GENERAL PATHOLOGY AND PATHOLOGICAL PHYSIOLOGY

Development of Hypertensive Status in NISAG Rats Reared by Normotensive Wistar Rats

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Parameters of the cardiovascular system and the content of corticosterone, thyrotrophin, thyroxin, and triiodothyronine in the plasma, and norepinephrine in the myocardium were determined in male NISAG rats (hereditary stress-induced arterial hypertension) reared by normotensive Wistar rats. Cross-rearing of hypertensive rat pups by normotensive females attenuated arterial hypertension with a tendency to normalization of the examined parameters. This confirms the possibility of modifying hypertensive phenotype by changing the conditions of the early postnatal development.

Key Words: *hormones; myocardium; arterial hypertension; stress*

Essential hypertension is the most prevalent form of cardiovascular pathology [3]. Arterial hypertension is formed during the development of physiological systems regulating blood pressure (BP) and after their maturation [2,14]. Genetic defects determining the disturbances in BP regulation and elevation of BP are realized with age, or not realized (under certain conditions preventing their realization). Hormonal background mediating the genotypic features [10] largely determines the development of arterial hypertension. Published data point to the possibility of modification of the hypertensive status by changing raising conditions during the early ontogeny characterized by rapid development and high sensitivity of fundamental biological systems to epigenetic factors[4]. In the present study we analyzed changes in the cardiovascular system and some hormonal parameters in hypertensive NISAG rats (hereditary stress-induced arterial hypertension) reared by normotensive Wistar females.

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MATERIALS AND METHODS

Normotensive Wistar rats and hypertensive NISAG rats were used in the study. The animals were kept under standard vivarium conditions a (Institute of Cytology and Genetics). Wistar and NISAG rat pups reared by their natural mothers comprised the control groups after attaining a 5-month age. Some NISAG pups were put in cages with Wistar dams (own pups of these dams were took away). The difference between the time of delivery in donor and recipient mothers did not exceed 12 h. Experimental group consisted of 5-month-old male NISAG rats reared by Wistar rats. All rat pups were reared by natural or recipient mothers for 1 month. Thereafter, the pups were separated from the mothers, the males were selected and kept in groups of 4-5 animals from the same litter.

Systolic BP was measured under ether raush narcosis by indirect sphygmography. For ECG recording, the rats were anesthesized with ether, placed into a

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screened chamber in the prone position, and connected to a Mingograph-34 cardiograph via needle electrodes. ECG was recorded in 3 standard and 3 amplified leads from limbs at 100 mm/sec tape speed and 20 mm/mV channel sensitivity. ECG was analyzed by measuring the width and amplitude of *P, R, S, T* waves and *QRS* complex, and by the length of *PQ, QRST*, and *RR* intervals.

The concentrations of thyrotropin (TSH), thyroxin (T_4), and triiodothyronine (T_3) were measured by radioimmunological method in rat plasma obtained after decapitation. Plasma corticosterone content was determined by competitive ligand binding assay. The concentration of norepinephrine in the myocardium was measured on an MPF-4 microspectrofluorimeter (Hitachi). Reactivity of muscular arteries to norepinephrine was studied *in vitro* on isolated segments of the caudal artery. The segment was perfused with Krebs—Henseleit buffer at 70 mm Hg and 37°C as described elsewhere [5]. Norepinephrine was injected into the perfusion system once in a concentration of 0.01 μg/ml in 5 ml perfusion medium and the effect was evaluated for 10 min by changes in the perfusion flow.

The data were processed statistically using Student's *t* test.

RESULTS

Parameters of the cardiovascular system in NISAG rat pups reared by normotensive Wistar dams from day 1 to day 25 of postnatal development underwent permanent changes and approximated the corresponding parameters in normotensive rats (Table 1). In adult NISAG rats reared by normotensive Wistar females practically all ECG parameters and index of vascular reactivity were intermediate between the corresponding parameters in control Wistar and NISAG rats reared by natural mothers. In adult NISAG rats reared by Wistar dams BP was significantly lower than in control NISAG rats and corresponded to the borderline between the norm and hypertension (Table 1).

