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Interaction between Angiotensin II and the Baroreceptor Reflex in the Control of Adrenocorticotropic Hormone Secretion and Heart Rate in Conscious Dogs

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SUMMARY The present studies were designed to examine the effect of angiotensin II on baroreflex control of adrenocorticotropic hormone secretion and heart rate in conscious dogs. Baroreflex function was assessed by examining the relationship between blood pressure and plasma corticosteroid concentration (used as an index of adrenocorticotropic hormone secretion) and between blood pressure and pulse interval (the inverse of heart rate). Blood pressure was varied by intravenous infusion of four doses (0.3, 0.6, 1.5, and 3.0 μg/kg per min) of the vasodilator nitroprusside. Nitroprusside infusion produced an increase in plasma corticosteroid concentration and a decrease in pulse interval, both of which were linearly related to the fall in arterial blood pressure. During infusion of angiotensin II (10 ng/kg per min), however, the lines relating blood pressure to plasma corticosteroid concentration or blood pressure to pulse interval were shifted to a higher pressure level, suggesting that angiotensin II resets the baroreceptor reflex Angiotensin II blockade with saralasin, an angiotensin II antagonist, or with captopril, a converting enzyme inhibitor, in sodium-depleted dogs with elevated plasma angiotensin II levels produced a shift in the opposite direction in these relationships Because baroreflex function in sodium-depleted dogs before angiotensin II blockade was similar to that in sodium-replete dogs, despite the increased plasma angiotensin II levels, and because treatment of sodium-replete dogs with saralasin did not affect baroreflex function, these results suggest that endogenous angiotensin II is necessary for the maintenance of normal baroreflex control of adrenocorticotropic hormone secretion and heart rate during sodium depletion. Previous studies designed to evaluate the physiological significance of angiotensin II in the control of adrenocorticotropic hormone secretion showed that high, perhaps supraphysiological, levels of exogenous angiotensin II are required to increase adrenocorticotropic hormone secretion. An additional finding of the present study was that exogenous angiotensin II produces a larger increase in adrenocorticotropic hormone secretion when the pressor effect of angiotensin II was eliminated with simultaneous infusion of the vasodilators nitroprusside or hydralazine This result suggests that experiments that evaluate the physiological role of angiotensin II in the control of adrenocorticotropic hormone secretion with infusions of exogenous AII may underestimate the importance of endogenously produced angiotensin II, which is normally released without an increase in pressure. (*Circ Res 58: 816–828, 1986*)

IT has been demonstrated that intravenous angiotensin II (AII) infusion stimulates adrenocorticotropic hormone (ACTH) release in conscious dogs (Maran and Yates, 1977; Ramsay et al., 1978; Reid et al., 1982). AII also increases arterial blood pressure, and this would be expected to inhibit ACTH secretion by stimulation of baroreceptor pathways (Ganong et al., 1967; Raff et al., 1983). Previous studies have shown that baroreflex control of the heart is altered during administration of AII, and that the pressor response induced by AII is not accompanied by a reflex bradycardia (Ismay et al., 1979, Guo and Abboud, 1984). The purpose of the present experiments was to determine whether AII also affects baroreflex-stimulated release of ACTH secretion. In these experiments, the relationship between blood pressure and ACTH secretion was examined in the presence and absence of AII.

Antagonists of the renin-angiotensin system have been used to examine the role of the renin-angiotensin system under conditions in which circulating AII levels are increased. For example, it is known that the antagonists lower arterial blood pressure in sodium-depleted animals, emphasizing the important action of AII to maintain arterial pressure in this situation (Brooks and Reid, 1983). Recently, we reported that plasma corticosteroid concentration, which was used as an index of ACTH release, was not increased by infusion of the competitive AII antagonist, saralasin, in sodium-depleted dogs, despite a marked fall in arterial pressure (Brooks and Reid, 1983). Since decreases in blood pressure nor-

mally stimulate ACTH release (Gann et al., 1981) it was of interest to know why ACTH release did not increase following saralasin administration. There is evidence that blockade of the renin-angiotensin alters baroreflex control of heart rate in sodium-depleted dogs (Hatton et al., 1981). Therefore, to determine whether AII blockade also affects baroreflex control of ACTH secretion, we investigated the effect of administration of saralasin or captopril, a converting enzyme inhibitor, on the relationship between blood pressure and plasma corticosteroid concentration in sodium depleted dogs

Methods

Experiments were performed on 12 mongrel dogs of either sex weighing between 16 and 30 kg.

