COMPARISON OF EFFECTS OF BRADYKININ AND ANGIOTENSIN II ON THE HEMODYNAMICS IN NORMOTENSIVE, SPONTANEOUSLY HYPERTENSIVE, AND RENOVASCULAR HYPERTENSIVE RATS

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UDC 616.127-005.6-085.204

KEY WORDS: bradykinin; angiotensin II; hemodynamics of rats.

The effect of bradykinin and angiotensin II on hemodynamics has been studied in fair detail [5, 6, 14, 15]. However, most of these investigations have been conducted on normotensive laboratory animals. Yet it has been shown that angiotensin and bradykinin, which have a directly opposite action on vascular tone and blood pressure (BP), participate in the pathogenesis of hypertension [9-11]. Accordingly a comparison of the effect of bradykinin and angiotensin II on the systemic hemodynamics and the pressor and baroreflex (cardiac component) response of normotensive rats (NR) and of animals with two different models of hypertension — spontaneously hypertensive rats (SHR) and rats with renovascular hypertension (RHR) — is particularly interesting.

EXPERIMENTAL METHOD

Experiments were carried out on male rats weighing 250-300 g divided into three groups: 1) control, noninbred NR; 2) SHR (Okamoto—Aoki line); 3) noninbred RHR, undergoing operation 28-30 days before the experiment (a coil with internal diameter of 0.35 mm was wound around the left renal artery, the right kidney was completely removed).

All the rats were anesthetized with urethane (600 mg/kg) and chloralose (40 mg/kg). BP was measured with an electromanometer by means of a polyethylene catheter introduced into the left carotid artery, the momentary heart rate was determined from the BP pulse wave, and these were recorded on a Mingograph-81 polygraph and stimultaneously led out to a digital printer through transforming amplifiers. The cardiac output was determined by means of an RPG2-2 tetrapolar rheograph [4, 13]. In a preliminary series of experiments on rats the stroke and minute volumes of the heart were determined simultaneously by tetrapolar rheography and by means of an electromagnetic flowmeter. The results demonstrated high correlation between the two methods ($r = 0.908$).

The following equation was used for the calculations:

$$\Delta V = K \cdot p \frac{L^2}{Z^2} \cdot Ad \cdot T_{ej},$$

where ΔV is the stroke volume of the heart (in cm^3), K a coefficient equal to 0.7, p the specific resistance of rats' blood (165 Ω/cm), L the distance between the thoracic electrodes (3 cm), Z the basal interelectrode impedance, determined on the scale of the instrument (in Ω), Ad the amplitude of the differential rheogram (in Ω/sec), T_{ej} the ejection time of blood by the heart, determined from the BP curve.

Values of the pressor response, reactive hyperemia, and the baroreceptor reflex (baroreflex) were determined by compressing the abdominal aorta (for 10 sec) where it emerges from beneath the diaphragm. The pressor response was measured by the increase in systolic pressure, reactive hyperemia by the fall in diastolic pressure, and the baroreflex by the decrease in heart rate in response to compression of the aorta.

Doses of bradykinin triacetate (from Reanal, Hungary) and angiotensin II (synthesized in the All-Union Cardiologic Scientific Center by Dr. Chem. Sci. M. I. Titov), were chosen so that, after intravenous injection into the external jugular vein in the course of 40-60 sec (the drugs were dissolved in 0.9% isotonic sodium chloride solution and injected in a volume

Laboratory of Pharmacology of Emotional Stress, Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 93, No. 3, pp. 57-61, March, 1982. Original article submitted November 13, 1981.

 0007-4888/82/9303-0296$07.50

TABLE 1. Effect of Bradykinin (10 μg/kg, intravenously) on Hemodynamics in NR, SHR, and RHR (seven rats in each group)

