 0030-0950/82/0004-0177 $2.00/0

ROLE OF ANGIOTENSIN II IN HEMORRHAGIC HYPOTENSION IN THE RAT[1]

R. W. GOTSHALL and R. D. MONTGOMERY, Department of Physiology, Wright State University, College of Science and Engineering, Dayton, OH 45435

ABSTRACT. The purpose of this study was to evaluate the role of the renin-angiotensin system in the acute regulation of blood pressure following hemorrhage in the anesthetized rat. Eleven Sprague-Dawley rats were anesthetized with sodium pentobarbital. After control blood pressure recordings from the femoral artery were made, the rats were hemorrhaged 6 ml/kg body weight. Forty minutes after hemorrhage, the Angiotensin II antagonist, 1-SAR-8-ALA-Angiotensin II (saralasin), was infused (10 μg/min/kg) for 35 min. Hemorrhage resulted in a 53% decrease in blood pressure which recovered to 82% of the control blood pressure in 40 minutes. Infusion of saralasin resulted in a 24% decrease ($p < 0.01$) in blood pressure within 15 min. Recovery from saralasin infusion occurred within 10 min as blood pressure increased back to control values. A second group of 5 rats was not hemorrhaged but was infused with saralasin. There were no significant changes in blood pressure; although, a tendency to decrease was noted reflecting the increase in plasma renin activity which occurs with anesthesia. It was concluded that the renin-angiotensin system can respond rapidly to a hypotensive event and aid in the restoration of blood pressure within minutes.

OHIO J. SCI. 82(4): 177, 1982

INTRODUCTION

Much attention has been focused on the role of the sympathetic nervous system and the carotid baroreceptors in maintaining arterial blood pressure during hemorrhage and other low pressure states (Chien 1967). Although the role of the kidney in the acute compensation of blood pressure following hemorrhage has been described, the kidney's role is understood less completely than that for the sympathetic nervous system (Powell and DuCharme 1969, Sapirstein et al. 1941).

Sapirstein et al. (1941) postulated that the renin-angiotensin system might be involved in the maintenance of arterial blood pressure. Furthermore, Powell and DuCharme (1969) presented circumstantial evidence that there was a renal vasopressor mechanism that helped preserve arterial pressure following a reduction in blood volume. It was also observed that the blood pressure of nephrectomized dogs fell more than that of normal dogs following hemorrhage (Brough et al. 1975). When intact and nephrectomized dogs were bled into arterial pressure stabilization reservoirs, the intact dogs lost significantly more blood than the nephrectomized dogs during the first 30 min (Brough et al. 1975). However, these earlier studies did not specifically demonstrate that the renin-angiotensin system was the renal vasopressor system responsible for maintenance of arterial pressure during hypotension.

With the synthesis of structural analogs of angiotension II, it has become possible to more specifically investigate the physiologic role of angiotensin II in the regulation of arterial blood pressure. One of the more widely used analogs is 1-SAR-8-ALA-Angiotensin II (saralasin or P113).

[1]Manuscript received 9 December 1980 and in revised form 17 December 1981 (#80-62).

Saralasin is a competitive antagonist of angiotensin II (Pals et al. 1971) and has been used to study the role of angiotensin II in blood pressure regulation in several hypotensive models (Pals et al. 1971).

The focus of the present study was to investigate the role of angiotensin II in the maintenance of arterial blood pressure following hemorrhage in the rat.

METHODS AND MATERIALS

Male Sprague-Dawley rats weighing 250-350 g were used in this study. After anesthetizing with intra-peritoneal sodium pentobarbital (60 mg/kg), 17 animals were placed on a heating board and body temperature maintained. Both left and right jugular veins were isolated and catheterized towards the heart with PE50 polyethylene tubing. The right jugular was connected to a 5 cc syringe for constant infusion using a Harvard 975 infusion pump. The left jugular was used for injection of angiotensin II using a microliter syringe. The femoral artery was catheterized with PE50 tubing for the monitoring of arterial blood pressure via a Stathem P23db transducer connected to a Gould strip chart recorder. This catheter was also used for the site of hemorrhage.

