in ISIAH rats is higher than in WAG rats. Nevertheless, this difference does not indicate a lesser ability of the kidneys of ISIAH rats to excrete sodium: the percentage of sodium excreted taken from sodium received, when drinking 1.5% salt solution, in ISIAH rats was 25.4%, and in WAG rats -21.0%.

The glomerular filtration rate in ISIAH rats receiving both isotonic and hypertonic salt solutions was significantly higher than in the corresponding groups of WAG rats. In control groups of WAG and ISIAH rats, the glomerular filtration rates did not differ significantly.

As for the hormonal status, it should be emphasized that in ISIAH rats, receiving a hypertonic solution was accompanied by an increase in the excretion of catecholamines in the urine. A significant increase was noted for norepinephrine and epinephrine (Figure 1). No significant changes were observed in WAG rats.

Such indicators of renin-angiotensin-aldosterone system functioning as the concentrations of aldosterone, renin and angiotensin-converting enzyme in the blood serum did not react at all to the transition of ISIAH rats to the salt loading (1.5% NaCl) (Figure 2). Also, no significant changes were found in these parameters in WAG rats, although the aldosterone/renin ratio decreased ($P < 0.05$) in those with salt loading, which may indicate a relative decrease in the sensitivity of aldosterone-producing cells to stimulating signals.

## Discussion

In discussions about the causes of hypertensive disease or essential hypertension, the following statement can be cited from literature as a typical: “despite many years of intensive research, the etiology of the disease remains unknown” [15,16], with mentioning multiple factors provoking or predisposing to the development of hypertension, for example, such as overweight (obesity), insulin resistance, addiction to alcohol, high salt intake, a sedentary lifestyle, age, stress, low consumption of potassium and calcium, etc. [17,18]. It is noteworthy that the word "kidney" does not appear directly in the listed factors. This is quite understandable, since the addition of a renal factor to the list of etiological causes inevitably translates hypertension into the status of secondary, or, specifically, renal hypertension. This contradiction, however, is not taken into account when the kidney is given a leading role in the pathogenesis of hypertension, which is expressed in the famous aphorism, “blood pressure follows the kidney” [19,20]. Of course, thanks to the brilliant work of Arthur Guyton and J. Hall [6-8], the kidney seems to deserve this appreciation. As already mentioned above, according to the authors' concept, the inability of the kidney to excrete sodium excess at the normal blood pressure leads to the fact that blood pressure must increase in order to maintain sodium balance, because of pressor diuresis and natriuresis. Thus, the restoration of sodium balance occurs due to increase in the blood pressure.

The state of sodium balance in the control hypertensive ISIAH rats that received tap water did not reveal any noticeable disturbances and differences when compared with the control normotensive WAG rats. Apparently, this is achieved due to compensatory mechanisms and to a significant increase in blood pressure in ISIAH rats. Additional sodium loading can be expected to disrupt the compensatory mechanisms of the renal function and sodium balance in hypertensive rats. However, this does not happen. Chronic salt loading did not produce any impairment in the ability of ISIAH rats to excrete sodium excess. Earlier, this conclusion was obtained for an acute salt loading (acute loading was carried out with an intragastric infusion via catheter of 0.9% or 2.0% NaCl 5ml/100 g bw [21,22]). Moreover, under acute salt loading, ISIAH rats excreted sodium much faster than normotensive WAG rats.

The present study showed that hypertensive ISIAH rats cope with chronic salt loading quite successfully, at least not worse, and perhaps even better, than normotensive WAG rats. Moreover, you can get an impression that ISIAH rats have an increased salt appetite, they drink more hypertonic salt solution per unit of body weight than WAG rats, and, accordingly, excrete more sodium with urine.

In ISIAH rats, compared with WAG rats, no significant changes were found in the parameters indicating functioning of renin-angiotensin system (RAS), but some features of the response to salt loading from the sympathetic adrenal system (SAS) were revealed in the group of ISIAH rats that received hypertonic solution: there was an increase in the concentrations of norepinephrine and epinephrine in the urine compared to the levels of these amines in the urine of ISIAH rats that received tap water. There was no such reaction in WAG rats. Hence, it can be concluded that hypertensive rats have an increased SAS reactivity. This conclusion is in agreement with our earlier data on the increased SAS response of ISIAH rats to emotional stress (handling), which could be determined by changes in the concentrations of norepinephrine and epinephrine in the peripheral blood plasma [23]. In this regard, the question naturally arises about the predominant role of the sympathetic nervous system in the genesis of arterial hypertension in ISIAH rats. The question of contribution of the renal and nervous factors in the formation and pathogenesis of hypertension is constantly discussed in the literature. Murray Esler [24] believes that the most widespread is the so-called neurogenic hypertension. Although the concept of the important role of nervous system and its sympathetic part in the pathogenesis of hypertension is not new [25,26], it is inferior to the concept of the leading role of the renin-angiotensin system (RAS), especially since the most popular antihypertensive drugs target RAS. On the other hand, a large number of studies shows that there are close interactions between RAS and SAS both in the regulation of blood pressure and in the renal functions [27,28].

