CENTRAL ADRENERGIC MECHANISMS OF BLOOD PRESSURE REGULATION IN SPONTANEOUSLY HYPERTENSIVE RATS

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As stated previously [2], by selection from inbred Wistar rats a new strain with stress-induced hereditary arterial hypertension (SIHAH), characterized by marked and stable elevation of blood pressure (BP), has been obtained. We know that stress can play an important role in the pathogenesis of essential hypertension [5, 6]. This suggests that the SIHAH strain can provide a more adequate model of this disease than the widely known SHR (Japan) strain of rats, in which the hypertension develops spontaneously [1, 4].

Adrenergic brain structures are known to participate directly in the regulation of BP and of reactivity to stress [1, 5, 8]. Accordingly, in the investigation described below mechanisms of central adrenergic regulation of BP were compared in rats of the SIHAH, SHR, and Wistar strains.

EXPERIMENTAL METHOD

Experiments were carried out on male rats, aged 5 months, belonging to three genetic groups (SIHAH, SHR, and Wistar) anesthetized with pentobarbital (50 mg/kg, intraperitoneally). A steel microcannula was introduced into the lateral ventricle. The ventral artery of the tail was cannulated with a Teflon catheter, connected to an electromanometer (Statham P32). The catheter was filled with heparin solution. While BP was recorded continuously the drugs or physiological saline, in a volume of 10 µl, were injected into the lateral ventricle (Table 1).

EXPERIMENTAL RESULTS

Injection of physiological saline into the lateral ventricle had virtually no effect on the BP level, which remained stable for 1 h (Fig. 1a). Significant differences between the strains were found as regards the level of BP. Consequently, despite the fact that the SIHAH rats were selected for elevation of BP under stress conditions, their resting BP was higher than that of Wistar rats.

Injection of noradrenalin caused significant changes in BP. The direct responses of hypertensive and normotensive rats were opposite in direction: a rise of BP in SIHAH and SHR rats, a fall of BP in Wistar rats (Fig. 1b). Responses of BP to adrenalin in hypertensive and normotensive rats also were qualitatively different: marked depression for 1 h in SIHAH and SHR rats, a significant rise during the first 10 min in Wistar rats (Fig. 1c). Differences in responses to noradrenalin and adrenalin were evidently connected with differences in the spectrum of excited receptors. Further investigation confirmed this view and showed with which type of adrenoreceptors the differences in response of BP in hypertensive rats were due.

Isolated excitation of α_1-receptors with phenylephrine (Fig. 2a), just as of α_2-receptors with clonidine (Fig. 2b), gave qualitatively different responses in hypertensive and normotensive animals. This indicates that in hereditarily determined arterial hypertension relations between α_1- and α_2-adrenoreceptors in the pressor and depressor systems of the brain are changed. Combined stimulation of α_1- and α_2-receptors with naphazoline led to a similar pressor-depressor response in SIHAH and Wistar rats (Fig. 2c).

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TABLE 1. Affinity of Adrenomimetics Used for Different Types of Adrenoreceptors

Drug	Dose, μg	Type of receptors excited by the given substance			
		α_1	α_2	β_1	β_2
Noradrenalin	10	++	+	++	+
Adrenalin	10	+	++	+	++
Phenylephrine	20	++			
Clonidine	14		++		
Naphazoline	14	++	++		
Dobutamine	20			++	
Orciprenaline (Alupent)	20				++
Isoprenaline	10			++	+ +

Legend. +) Lower affinity, ++) higher affinity [3, 7, 9].

