ENDOCRINE-METABOLIC RELATIONS IN RATS WITH INHERITED STRESS-INDUCED ARTERIAL HYPERTENSION

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Genetic models of arterial hypertension in rats are nowadays considered the closest laboratory analogs of human essential hypertension [2]. As a result of selection for the blood pressure (BP) level against a background of emotional stress, a strain of animals with inherited stress-induced arterial hypertension (ISIAH line) has been obtained at the Institute of Cytology and Genetics, Siberian Branch, Academy of Sciences of the USSR, from a population of Wistar rats [5]. By now the rats of this strain have been characterized with respect to behavior [7], central adrenergic mechanisms of BP regulation [8, 10], and reactivity of the myocardium [6] and hypothalamo-hypophyseo-adrenocortical [3, 9], but the activity of other peripheral endocrine glands and coupled metabolic reactions have not been investigated.

The aim of this investigation was to compare endocrine regulation of metabolic reactions in ISIAH and Wistar rats.

EXPERIMENTAL METHOD

The experiments were carried out in the Winter and Spring on sexually mature male ISIAH rats (bred at the Institute of Cytology and Genetics, Siberian Branch, Academy of Sciences of the USSR) and Wistar rats (from the "Stolbovaya" nursery, Academy of Medical Sciences of the USSR).

Hypertensive rats of this new ISIAH line were selected under conditions of emotional stress, which induced elevation of BP, which explains the name given to this strain of rats [5]. The basal BP level in the ISIAH rats was about 150-160 mm Hg. No significant differences were observed in this parameter in animals of different filial generations (F_{12}, F_{17}, F_{19}, F_{20}, F_{22}, F_{24}). Meanwhile, emotional stress, induced by keeping the animal in a constraining cage, led to a sharp rise of BP to 200-220 mm Hg (F_{18}-F_{24}). Other emotiogenic factors act in a similar way on these animals. The basal BP level in control Wistar rats (the ancestral strain on the basis of which the ISIAH rats were bred) averaged 120 mm Hg. The rise of BP under conditions of emotional stress in Wistar rats did not exceed on average 10-15 mm Hg. We know from the literature that an enhanced reaction of BP is observed in certain types of stress in spontaneously hypertensive rats (SHR strain) [16], but the gradient of this increase is much less than in rats of the ISIAH strain. SHR rats are characterized chiefly by a spontaneous rise of BP, thus accounting for the name given to these rats also.

The experimental ISIAH and Wistar rats were kept in individual cages under standard animal house conditions. The following parameters were compared: concentrations of tri-iodothyronine (T_3), thyroxine (T_4), immunoreactive insulin (IRI), glucose, and free fatty acids (FFA) in the blood, adrenalin (A) and noradrenalin (NA) in the adrenals, glycogen in the liver, and activity of phenylethanolamine-N-methyltransferase — PNMT (E.C. 2.1.1.28) in the adrenals, hexokinase — HK (E.C. 2.7.1.1) and glucose-6-phosphatase — G6Pase (E.C. 3.1.3.9) in the liver, and the glucose tolerance test (GTT) was carried out.

Blood hormone levels were determined with the aid of standard kits for radioimmunoassay, levels of A and NA were determined fluorometrically [14], metabolites with the aid of standard color reactions, PNMT activity was measured as in [15],

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TABLE 1. Endocrine-Metabolic Parameters in ISIAH and Wistar Rats

Parameter	ISIAH	Wistar	P <
A, μ moles/g wt. adrenals	5.88 + 0.41	4.28 ± 0.14	0.01
NA, μ moles/g wt. adrenals	1.73 ± 0.21	1.59 ± 0.09	
PNMT activity, cpm/mg proting × 10^3	2.71 ± 0.13	1.84 ± 0.24	0.05
T_3, nmoles/l serum	2.19 ± 0.31	1.62 ± 0.31	
T_4, nmoles/l serum	103.5 ± 8.0	84.1 ± 3.2	0.05
IRI, pmoles/l blood	118.8 ± 25.7	208.6 ± 5.1	0.001
Glucose, mmoles/l serum	4.3 ± 0.2	4.9 ± 0.1	
FFA, mmoles/l serum	0.71 ± 0.05	0.55 ± 0.02	0.01
Glycogen, g/100 g wt. liver	2.96 ± 0.29	5.26 ± 0.20	0.001
HK activity in liver, μmoles NADPH/min·mg protein	43.0 ± 4.0	30.0 ± 2.0	0.01
G6Pase activity in liver, μmoles P/min·mg protein	17.0 ± 1.0	11.6 ± 1.6	0.001

HK as in [3], and G6Pase as in [11]. For the GTT, glucose was injected intraperitoneally in a dose of 5 g/kg body weight and its concentration was determined in blood taken from the caudal vein before and 30, 60, and 150 min after injection of the preparation.