Surgical Preparation

Dogs received subcutaneous injections of acepromazine maleate (1 mg/kg, Ayerst Laboratories) and subsequently were anesthetized with pentobarbital sodium (15 mg/kg, injected intravenously) Silastic cannulas (0.5 mm i d) were implanted into the abdominal aorta and vena cava via a femoral artery and vein. In some dogs, right atrial catheters were placed via the right jugular vein, or left atrial catheters were implanted via a left thoracotomy. All catheters were led subcutaneously to an area between the scapulae where they emerged and were protected by a nylon jacket (Medical Arts). During the first 5 days after surgery, the dogs were treated with penicillin and streptomycin (Henry Schein, Inc.). 3 ml/day, im) Catheters were flushed 3 times weekly and filled with sodium heparin (1,000 U/ml) For most dogs, a minimum of 5 days elapsed before the first experiment was performed. Dogs subjected to a thoracotomy were allowed 2 weeks of recovery. After surgery, the animals were fed one of two diets Sodium-replete dogs were fed a diet which provided approximately 70 mEq/day sodium Sodium-deprived dogs were fed two cans H/D Prescription Diet, Riviana Foods, which provided approximately 10 mEq sodium/day and were injected with furosemide (20 mg, im, on alternate days for 1 week).

Experimental Protocols

On the day of the experiment, the dogs were brought to the laboratory where they were loosely restrained in a nylon sling that allowed them to stand or rest comfortably in an upright position. Mean and pulsatile arterial pressure and heart rate were measured via the femoral arterial catheter with a Statham strain gauge and a Grass polygraph Right and left atrial pressures were also recorded Transducers were placed so that the zero pressure point was at the level of the heart Because of the difficulty in accurately determining the zero reference point for atrial pressures, atrial pressure data were analyzed by paired *t*-tests and analysis of variance for repeated measures, which adjust for differences in control values between dogs, and by analyzing the change in atrial pressure from control values After a 45-minute equilibration period, one of the following two protocols was performed

Protocol 1

Immediately after a control arterial blood sample was obtained, an intravenous infusion of either AII (10 ng/kg per min, Schwarz-Mann or Bachem), saralasin (1 μg/kg per min; Bachem), captopril (20 μg/kg per min following a 1 mg/kg prime; E R Squibb and Sons, Inc.), or 5% dextrose was begun at an infusion rate of 0.5 ml/min. These infusions were continued for the duration of the experiment Fifteen minutes later, another blood sample was taken and an iv infusion of nitroprusside (Nipride, Roche Laboratories) at 0.3 μg/kg per min was begun Every 15 minutes, the dose of nitroprusside was increased until a total of four doses (0 3, 0.6, 1.5, 3.0 μg/kg per min) had been given. An arterial blood sample was collected just before the dose of nitroprusside was increased. All blood samples (13 ml) were replaced with an equal volume of isotonic saline. Sodium-replete dogs received either AII and nitroprusside, saralasin and nitroprusside, or nitroprusside alone In sodium-depleted dogs, saralasin or captopril was infused with nitroprusside, or nitroprusside alone was infused In control experiments, sodium-depleted and -replete dogs received intravenous infusions (0.5 ml/min) of the drug vehicle, 5% dextrose, and blood samples were taken every 15 minutes as described above.

Protocol II

Experiments were performed to evaluate the effect of reducing the pressor response of AII with another vasodilator, hydralazine (Apresoline HCL, Taylor Pharmacal Co.) In these experiments, two control blood samples, 15 minutes apart, were collected The dogs then received either AII (10 ng/kg per min) alone, or the same dose of AII infused with either nitroprusside (3 μg/kg per min) or hydralazine (15–20 mg, injected as bolus). Blood samples (13 ml) were collected 15 and 30 minutes after the AII infusion was begun. The AII infusions were terminated, and 30 minutes later a recovery blood sample was collected. AII and nitroprusside were diluted with 5% dextrose

Hormone Assays

Plasma corticosteroid concentration was measured by radioimmunoassay (Abraham et al , 1977) and was used as an index of ACTH secretion. Plasma renin activity (PRA) was measured by using a radioimmunoassay for AI (Stockigt et al., 1971) and was expressed as nanograms of AI generated per milliliter of plasma during a 3-hour incubation at 37°C (ng AI/ml per 3 hours). Plasma AII was measured by radioimmunoassay (Reid, 1981) In some cases, plasma ACTH concentration was measured with a radioimmunoassay purchased from Immuno Nuclear Corporation. Between-assay variability was 12 6% (n = 15) and within-assay variability was 7 4% (n = 22).