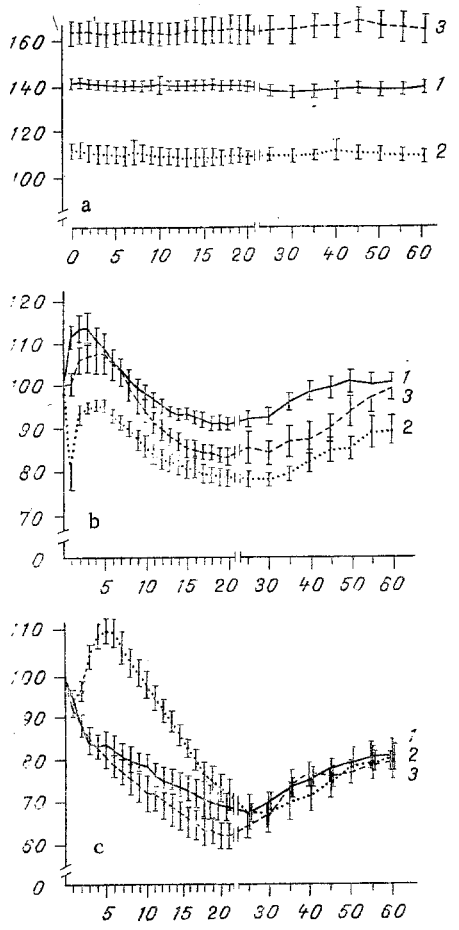

Fig. 1

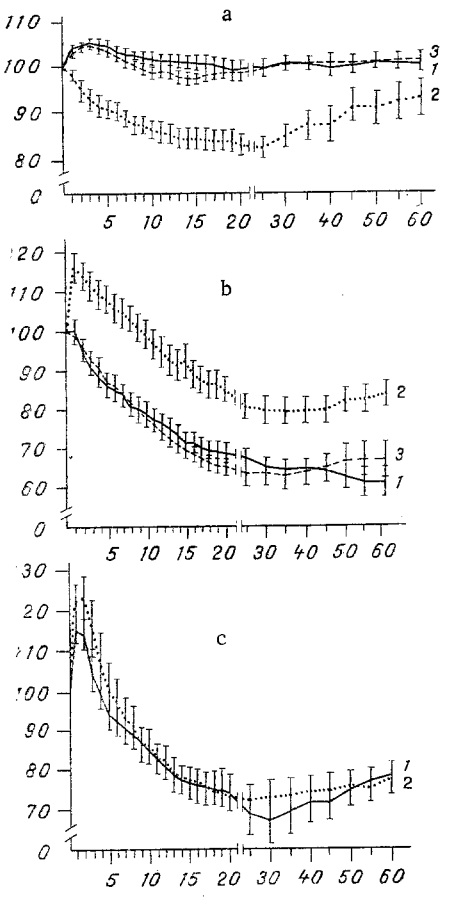

Fig. 2

Fig. 1. Response of BP to injection of physiological saline (a), noradrenalin (b), and adrenalin (c). Abscissa, time (in min); ordinate: a) mm Hg, b and c) % of initial BP level. 1) SIHAH rats, 2) Wistar rats, 3) SHR rats.

Fig. 2. Response of BP (in % of initial level) to injection of phenylephrine (a), clonidine (b), and naphazoline (c). Remainder of legend as to Fig. 1.

It follows from the results of the experiments with naphazoline that the total number of ($\alpha_1 + \alpha_2$) adrenoreceptors is roughly the same in hypertensive and normotensive rats, and it is evident that they are simply redistributed. In all probability the fraction of α_1-receptors is increased in the pressor and reduced in the depressor systems of the brain in rats with

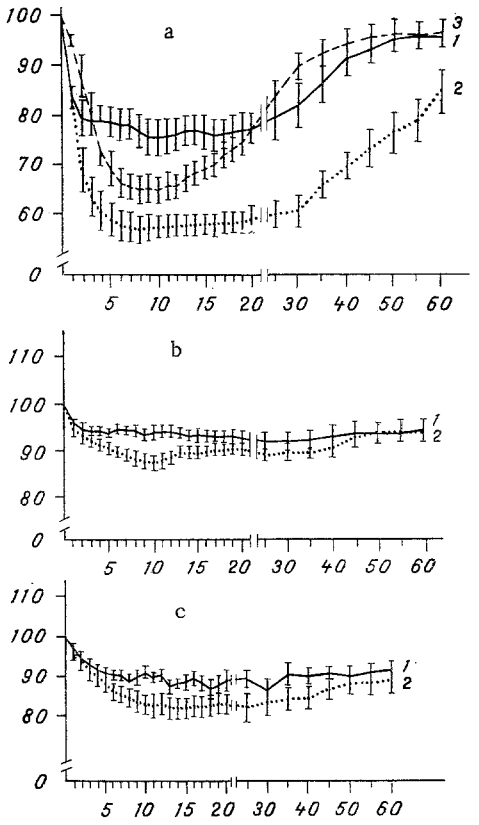

Fig. 3. Response of BP (in % of initial level) to injection of isoprenaline (a), orciprenaline (b), and dobutamine (c). Remainder of legend as to Fig. 1.

arterial hypertension, compared with their proportions in Wistar rats. The fraction of α_2-receptors, on the other hand, is increased in the depressor and reduced in the pressor systems of the brain of hypertensive rats.