GROUP 1. After the blood pressure was stabilized (15-20 min) 11 animals were hemorrhaged 6.0 ml/kg body weight. Forty minutes following hemorrhage, 3 μg/min saralasin was infused for 35 min at 0.013 ml/min. The infusion was then stopped and a 15 min recovery recorded. The blood pressure response to 100 ng of angiotensin II (AII) was determined during control, saralasin and recovery to verify pharmacological blockage of AII.

GROUP 2. This group of 5 animals served as a non-hemorrhaged control group. They were submitted to the same protocol as Group 1 except they were not hemorrhaged. This permitted the determination of the effects of saralasin on blood pressure in the normotensive rat.

In an additional animal, saline was infused in place of the saralasin in a hemorrhaged rat. This was to determine any volume effect the infusion might have had on blood pressure. This animal is designated Group 3 in the figures.

Within group analysis was accomplished with analysis of variance. Between group analysis utilized Student's group t-statistic.

RESULTS

The average values of mean arterial blood pressure was calculated at 5–min intervals and plotted in fig. 1. Fig. 2 presents the average values for mean arterial blood pressure for Groups 1 and 2 comparing the 5 periods.

Control blood pressures for Group 1 was 101 ±4 mmHg. Hemorrhage significantly reduced blood pressure 55 ±5 mmHg to a pressure of 46

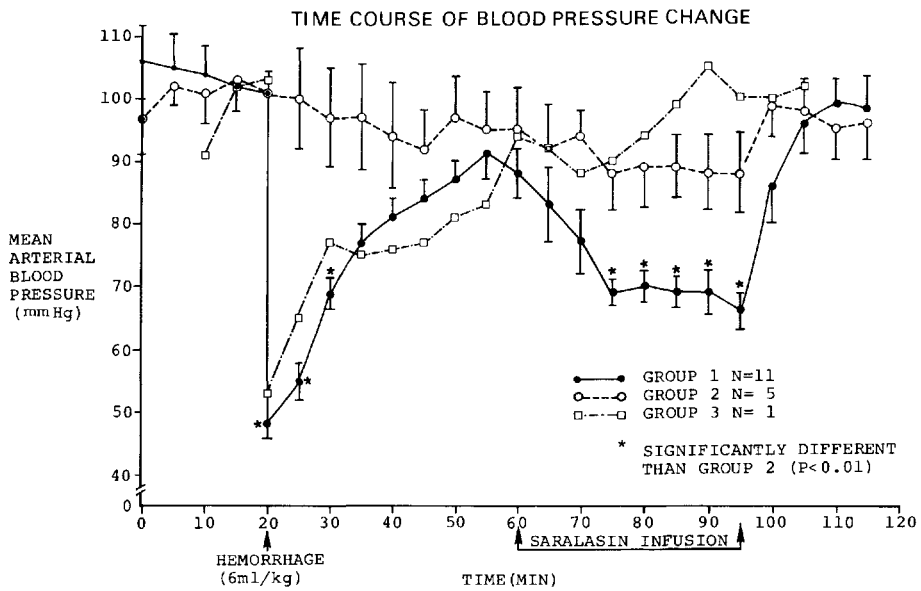

FIGURE 1. Time course of mean arterial blood pressure at 5–min intervals.