Time after injection, min	Group of animals	BP, mm Hg	PR, mm Hg	RH, mm Hg	HR, beats/min	BR	SV, ml	CO, ml/min	TPR, mm Hg/ml/min
Background	NR	98±3,88	47±3,53	39±3,71	403±8,30	36,5±2,82	0,149±0,007	60,0±1,29	1,66±0,06
	RHR	145±6,36‡	70±7,07‡	55±3,53‡	425±5,65	8,8±0,80‡	0,140±0,005	59,4±1,97	2,44±0,04*
	SHR	149±7,42‡	74±3,35‡	55±3,18‡	412±10,6	8,4±0,88‡	0,142±0,004	58,5±2,12	2,54±0,07*
1	NR	—24±1,06	+7±1,18	—4±0,76	—1±0,86	—4±1,82	+0,009±0,003	+3,5±0,31	—0,50±0,05
	RHR	—56±2,80‡	+6±0,65	—12±2,74†	—1±0,94	+19,3±2,06‡	+0,005±0,001	+1,9±0,04	—1,02±0,03*
	SHR	—53±1,94‡	+9±1,07	+2±0,32†	+5±2,29*	+14,8±2,12‡	+0,005±0,002	+2,6±0,45	—1,06±0,04*
3	NR	—7±1,06	+3±0,76	+4±1,59	+3±1,94	+0,4±0,29	+0,004±0,002	+2,0±0,27	—0,19±0,04
	RHR	—13±4,66	+5±0,94	—3±2,47	—1±0,87	+16,2±2,47‡	+0,001±0,0003	+0,3±0,29	—0,26±0,08
	SHR	—15±2,88*	—1±0,28	—1±0,70	+2±0,53	+3,7±1,59	0±0,0008	+0,3±0,04	—0,49±0,07
5	NR	0±0,23	+2±0,88	0±0,17	+2±2,29	—2,0±0,89	+0,001±0,0005	+0,6±0,06	—0,05±0,05
	RHR	—6±0,18	+5±0,29	+1±2,65	—3±1,21	+9,5±1,94†	+0,002±0,001	+0,4±0,09	—0,3±0,09
	SHR	—10±2,12	0±0,60	—3±1,41	—5±1,94	+4,0±2,74*	—0,001±0,005	—0,9±0,08	—0,28±0,08

Legend. Here and in Table 2: PR) pressor response, RH) reactive hyperemia, HR) heart rate, BR) baroreflex, SV) stroke volume of the heart, CO) cardiac output, TPR) total peripheral resistance; *) differences between control and experimental values significant at the $P < 0.05$ level, †) at $P < 0.02$, ‡) at $P < 0.01$.

TABLE 2. Effect of Angiotensin II (0.5 μg/kg, intravenously) on Hemodynamics in NR, SHR, and RHR (seven rats in each group)

Time after injection, min	Group of animals	BP, mm Hg	PR, mm Hg	RH, mm Hg	HR, beats/min	BR	SV, ml	CO, ml/min	TPR, mm Hg/ml/min
Background	NR	100±3,88	50±3,53	37±2,65	426±11,13	39,5±1,94	0,154±0,008	65,6±2,82	1,51±0,02
	RHR	137±2,65‡	69±3,46‡	54±1,76	415±20,15	10,0±1,59‡	0,148±0,006	61,5±2,47	2,23±0,03*
	SHR	143±2,29‡	70±2,65‡	49±3,53	402±11,31	9,0±1,06‡	0,150±0,009	60,3±1,59	2,37±0,04*
1	NR	+32±2,65	+20±4,41	+15±3,35	—12±3,72	+11,6±2,64	—0,013±0,007	—7,3±3,24	+0,74±0,44
	RHR	+27±4,06	+15±3,53	+10±2,65	—10±4,41	+2,0±1,06‡	—0,002±0,003	—2,3±0,53	+0,55±0,45
	SHR	+31±2,47	+17±4,24	+5±1,06	—7±1,59	+1,3±1,10‡	—0,003±0,002	—2,2±0,71	+0,63±0,28
3	NR	+15±3,53	+13±3,51	+3±1,76	—3±2,65	+4,0±2,83	—0,003±0,0031	—1,8±0,31	+0,28±0,17
	RHR	+9±0,82	+9±2,41	+3±2,82	—5±2,30	+1,3±2,12	—0,003±0,002	—1,9±0,61	+0,16±0,21
	SHR	+10±1,06	+15±3,18	+4±0,88	—2±1,23	—2,1±1,23*	—0,001±0,0004	—0,7±0,20	+0,18±0,19
5	NR	—2±0,71	+5±2,65	+3±1,76	+5±1,74	+3±1,81	—0,002±0,001	—0,2±0,24	—0,07±0,31
	RHR	0±0,06	+2±1,76	+4±1,04	—5±3,18	+0,1±0,04	—0,002±0,001	—1,6±0,26	+0,06±0,07
	SHR	+1±0,23	+8±2,47	+6±1,06	—5±1,23	0±1,41	—0,001±0,0004	—1,2±0,31	+0,09±0,11