Injection of β-adrenomimetics into the lateral ventricle lowered BP in rats of all three genetic groups (Fig. 3). However, the fall of BP in SHR and SIHAH rats after injection of isoprenaline was less marked than in Wistar rats (Fig. 3a). Responses to injection of selective stimulators of β_1 and α_2-receptors (dobutamine and orciprenaline) in SIHAH rats also were depressor and were weaker than in Wistar rats (Fig. 3b, c).

β-Receptors evidently lead mainly into the depressor structures of the brain, for during their stimulation BP fell in all cases. Reduction of the effect of β-receptor stimulation in rats of hypertensive strains may be connected with a reduction in their number in the corresponding brain structures. A decrease in the number of β-receptors has been demonstrated in the frontal cortex of SHR rats [9].

Attention is drawn to similarity of the response of BP in rats of hypertensive strains (SHR and SIHAH) and their difference from responses of BP in the control animals (Wistar rats). Selection for hypertension is evidently accompanied by significant reorganization of the adrenergic structures of the brain involved in BP regulation. This reorganization takes place similarly in SHR and SIHAH rats, despite the fact that the criteria for selection of these lines were different. Consequently, it can be postulated that changes in the adrenergic mechanisms of the brain may lie at the basis of formation of hereditarily determined hypertensive states and may be a key mechanism of their development.

The following conclusions can be drawn from these experiments. In rats of two hypertensive strains (SHR and SIHAH) similarity of responses of BP is found to stimulation of adrenergic brain structures. Meanwhile responses of hypertensive and normotensive rats to this stimulation differ significantly, possibly due to a change in the relative numbers of α_1 and

α_2-adrenoreceptors and to a decrease in the number of β-adrenoreceptors in brain structures involved in BP regulation.

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MYOCARDIAL ENERGY METABOLISM AND ULTRASTRUCTURE IN AUTOIMMUNE CARDIOMYOPATHY

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Autoimmune myocardial damage plays a leading role in the pathogenesis of cardiomyopathies (CMP), and for that reason we also chose autoimmune CMP as an experimental model [7, 8, 10, 12, 14, 15]. In autoimmune CMP primary specific injury to the myocytes is observed, and not until later are the other vascular elements of the heart involved [1, 3, 4]. Autoimmune CMP can accordingly be used as the nearest approximation to the so-called noncoronary heart disease. In previous clinical and experimental investigations the writers found a disturbance of contractility and relaxation of the myocardium — a process based on disturbances of energy metabolism.

The aim of the present investigation was to study the systems of energy metabolism of the heart, the state of respiratory and phosphorylating activity of the mitochondria, early defects in the sarcolemma of the cardiomyocytes, and the resistance of the heart with CMP to ischemic damage. These parameters can be used to judge the mechanisms of disturbance of energy metabolism in CMP.

EXPERIMENTAL METHOD

Rats weighing 220-250 g with autoimmune CMP, induced by subcutaneous injection of heart muscle homogenate with Freund's complete adjuvant twice a month for 2 months [1], were used in the experiments. After the development of the disease the rats were anesthetized with urethane and the heart quickly removed, placed in cold Krebs–Henseleit solution, which quickly stopped it from beating, and then perfused through the aorta by Langendorf's method with Krebs–Henseleit solution, saturated with carbogen and warmed to 37-38°C. The rate of flow was 10 ml/min/g weight of tissue. The systolic, diastolic, and developed pressures were recorded. Perfusion was accompanied by electrical stimulation of the heart (4 Hz, —4 V) in accordance with the following scheme: group 1) 20 min of perfusion; group 2) 20 min of perfusion + 20 min of ischemia; group 3) 20 min of perfusion + 1, 5, and 15 min of ischemia. At

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