Thus, rearing of hypertensive NISAG rats by normotensive Wistar females induces an integral shift of cardiovascular system parameters toward the normal. Though most test parameters differed significantly from those in Wistar rats, the obtained results attest to a significant influence of maternal environment during the early postnatal ontogeny on the formation of hypertensive status in NISAG rats. The main maternal factors are maternal behavior [9,10] and specific factors of maternal milk [11,13], in particular, hormones (concentrations of hormones in maternal milk considerably variy in different animal strains) or nonhormonal components, *e.g.* electrolytes. Evaluation of the hormonal status of these rats helps to elucidate some physiological mechanisms underlying BP decrease in NISAG rats reared by normotensive Wistar mothers.

Thus, in hypertensive rats reared by normotensive females the concentration of T_4 became similar to that in Wistar rats (Table 2). This decrease can result in a decreased density of β_2-adrenoreceptor [6] in the myocardium of hypertensive rats. Changes in the number of β_2-adrenoreceptors play a significant role in myocardial hypertrophy [8], which was previously described in NISAG rats [7]. At the same time the T_3/T_4 ratio in NISAG rats reared by Wistar mothers sur-

TABLE 1. Parameters of ECG in 6-Month-Old NISAG Rat Pups Reared by Wistar Female Rats (*M±m*)

Parameter	Wistar (*n*=58)	NISAG	
		control (*n*=63)	experiment (n=9)
P, msec	19.0±1.0	22.0±1.0*	21.0±1.0*
	1.5±0.1	1.5±0.1	1.47±0.15
PQ, msec	58.0±1.0	62.0±1.0**	60.70±1.21
QRS, msec	19.00±0.75	24.0±1.0**	22.50±1.32
	9.90±0.61	3.21±0.71*	4.57±1.10**
QRST, msec	67.0±2.0	53.0±1.0*	57.7±2.8***
RR, msec	182.0±2.0	153.0±2.0*	163.3±3.1**
Systolic interval	36.8±1.5	34.6±1.0	35.3±1.4
Angle a, °	37.4±3.7	0.2±6.2*	10.7±7.0*
BP, mm Hg	118.0±3.7	171.0±3.0*+	147.0±1.8*
Index of arterial reactivity	1.27±0.13	3.25±0.93***	2.12±0.55

Note. BP was measured in 13 Wistar rats, 23 control, and 25 experimental NISAG rats. Index of arterial reactivity was determined in 10 Wistar rats, 10 control, and 9 NISAG experimental rats. Here and in Table 2: *p<0.001, **p<0.01, *p<0.05 compared to Wistar rats, +p<0.001 compared to control NISAG rats.

TABLE 2. Hormonal Parameters in 6-Month-Old NISAG Rat Pups Reared by Wistar Females (*M*±*m*)

Parameter	Wistar (*n*=58)	NISAG	
		control (*n*=63)	experiment (*n*=9)
Corticosterone, μg/100 ml	1.60±0.37 (13)	5.5±1.56*** (23)	8.2±3.35 (25)
TSH, μU/ml	0.203±0.075 (9)	0.261±0.070 (9)	0.245±0.085 (9)
T_3, ng/ml	0.794±0.040 (9)	0.787±0.020 (9)	0.777±0.050 (9)
T_4, nmol/l	33.5±3.1 (9)	43.4±2.0** (9)	35.3±2.5 (9)
Norepinephrine, ng/g myocardial tissue	1142±155 (7)	731±39*** (7)	900±50 (5)

Note. Number of measurements is indicated in brackets.

passes that of control NISAG rats (0.022 and 0.01, respectively). This change reflects a shift to a more active thyroid hormone (T_3) and high energetic value of adaptation in hypertensive rats [1]. Since corticosterone concentration in NISAG rats remains higher than in Wistar rats, it can be assumed that endocrine components of the pressor system are the factors determining residual hypertension. The concentration of norepinephrine in the myocardium in these rats slightly increased compared to control NISAG rats (Table 2), which suggests less intensive sympathetic stimulation of the myocardium in experimental NISAG rats. Thus, it can be concluded that attenuation of arterial hypertension in NISAG rats reared by normotensive Wistar females depends on attenuation of the sympathetic tone, rather than on decreased function of the adrenal cortex. This assumption is supported by our previous data [14] on the role of increased sympathetic nervous activity in the development of stress-induced arterial hypertension in NISAG rats. Molecular genetic studies on (WAG×NISAG)F_2 rats revealed co-segregation of BP level with alleles of *NGFR* locus encoding nerve growth factor receptor (p75) [12], which, in turn, determines the level of sympathetic innervation of cardiovascular system.

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