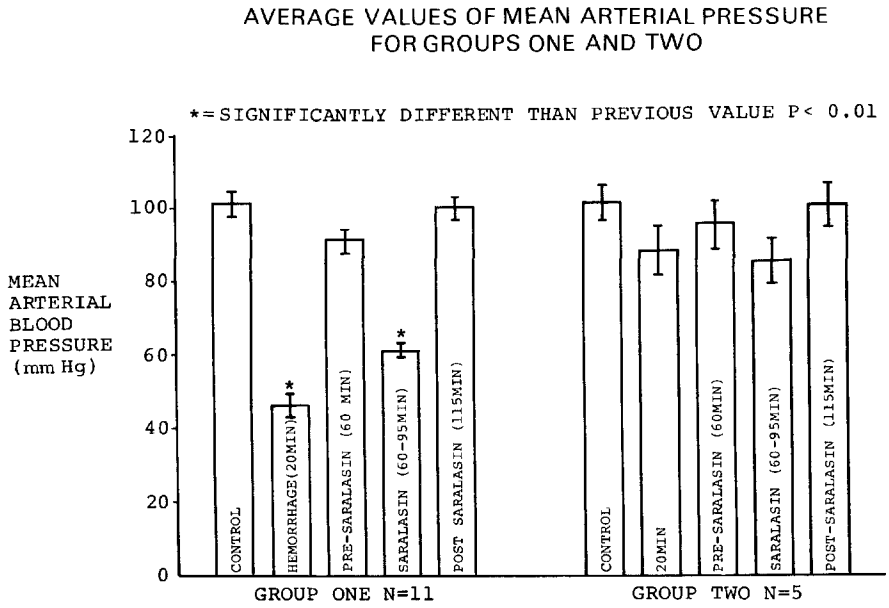

FIGURE 2. Average values of mean arterial blood pressure for Groups 1 and 2 for each of the 5 periods.

±3 mmHg. Forty minutes later, blood pressure had recovered to 91 ±3 mmHG. During saralasin infusion, pressure fell significantly to 61 ±2 mmHg. Following cessation of saralasin infusion blood pressure returned to 99 ±4 mmHg.

The animals of Group 2 were not hemorrhaged. The average control blood pressure of this group was 101 ±5 mmHg, not different from Group 1. There were no significant changes in blood pressure throughout the time course of the experiment. However, during saralasin infusion there was a consistent but insignificant decrease in pressure which recovered after cessation of the infusion.

The animal in Group 3 served to demonstrate the time course of recovery from hemorrhage. Saline only was infused between 60 and 95 min. The control blood pressure was 103 mmHg. Blood pressure fell to 53 mmHg after hemorrhage, rapidly recovered to 83 mmHg within 10 min. Pressure then rose more slowly to 94 mmHg prior to saline infusion. Pressure continued to rise slowly to a final pressure of 102 mmHg at 115 min.

DISCUSSION

The renin-angiotensin system has been shown to be at least partially responsible for the maintenance of "normal" blood pressure during several hypotensive states including chronic caval constriction in dogs (Bravo et al. 1976, Brough et al. 1975), chronic sodium depletion in dogs (Davis and Freeman 1976), and chronic sodium depletion in rats (Spielman and Davis 1974). In addition, the renin-angiotensin system has been implicated in the acute compensations in blood pressure in response to hemorrhage induced hypotension in conscious dogs (Freeman et al. 1975). The emphasis of the present study has been on the role of the kidney, particularly the renin-angiotensin system, in regulating blood pressure during hemorrhagic hypotension in the anesthetized rat.

It is evident from the present study that angiotensin II contributes to the recovery of blood pressure following hemorrhage. In hemorrhaged rats, competitive antagonism of angiotensin II with saralasin resulted in a rapid and striking decrease in blood pressure. In non-hemorrhaged rats,

saralasin had no significant effect on blood pressure. Thus, in rats, as in dogs (Freeman et al. 1975), angiotensin II contributes to blood pressure regulation following hemorrhage.

In the normotensive non-hemorrhaged group, a slight tendency for blood pressure to decrease during saralasin infusion was noted. This is due to the fact that in the anesthetized animal there is an elevation of plasma renin and circulating angiotensin II (Bing and Nielson 1973, Priano et al. 1969, Spielman and Davis 1974). Thus, upon inhibition of angiotensin II, blood pressure falls somewhat in these animals. However, this was not a significant decrease.

Upon cessation of saralasin infusion, blood pressure rose rapidly and often rose to values higher than control. This "overshoot" of blood pressure is explained by the fact that during saralasin infusion plasma renin is increased due to either the reduction in blood pressure or removal of angiotensin II feedback on renin release; or to both (Freeman et al. 1975). Upon removal of competitive blockade of angiotensin II, this elevated concentration acts to rapidly increase blood pressure even to above control levels.

