sible action not only on the receptor apparatus, but also on the excitable presynaptic membrane, i.e., on the conduction of impulses along fibers. An indication that this is so is given by the change in amplitude of the presynaptic component. A more detailed analysis of the mechanism of action of the drug may be obtained by studying single unit activity.

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HEMODYNAMIC RESPONSE OF NORMOTENSIVE AND HYPERTENSIVE RATS TO PROSTAGLANDINS AND INDOMETHACIN

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High arterial pressure in spontaneously hypertensive rats (SHR; Okamoto-Aoki line) is associated with increased tone of the sympathetic nervous system [6, 8, 9], whereas in rats with renovascular hypertension it is associated with increased activity of the renin-angiotensin system [5]. It has recently been shown [4], however, that intravenous injection of depressor prostaglandins (PG) is accompanied by more severe hypotension in spontaneously hypertensive than in normotensive animals. Meanwhile, in rats with renovascular hypertension, definite inhibition of PG biosynthesis has been found in the kidney and other tissues. These and other investigations suggest that depressor PG play a role in the development of hypertension [1].

The aim of this investigation was to compare the effects of PGI_2, PGE_1, and $PGF_{2\alpha}$ and of indomethacin, which inhibits PG synthesis, on the hemodynamics in rats of the above groups.

EXPERIMENTAL METHOD

Male rats weighing 250-300 g were divided into three groups: noninbred normotensive rats — NR (control), SHR (Okamoto-Aoki line), and rats with renovascular hypertension (RVHR). A coil with internal diameter of 0.35 mm was wound around the left renal artery of the last group 28-30 days before the experiment, and their right kidney was completely removed.

The rats were anesthetized with urethane (600 mg/kg) and chloralose (40 mg/kg). The arterial pressure (BP) was measured in the carotid artery by an EMT-34 electromanometer. Momentary values of the heart rate (HR) were determined with a digital pulsotachometer, triggered

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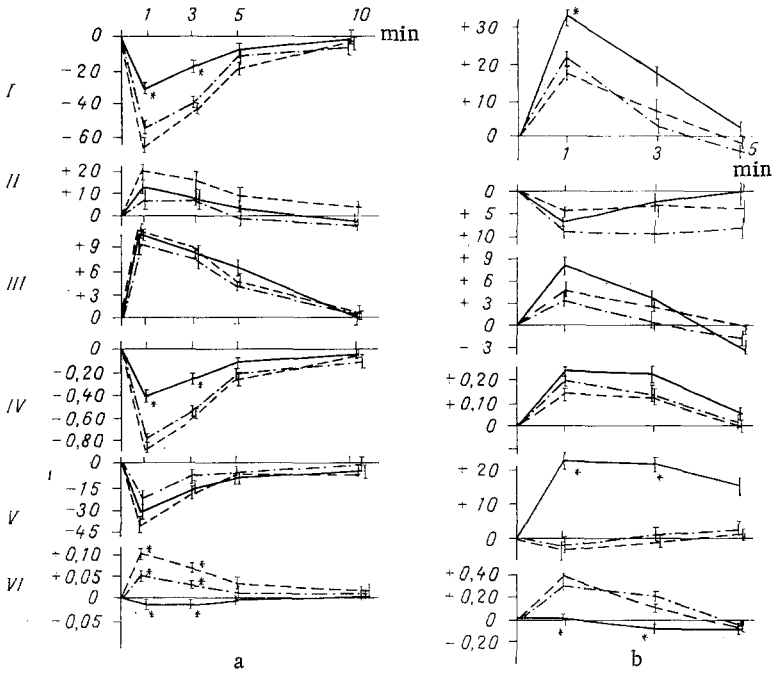

Fig. 1. Effect of PGI_2 (a) and $PGF_{2\alpha}$ (b) on hemodynamics of NR (continuous line), RVHR (broken line), and SHR (line of dots and dashes). Abscissa, time (in min); ordinate, changes in test parameters in absolute values. I) BP (in mm Hg), II) HR (beats/min); III) CO (in ml/min), IV) TPR (in mm Hg/ml/min), V) pressor response (in mm Hg), VI) baroreflex response (in msec/mm Hg). *P < 0.05 relative to other groups.