EXPERIMENTAL RESULTS

The content of A and PNMT activity were increased in the adrenals of ISIAH rats compared with Wistar rats (Table 1), evidence of increased synthesis of A. The level of NA, the precursor in A synthesis, was not lowered but had a tendency to rise (Table 1). The results indicate increased sympathoadrenal activity in the hypertensive rats. We know from the literature that the content of biogenic amines in the adrenals also is increased in SHR rats with genetically determined spontaneous hypertension [18]. The authors cited link this fact with changes in the central regulatory mechanisms.

Concentrations of thyroid hormones in the blood were higher in ISIAH than in Wistar rats (Table 1), and in turn, this may increase the sensitivity of the tissues to catecholamines. This combined increase of sympathetic tone and of the concentrations of thyroid hormones in ISIAH rats leads to activation of lipolysis, as shown by the higher blood FFA level than in Wistar rats (Table 1).

The IRI level in the plasma was lower in the hypertensive than in the Wistar rats (Table 1). It can be tentatively suggested that this is connected with the increased sympathetic activity in ISIAH rats and direct inhibition of insulin secretion through α-adrenoreceptors [1]. In SHR rats the number of insulin-forming cells of the insular apparatus of the pancreas has been found to be reduced [13]. According to the authors cited, the primary defect in SHR rats is a change in membrane permeability for sodium and potassium ions and facilitation of transmembrane permeability for sodium and potassium ions and facilitation of transmembrane glucose transport, reducing the insulin demand and leading to reduction of the pancreatic islet-cell apparatus [12].

HK activity in the liver was higher in ISIAH than in Wistar rats (Table 1), evidence of an increase in the flow of glucose into the organ. Glucose is not stored as glycogen, for its concentration in the hepatocytes is lowered (Table 1). A combination of a low blood IRI and high FFA concentration probably leads to inhibition of glycolysis and to oxidation of glucose in the Krebs' cycle, and this in turn creates an excess of intracellular glucose in the form of glucose-6-phosphate. The increase in G6Pase activity in the liver of ISIAH rats (Table 1) evidently enables the intracellular glucose-6-phosphate content to be balanced.

Sugar loading revealed a decrease of tolerance of the ISIAH rats to glucose. The maximal rise of the glucose concentration in animals of the groups compared did not differ at the 30th minute of the test, but at the 60th and 150th minutes the blood glucose level was significantly higher in the ISIAH than in the Wistar rats (Table 2). We know that in SHR rats insufficiency of insulin production likewise was not manifested when the glucose level was normal, but showed itself after sugar loading, when glucose tolerance was depressed [12].

Thus, this genetically determined increase in activity of the sympathoadrenal and pituitary-thyroid systems in ISIAH rats leads to lowering of the blood IRI level, activation of lipolysis, and a disturbance of glucose tolerance. According to data in the literature, similar endocrine-metabolic changes also are found in SHR rats. Meanwhile, previous investigations [5-7, 14] indicate

TABLE 2. GTT in ISIAH and Wistar Rats

Glucose (in mmoles/liter blood after sugar loading)	ISIAH	Wistar	p
After 0 min	4,9±0,2	4,4±0,1	
After 30 min	16,5±1,4	15,7±0,8	
After 60 min	17,0±0,9	13,8±0,9	0,05
After 150 min	12,4±1,2	9,0±0,6	0,01

the existence of several significant features distinguishing ISIAH rats from SHR. It can be tentatively suggested that similar changes in metabolism in ISIAH and SHR rats behave as constant companions in the formation of genetically determined hypertensive states. However, the problem of whether these changes are primary with respect to elevation of BP, or whether they are a result of it, still remains unanswered.

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