It is clear from this data that angiotensin II participates in the acute recovery of blood pressure following hemorrhage. In fact, it appears that angiotensin II accounts for approximately 51% of the blood pressure compensation since, following hemorrhage, blood pressure increased 43 mmHg and upon infusion of saralasin blood pressure decreased 22 mmHg. The contribution of angiotensin II may actually be greater because in the present study, as blood pressure fell due to saralasin infusion, the intact neurogenic reflexes would have been activated to limit the decrease in blood pressure. This is supported by a previous study by Brough et al. (1975). In a study using areflexic dogs, the compensation in blood pressure following hemorrhage was 65% of the decrease in blood pressure due to hemorrhage. Thus, in animals without neurogenic reflexes, a substantial compensation in blood pressure following hemorrhage can still be accomplished and is mainly attributed to the action of the renin-angiotensin system. In further support of the concept, Brough et al. (1975) also hemorrhaged nephrectomized, areflexive dogs. In this case, the compensation in blood pressure was only 25%. Thus, the remaining 40% was attributable to the renin-antiotensin system. From these experiments one can conclude that the contribution of the renin-angiotensin system to the compensation in blood pressure following hemorrhage is substantial, and along with the nervous system represents an effective mechanism to regulate blood pressure. This is emphasized by the fact that in the present study, blood pressure compensation was 82% by 40 min following a substantial hemorrhage (6 ml/kg).

In conclusion, based on the fact that saralasin caused a decrease in blood pressure in hemorrhaged rats, it seems clear that the renin-angiotensin is involved in the acute compensations to blood pressure during hypotension in the rat. This indicates that the renin-angiotensin system is capable of responding rapidly to changes in blood pressure and can act in concert with the nervous system in the acute regulation of arterial blood pressure.

ACKNOWLEDGMENTS. This work was supported by NIH Biomedical Research Support Grant #1-S07-RR07155-01.

LITERATURE CITED

Bing, J. and K. Nielson 1973 Role of the renin system in normo- and hypertension. Acta Path. Microbiol. Scand. (A). 81: 254–262.

Bravo, E. L., M. C. Khosla and F. M. Bumpus 1976 Differential effects of ASP^1-AII and SAR^1-AII on vascular and adrenal receptors in the dog. Clin. Sci. Mol. Med. 51:41–45.

Brough, R. B., Jr., A. W. Cowley, Jr. and A. C. Guyton 1975 Quantitative analysis of the acute response to hemorrhage of the renin angiotensin-vasoconstrictor feedback loop in areflexic dogs. Cardiovas. Res. 9: 722–733.

Chien, S. 1967 Role of the sympathetic nervous system in hemorrhage. Physiol. Rev. 47: 214–288.

Davis, J. O. and R. H. Freeman 1976 The use of angiotensin antagonists to study adrenal steroid secretion. Fed. Proc. 35: 2508–2511.

Freeman, R. H., J. O. Davis, J. A. Johnson, W. S. Spielman and M. L. Zatzman 1975 Arterial pressure regulation during hemorrhage: Homeostatic role of renin. Proc. Soc. Exp. Biol. Med. 149: 19–22.

Pals, D. T., F. D. Masucci, G. S. Dennings, Jr., F. Sipas and D. Fessler 1971 Role of the pressor action of angiotensin II in experimental hypertension. Circ. Res. 29: 673–689.

Powell, J. R. and D. W. DuCharme 1969 Effect of renal pressor systems on vascular capacity during hemorrhage. Amer. J. Physiol. 226: 168–172.

Priano, L. L., D. L. Traber and R. D. Wilson 1969 Barbiturate anesthesia: An abnormal physiologic situation. J. Pharm. Exp. Ther. 165: 126–135.

Sapirstein, L. A., E. Ogdan and F. D. Southard, Jr. 1941 Renin-like substance in the blood after hemorrhage. Proc. Soc. Exp. Biol. Med. 48: 505–508.

Spielman, W. S. and J. O. Davis 1974 The renin-angiotensin system and aldosterone secretion during sodium depletion in the rat. Circ. Res. 35: 615–624.