TABLE 1. Initial Parameters of Hemodynamics in NR, RVHR, and SHR after Injection of PGI_2 (I), PGE_1 (II), $PGF_{2\alpha}$ (III), and Indomethacin (IV)

Substances	Group of animals	No. of animals	BP, mm Hg	HR, beats/min	CO, ml/min	TPR, mm Hg/min	Pressor response, mm Hg	Baroreflex response, msec/mm Hg
I	NR	6	—91,2±3,55	415±7,26	72,7±2,06	1,23±0,09	47,1±3,01	0,302±0,006
	RVHR	6	—152,4±4,14	411±4,92	67,0±2,43	2,26±0,10	75,9±2,77	0,048±0,002
	SHR	7	—145,7±3,80	408±5,11	65,3±3,01	2,23±0,11	71,2±3,52	0,050±0,002
II	NR	7	—99,1±4,31	420±8,23	68,4±2,49	1,45±0,11	54,5±2,11	0,255±0,004
	RVHR	6	—145,0±6,82	430±5,94	66,9±3,20	2,16±0,17	73,4±3,80	0,050±0,001
	SHR	6	—146,8±5,76	411±7,64	65,1±2,43	2,24±0,13	67,7±1,12	0,065±0,002
III	NR	7	—97,5±2,67	431±5,19	64,0±1,84	1,51±0,09	48,9±3,06	0,296±0,005
	RVHR	6	—140,9±3,24	427±7,24	62,4±2,11	2,32±0,11	75,2±2,91	0,040±0,002
	SHR	7	—141,3±4,38	415±6,81	63,9±1,65	2,27±0,09	73,4±3,10	0,053±0,003
IV	NR	8	—86,1±3,06	398±5,87	61,5±3,01	1,39±0,14	53,1±2,11	0,272±0,004
	RVHR	7	—159,2±5,49	404±3,99	56,1±2,42	2,83±0,21	74,1±4,08	0,036±0,002
	SHR	6	—143,0±5,18	387±6,02	57,4±2,75	2,69±0,20	71,5±2,90	0,052±0,003

by the pulse wave of BP. Parameters of the hemodynamics were recorded in analog form on a Mingograph-81, and digital values of BP and HR were recorded on a digital printer. The cardiac output was measured by tetrapolar rheography on the RPG2-02 instrument [2]. The cardiac component of the baroreceptor reflex was induced by brief (10 sec) compression of the abdominal aorta in the region where it emerges from beneath the diaphragm. The pressor response was measured as the increase in systolic pressure in mm Hg, and the sensitivity of the baroreflex as the change in intersystolic interval in response to elevation of BP in msec/mm Hg.

Doses of PG (from Upjohn, USA) were chosen so that, when injected intravenously into NR, the value of the hypotensive and hypertensive effect did not exceed 25-30%. Indomethacin was injected in a dose of 10 mg/kg (according to data in the literature [7], 5 min after injection of this dose PG biosynthesis in the animal's tissues ceases completely). All the substances for testing were injected into the external jugular vein in a volume of 0.2 ml in the course

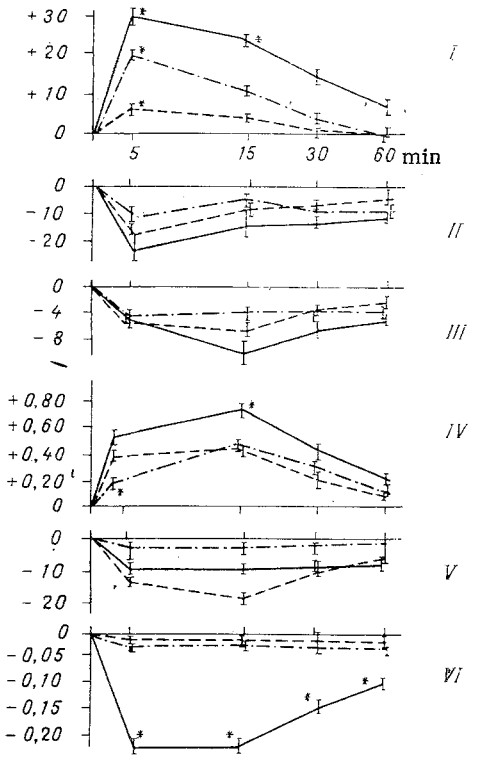

Fig. 2. Effect of indomethacin on hemodynamics in NR (continuous line), RVHR (broken line), and SHR (line of dots and dashes). Legend as to Fig. 1.

of 60 sec. Statistical analysis was by the method of analysis of variance and by Student's t test.