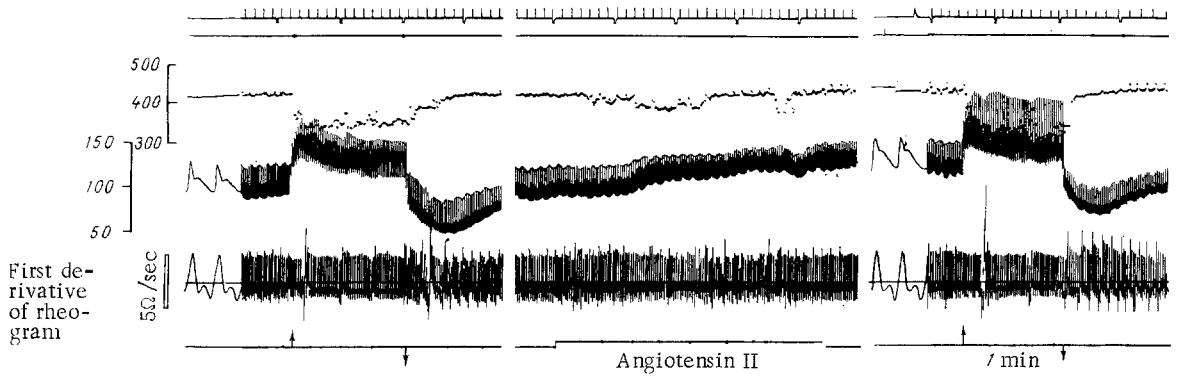

Fig. 1. Effect of angiotensin II (0.5 μg/kg, intravenously) on hemodynamics in normotensive rats. From top to bottom: heart rate (beats/min), BP (in mm Hg), differential rheogram. Arrows indicate beginning and end of compression of abdominal aorta.

of 0.2 ml) into NR the degree of hypertension or hypotension did not exceed 25-30%. In the control injection of 0.2 ml of 0.9% isotonic sodium chloride solution caused no change in the hemodynamics of rats of the three groups. The experimental results were subjected to statistical analysis of variants and Student's t test (Fig. 1).

EXPERIMENTAL RESULTS

Intravenous injection of bradykinin in a dose of 10 μg/kg was accompanied by a fall in systemic BP in rats of all three groups (Table 1). Hypotension was due to peripheral vasodilation, as shown by the clear decrease in total peripheral resistance. Although shifts in the hemodynamics were qualitatively in the same direction, statistically significant differences were observed between the control and the two experimental groups in the fall of BP and total peripheral resistance in RHR and SHR was about twice that observed in NR. Against the background of the action of bradykinin there was a tendency for the pressor response and the stroke and minute volumes of the heart to increase. The data for the cardiac component of the baroreflex to compression of the aorta deserve particular attention. For instance, the initial values in SHR and RHR, compared with those in NR, showed definite depression (by 76%) of the baroreflex to brief compression of the aorta. Injection of bradykinin was followed by a marked increase in the cardiac component of the baroreflex system by 133% in SHR and by 173% in RHR, whereas in NR it was reduced by 6% (at the $P < 0.01$ level between the control and groups 2 and 3).

The lungs are known to contain the powerful enzyme kininase II, whose function is evidently disturbed in hypertensive states [3]. It was therefore important to compare the effect of the same dose of bradykinin when injected into the aorta. Hypotension in response to injection of bradykinin into the aorta was more marked than after intravenous injection. For instance, BP in NR was lowered by 49 ± 5.74 mm Hg, in SHR by 75 ± 6.24 mm Hg, and in RHR by 78 ± 5,68 mm Hg (at the $P < 0.02$ level between the control and groups 2 and 3).