The role of SAS in the operational regulation of vascular tone and cardiac function and, consequently, the blood pressure, is well proven, while the possibility of long-term BP regulation by SAS is a subject of constant debate [28-32]. Nevertheless, many facts suggest that SAS hyperfunction can lead to a sustained increase in blood pressure. Back in the 1950s, the high efficiency of regional surgical sympathectomy in the treatment of hypertension was shown [33]. Later, other effective methods of treating hypertension were developed by affecting the SNS. Thus, a direct decrease in the general sympathetic tone was achieved by chronic stimulation of carotid baroreceptors [34,35]. At the same time, in patients with hypertension resistant to drug therapy, a persistent decrease in blood pressure occurred. The same persistent reduction in blood pressure in resistant hypertension can be achieved with catheter radiofrequency ablation of kidney sympathetic nerves [27,36]. Verification of the role of SAS in the genesis of hypertension essentially comes from the negative proof: that is, with sympathetic

blockade, already existing high blood pressure decreases, but is it possible to obtain a persistent increase in blood pressure by increasing sympathetic stimulation? Clinical data show that chronic emotional stress, which increases the tone of the sympathetic nervous system, may be the cause of the development of an initially unstable hypertensive state, which ultimately results in persistent hypertension [37-39]. Similar results were obtained in the experiments on rat strains [40,41]. Moreover, it has been shown that the development of arterial hypertension under stress in both humans and experimental animals depends on the genotype [42]. Actually, such an example is our strain of ISIAH rats. This strain was obtained by genetic selection for an increase in blood pressure under conditions of mild emotional stress, which is reflected in the name of the strain – inherited stress-induced arterial hypertension (abbreviated as ISIAH) [43]. The fact that these rats have an increased reactivity of the sympathetic adrenal system, as well as the hypothalamic-pituitary-adrenocortical system, to stressful stimulation, is confirmed by our earlier data on the analysis of neuroendocrine profiling in the ISIAH rats [44]. Tyrosine hydroxylase-mRNA in adrenals of ISIAH rats showed a persistent increase, along with higher expression of corticotropin releasing hormone-mRNA in hypothalamus and proopiomelanocortin-mRNA in pituitary gland after restraint stress, as compared to control WAG rats [23]. Transcriptome analysis of the adrenal glands in ISIAH rats revealed several differentially expressed genes associated with arterial hypertension, including two transcriptional factors genes (Nr4a3 and Ppard), which may be related to the predominant activation of the sympathetic-adrenal medullary axis [45]. Indications of increased sympathoadrenal activity were provided also by immunohistochemical analysis of adrenal chromaffin cells of ISIAH rats, showing more intense reaction to chromogranin A, compared to WAG rats [46]. Chromogranin A mediates the accumulation of catecholamines and is used as a prognostic parameter in different cardiovascular diseases [47]. Buzueva et al. [46] also demonstrated differences in morphometric parameters of adrenal glands between ISIAH and WAG rats: the relative weights and volumes of the adrenal cortex and medulla were significantly higher in hypertensive ISIAH rats.

Thus, based on earlier data and on the results obtained, it can be assumed that the disturbance of nervous regulatory system, namely the functioning of SAS, is the primary link in the pathogenetic chain of events that lead to the development of hypertension in ISIAH rats. Nevertheless, kidneys, apparently, are also involved into the mechanism of pathogenesis of the studied hypertension, most likely, along with the assistance of sympathetic nervous system. We showed earlier that vascular resistance is increased in renal arteries of ISIAH rats, and this may be a cause to enhance the blood pressure to support the adequate kidney perfusion [48]. We assume that normal kidney function in ISIAH rats is possible only under conditions of increased blood pressure. This is due to the fact that increased sympathetic tone affects not only systemic hemodynamics, but also, which is very important, intrarenal hemodynamics. This, in turn, can shift the curve of the ratio of sodium excretion and renal perfusion pressure on the Guyton's graph to the right [6]. As a result, the natriuretic function of the kidney remains intact, while hemodynamics changed, and blood pressure increases. Thus, our results are in accordance with the statements of Kurtz et al. [9] on the role of hemodynamic processes in the regulation of sodium balance under additional salt loadings at arterial hypertension.

## Funding statement

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