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Sodium, angiotensin II, blood pressure, and cardiac hypertrophy

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Sodium, angiotensin II, blood pressure, and cardiac hypertrophy. Blood pressure (BP) in rats was elevated intermittently by i.p. injections of angiotensin II (Ang II; 200 μg/kg), and the effect on cardiac index was determined. The BP response was assessed in selected rats by telemetry. Elevation of BP between 8:00 and 12:00 produced cardiac enlargement similar to that produced by continuous Ang II infusion, and the response correlated better with the acute BP elevation than with 24-hour cardiac work. A high-sodium diet also increased left-ventricular hypertrophy (LVH) without a major effect on BP. The addition of Ang II intensified this response. A low-sodium diet had no significant effect on BP or on cardiac size, but prevented the cardiac hypertrophy produced by Ang II without altering the BP response. These results suggest that acute BP elevation, probably working through increased wall tension, is a more potent stimulus for cardiac hypertrophy than 24-hour workload. The sodium intake of the rat plays an important role influencing the cardiac but not the BP response to Ang II. These results infer that it is important to avoid episodes of acute BP elevation.

Cardiac hypertrophy is an important and independent predictor of cardiac morbidity and mortality [1]. However, the factors responsible for its production are poorly understood. There is a correlation with total cardiac work, but this explains 40% or less of the causation [2, 3]. Humoral factors [angiotensin II (Ang II), growth hormone, insulin-like growth factor) clearly influence the response. Whether these factors produce hypertrophy *in vivo* independent of a rise in blood pressure (BP) is unclear. BP does have an important influence on the size of the left ventricle, but the stimulus that activates the cascade of events leading to left-ventricular hypertrophy (LVH) is not known. Cardiac wall stress, which increases with acute elevations in BP, is believed to be a more important signal than 24-hour cardiac workload [4, 5]. This study was undertaken in rats to determine whether intermittent elevation of BP produces cardiac hypertrophy. The BP response to the procedures used was assessed by telemetry (Dataquest; Data Sciences, MN, USA). A preliminary report of some of these experiments has been presented previously [5].

Key words: renin, left ventricular hypertrophy, dietary sodium, cardiac index.

METHODS

Three different protocols were followed. Wistar rats weighing about 200 g were given i.p. injections of Ang II (200 μg/kg) at 8:00, 9:00, 10:00, and 11:00 a.m. for two weeks. A control group was injected at the same time with normal saline. A third group was given a continuous s.c. infusion of Ang II for 14 days by Alzet osmotic minipump to give 200 ng/kg/min. The BP response to these procedures was assessed by the effect achieved in similarly sized rats with a telemeter inserted into the abdominal aorta two weeks prior to the experiment. There was one telemeter rat for each four experimental rats. Data were compiled continuously and collected for analysis over a 30-second period every 10 minutes. At the end of two weeks, the rats were anesthetized; the heart was removed, and the atria was dissected from the ventricles. The hearts were weighed, and a cardiac index was determined from this value and the weight of the rat. From the telemeter system, mean and peak BP could be determined.

The second and third protocols were undertaken in Sprague Dawley rats weighing 300 g. Rats received injections of saline or saline plus Ang II four times daily as in the protocol mentioned earlier here, but the experiment continued for four weeks. In the second protocol, there were four different groups: normal-sodium diet (1% NaCl), normal-sodium diet plus Ang II, high-sodium diet (4% NaCl), and high-sodium diet plus Ang II. In the third protocol, the diets were normal-sodium diet, normal-sodium diet plus Ang II, low-sodium diet (0.4% NaCl), and low-sodium diet plus Ang II. Similar data were collected after four weeks as in the first experiment.

All invasive procedures were performed with the animals under fluothane anesthesia. The data were analyzed by unpaired *t*-tests with the Bonferoni correction and by analysis of variance.

RESULTS AND DISCUSSION

Ang II (200 μg/kg) i.p. increased BP by approximately 60/40 mm Hg for 20 minutes, with a mean rise over the one-hour interval of 45/25 mm Hg ($P < 0.0001$). The mean BP achieved in the four hours from 8:00 to 12:00 in the Wistar rats was 164/111 mm Hg compared with 111/70 in the saline-injected controls (Table 1). The 24-hour mean

Table 1. Blood pressure (BP) by telemetry in the various groups (sys systolic BP, diast diastolic BP, *N* number of rats)

		Mean BP *mm Hg*			
		24-hr Mean		08:00-12:00 Mean	
	N	Sys	Diast	Sys	Diast
Wistar rats					
Control	2	114	76	111	80
Intermittent Ang II	2	122[a]	82[a]	164[a]	111[a]
Continuous Ang II	3	166[a]	113[a]	165[a]	106[a]
Sprague-Dawley rats					
Control	4	105	71	100	68
Ang II	4	112	74[a]	153	102[a]
High sodium	2	108	74	105	72
High sodium + Ang II	2	120	76[a]	164	108[a]
Low sodium	2	102	70	100	63
Low sodium + Ang II	2	112	75[a]	150	101[a]

No statistical analysis was made, but in the groups marked [a] there was no overlap with contol values.