Intravenous injection of angiotensin II in a dose of 0.5 μg/kg increased BP in rats of all three groups, due to an increase in the total peripheral resistance. The heart rate, stroke volume, and cardiac output showed no significant change but had a tendency to decline. An increase in the pressor response and potentiation of reactive hyperemia were noted. The baroreflex to compression of the aorta increased statistically significantly only in NR. The results thus indicate that despite differences in the pathogenesis of development of hypertension in SHR and RHR, the general picture of the hemodynamics and its response to injection of both bradykinin and angiotensin II were basically the same. Increased sensitivity of the cardiovascular system of the hypertensive animals to bradykinin was not due to any change in the kininase activity of the lungs, for both intra-aortic and intravenous injection of bradykinin was followed by more marked hypotension in the hypertensive rats than in NR. This can evidently be attributed to the fact that the kinin system, one of the depressor systems participating in the regulation of vascular tone, was depressed in the hypertensive animals [2]. It can accordingly be postulated that the degree of inhibition of the kinin system was about the same in the two types of hypertensive rats.

The baroreflex system is known to play a direct part in the regulation of the systemic BP and disturbance of its sensitivity (suppression or depression) is one cause of the onset and development of hypertension [7]. The results of the present experiments show that bradykinin significantly increases the sensitivity of the cardiac component of the baroreflex system in SHR and RHR, whereas no significant changes were observed in the normotensive animals. This suggests a role for bradykinin in the regulation or modulation of the baroreflex system. Consequently, suppression of the kinin system in the course of development of hypertension is one of the many causes of disturbance not only of vascular tone [5], but also the sensitivity of the baroreflex system.

The pressor response to intravenous injection of angiotensin II is known to be largely connected with its direct vasoconstrictor action, on account of contraction of the smooth muscles of the vessel wall, and to a lesser degree with its effect on the central and peripheral sympathetic nervous system [1]. It follows from the results described above that angiotensin II caused an equal increase in BP in the rats of all three groups. However, a stronger hypertensive response was described in [8] in unanesthetized SHR than in normotensive (Wistar–Kyoto line) rats to intravenous injection of angiotensin II. This difference in the experimental results was evidently attributable mainly to the fact that the present experiments were conducted on anesthetized animals.

The more marked increase in the baroreflex response of NR than of SHR and RHR to intravenous injection of angiotensin II can evidently be explained on the grounds that the baroreflex to a rapid increase in BP is depressed in hypertensive rats [7].

LITERATURE CITED

1. A. M. Vikhert and A. F. Ushkalov, Kardiologiya, No. 3, 143 (1971).
2. O. A. Gomazkov, Kardiologiya, No. 2, 141 (1969).
3. O. A. Gomazkov, M. V. Shimkovich, and A. M. Chernukh, Kardiologiya, No. 1, 103 (1977).
4. Yu. T. Pushkar', V. M. Bol'shov, N. A. Elizarova, et al., Kardiologiya, No. 7, 85 (1977).
5. Yu. A. Serebrovskaya, Kardiologiya, No. 12, 114 (1974).
6. A. M. Chernukh, P. Oeme, and O. A. Gomazkov, Byull. Eksp. Biol. Med., No. 9, 259 (1980).
7. R. D. Buang, A. E. Eferakeya, and D. S. Langdon, Am. J. Physiol., 226, 217 (1975).
8. W. E. Hoffman, M. J. Phillips, and P. G. Schmid, Am. J. Physiol., 232, H426 (1977).
9. B. M. Goldstein, D. C. Neitz, et al., Eur. J. Pharmacol., 26, 212 (1974).
10. J. H. Laragh, L. Baer, et al., Am. J. Med., 52, 633 (1972).
11. J. C. McGiff and R. G. Geller, in: Arterial Hypertension [Russian translation], Moscow (1980), pp. 70–78.
12. J. Nyboer, T. R. Weng, and G. Polgar, in: The Bioelectrical Impedance, Lyon (1978), pp. 216–230.
13. G. Tallarido, F. Baldoni, et al., J. Pharmacol. Exp. Ther., 208, 319 (1979).
14. H. Vierhapper and W. Waldhausl, Acta Endocrinol. (Copenhagen), 91, 352 (1979).