EXPERIMENTAL RESULTS

Intravenous injection of PGI_2 in a dose of 0.15 μg/kg caused the systemic BP to fall in rats of all three groups (Fig. 1). The maximal fall in BP of NR was by 30.2 ± 2.41 mm Hg and of RVHR and SHR by 66.7 ± 3.75 and 56.4 ± 2.08 mm Hg, respectively. Differences in the degree of hypotension developing after PGI_2 in NR compared with in RVHR and SHR were statistically significant ($P < 0.01$). HR and the cardiac output (CO) were increased about equally in all the animals. The hypotensive effect of PGI_2 is due to peripheral vasodilatation, as shown by a distinct fall in the total peripheral resistance (TPR). It was reduced by a greater degree in RVHR and SHR (by 1.16 ± 0.07 and 1.02 ± 0.08 mm Hg/ml/min, respectively) than in NR (by 0.53 ± 0.05 mm Hg/ml/min). A statistically significant difference ($P < 0.05$) also was found in the decrease in TPR between the control and hypertensive animals. The pressor response (to compression of the abdominal aorta) in SHR after injection of PGI_2 was reduced by 36.6% compared with initially, whereas in NR and RVHR it was reduced by 68.4 and 57.3%, respectively. The sensitivity of the baroreceptor system in NR showed a tendency to fall after administration of PGI_2. In SHR and RVHR, however, it increased significantly ($P < 0.01$) by 104 and 212%, respectively.

PGE_1 (5 μg/kg) led to mainly similar changes. However, the intensity of these changes was a little less than after administration of PGI_2. The only difference was an increase in sensitivity of the baroreflex system not only in SHR (by 34%) and RVHR (by 40%), but also in NR (by 17%).

Although the direction of the changes in the hemodynamic parameters was almost the same after injection of the two depressor PG, the dose of PGE_1 was 33 times greater than that of PGI_2. This indicates a more important and specific role for PGI_2 in regulation of the hemodynamics. Data on the effect of PGI_2 and PGE_1 on sensitivity of the baroreflex system deserve particular attention. The role of the baroreceptor system is known to be to lower BP on account of slowing of HR and a decrease in CO (the cardiac component) and dilatation of some vascular

regions (the vascular component) in response to hypertensive reactions. However, the mechanism by which activity of the baroreflex system increases against the background of a hypotensive state and a decrease in pressor reactions evoked by PGI_2 and PGE_1, especially in hypertensive rats, is not yet clear. The possibility cannot be ruled out that the action of PGE_1 and PGI_2 on the baroreflex is mediated through their effect on unmyelinated nerve endings of the carotid sinus or through chemoreceptors of the carotid body. The absence of an increase in the baroreflex in NR after injection of PGI_2 can evidently be explained on the grounds that in animals of this group, because of the considerable hypotension and inhibition of pressor responses, the activity of the baroreceptor system is definitely reduced and the true effect of PGI_2 is not revealed.

$PGF_{2\alpha}$ (10 μg/kg) caused hypertension in NR (Fig. 1), which was significantly higher in them than in RVHR and SHR ($P < 0.05$). The increase in CO and TPR evidently also was responsible for systemic hypertension due to the action of $PGF_{2\alpha}$ in rats of all three groups. The sensitivity of the baroreflex system was increased only in RVHR and SHR, by 100 and 64%, respectively. However, this increase as a rule was accompanied by an inappropriate bradycardia, combined with arrhythmia, even after the end of occlusion of the abdominal aorta, and this evidently reflects excessively high tone of the vagus nerve. Differences in the degree of the hypertensive effect in normotensive and hypertensive rats may be attributable to the fact that in the latter biosynthesis of PG of the S group was increased in the vascular tissue and their blood concentrations were higher than in intact rats [1]. These circumstances evidently also determined the relatively high tolerance of the vascular smooth muscles of RVHR and SHR to exogenous $PGF_{2\alpha}$.

Indomethacin, in a dose of 10 mg/kg increased BP in all animals (Fig. 2). The degree of hypertension in rats of the three groups differed statistically: in NR, BP rose by 33%, in SHR by 16%, but in RVHR by only 5%. HR and CO decreased under these circumstances, whereas TPR increased in all the animals. The cardiac component of the baroreflex was considerably reduced, moreover, in NR (from 0.272 to 0.064 msec/mm Hg, i.e., by 208%). The level to which sensitivity of the baroreflex fell in NR was close to its initial level in hypertensive rats. In SHR and RVHR the baroreflex had a tendency to fall after injection of indomethacin. The mechanism of indomethacin hypertension is connected with inhibition of biosynthesis of depressor PG. The results of this series of experiments indicate inhibition of depressor PG in hypertensive rats. It can be postulated that in RVHR biosynthesis of depressor PG is depressed more severely than in SHR. This is also shown by the fact that the hemodynamic response to PGI_2 and PGE_1 was more marked in RVHR. The fall in the sensitivity of the baroreceptor system in NR (to the level characteristic of hypertensive rats) after injection of indomethacin points unquestionably to the important role of PG in modulation of the baroreflex system.

It can be concluded from these results that during stabilization and progression of the hypertensive state (in particular, in RVHR and SHR) not only does the activity of the pressor systems increase, but synthesis of depressor PG also is inhibited.

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