Table 2. Body and cardiac weights and cardiac index at the end of the experiment (means ± SEM)

	N	Body weight *g*	Cardiac weight *mg*	Cardiac index *mg/g*
Wistar rats				
Control	10	306 ± 9	698 ± 14	2.28 ± 0.06
Intermittent Ang II	10	292 ± 10	752 ± 16	2.58 ± 0.05[a]
Continuous Ang II	7	297 ± 12	772 ± 14[a]	2.60 ± 0.05[a]
Sprague-Dawley rats				
Control	16	506 ± 12	1105 ± 21	2.18 ± 0.02
Ang II	16	478 ± 12	1180 ± 17	2.47 ± 0.02[a]
NaCl 4%	8	523 ± 11	1246 ± 17[a]	2.37 ± 0.04[a]
NaCl 4% + Ang II	8	445 ± 6[a]	1127 ± 19	2.57 ± 0.03[ab]
NaCl 0.4%	8	481 ± 12	1034 ± 32	2.15 ± 0.03
NaCl 0.4% + Ang II	8	470 ± 15	1048 ± 33	2.33 ± 0.03

[a] $P < 0.01$; [b] $P = 0.06$ vs. NaCl 4%

BP was 122/82 compared with 114/76 in the saline-injected controls (Table 1). The mean 24-hour BP in the rats continuously infused with Ang II in the second week was 164/113 mm Hg, which was higher than the value in rats with intermittent injections of Ang II. The BP from 8:00 to 12:00 did not differ between the two Ang II groups. The response to the intermittent injections of Ang II was similar at the start and end of the experiment [5]. Similar changes in BP were measured in the Sprague Dawley rats, but overall, the BP levels were lower.

There were some differences in the growth of the rats. All groups in each protocol at the start of the experiment had similar weights. Rats given Ang II, whether by intermittent or continuous infusion, tended to weigh less at the end of the study than controls. In the Sprague Dawley rats, the weights were similar when allocated to the various groups. Again, rats given Ang II intermittently tended to weigh less, whether on a high, low, or normal sodium intake.

Cardiac mass was increased in some of the Ang II-treated groups but did not always differ from the control, possibly because of the lesser body weight gain. The cardiac index was increased significantly (Table 2) in the rats on normal diet plus Ang II. The increase with intermittent Ang II was similar to that seen with continuous Ang II infusion. A high-sodium intake increased cardiac index compared with the normal diet, but Ang II did not cause a further significant increase in cardiac index, although the cardiac index in Sprague Dawley rats on a high-salt intake plus Ang II was the largest value recorded. A low-sodium intake had no significant effect on cardiac weight or index. Ang II had no significant effect on cardiac weight or index in rats on a low-sodium diet (Table 2).

To summarize the findings, intermittent elevation of BP between 8:00 and 12:00, which is the sleep time of these rats, caused a significant increase in cardiac index. This increase was similar to that obtained by continuous infusion of Ang II, which caused a much greater increase in mean 24-hour BP and hence cardiac work. The increase in cardiac index with continuous infusion was similar to that seen in other studies [6, 7]. The similarity of the cardiac response with continuous and intermittent BP elevation suggests that acute BP elevation probably mediated by increased wall stress is a more important determinant of LVH than total workload. Furthermore, elevation of BP over a relatively short time interval (four hours) appears to activate the processes that lead to LVH. This may be attributable to the trophic effect of Ang II [6, 7] rather than BP elevation, and this group of experiments does not allow this to be clearly resolved.

Altering the NaCl content of the diet had significant effects on cardiac size. A high-sodium diet increased cardiac mass and index [8]. The addition of Ang II in this group had a significant effect reducing the growth of the animal but did not cause a further significant increase in cardiac index ($P = 0.06$). This may have been due to lack of power to detect an additional cardiac size change. A reduced sodium intake had no significant effect on cardiac mass or index but prevented the increase in cardiac index seen in other circumstances with Ang II. These interactions did not appear to be mediated by alterations in the BP response as these were similar (Table 1). However, although the response in a single rat was recorded with precision, relatively few rats had BP measured, and small differences in response are possible.

This study indicates that when BP is elevated during the sleeping hours, LVH results despite BP being normal for 20 of the 24 hours. This suggests that acute wall stress may be the signal that activates the cascade of events leading to LVH [5].

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