Statistics

For the corticosteroid and ACTH results, a linear equation was fitted from individual data points for all dogs in each group by least squares regression analysis; the groups were compared by testing for differences in the slopes and intercepts of the line (Winer, 1971) These calculated regression lines and the mean ± SEM values for blood pressure and plasma corticosteroid or ACTH concentration for each dose of nitroprusside are graphed in the figures Where indicated, the paired *t*-test was also used (Winer, 1971). For the PRA and AII results, within group changes were analyzed with one-way analysis of variance for repeated measures (Winer, 1971). Between group differences were assessed with two-way analysis of variance repeated one-way (Winer, 1971) In experiments in which

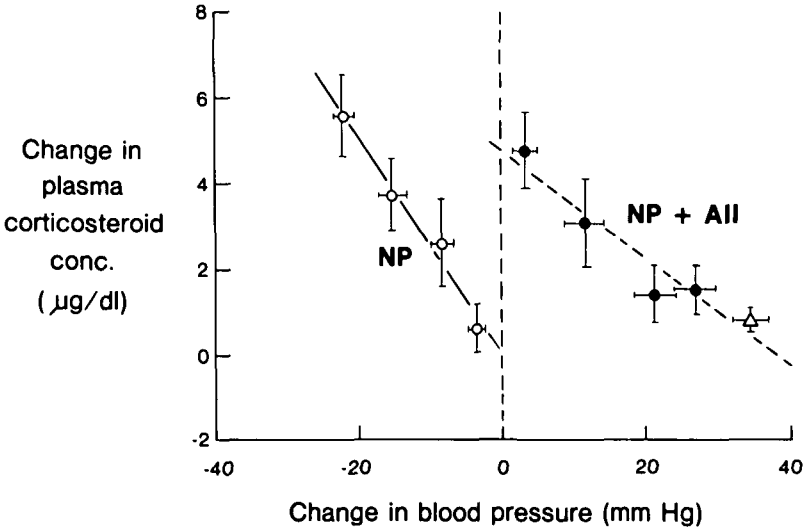

FIGURE 1. *Relationship between the change in blood pressure and the change in plasma corticosteroid concentration during intravenous infusion of nitroprusside (NP) (n = 7) or nitroprusside and angiotensin II (NP + AII) (n = 7). The open triangle represents the mean ± SEM effect of angiotensin II alone on the change in blood pressure and the change in plasma corticosteroid concentration Control blood pressures were 109 ± 1 (NP) and 105 ± 2 (NP + AII) mm Hg. Control corticosteroid levels were 1 4 ± 0 2 (NP) and 2.0 ± 0 5 (NP + AII) μg/dl n = number of dogs in each group*

several doses of nitroprusside were infused, heart rate changes were assessed as a function of the fall in blood pressure It has been shown that if pulse interval (inverse of heart rate) is plotted vs. blood pressure, a sigmoidal relationship is obtained (Smyth et al., 1969). The linear portion of this curve can be used to analyze baroreceptor control of the heart The slope of the line is a measure of baroreflex sensitivity or gain, while the intercept has been used as an index of the "setpoint" of this control system. In the current experiments, pulse interval was plotted vs. the change in blood pressure. In those instances in which the linear part of the curve is depicted, regression analysis and tests for differences in slope and intercept were performed (Winer et al., 1971). In some cases, sufficient data were not obtained on the linear part of the curve, and no statistical comparisons were made.

Results

Plasma Corticosteroid Concentration and ACTH

The relationship between blood pressure and plasma corticosteroid concentration obtained from dogs treated with nitroprusside or AII and nitroprusside is illustrated in Figure 1. Nitroprusside alone caused an increase in plasma corticosteroid concentration which was linearly related to the fall in arterial pressure (Fig. 1; Table 1). Nitroprusside also increased corticosteroid levels when infused in combination with AII, but the line relating the change in blood pressure to the change in plasma corticosteroid concentration was shifted to the right with a significant increase in intercept (Fig. 1; Table 1). Closer inspection of the relationship between blood pressure and plasma corticosteroid concentration during infusion of AII and nitroprusside reveals an additional finding (Fig. 1). In this experiment, AII alone increased blood pressure by 34 ± 3 mm Hg ($P < 0.001$) and increased plasma corticosteroid concentration by 0 8 ± 0.3 μg/dl ($P < 0.05$). When increasing doses of nitroprusside were infused together with AII, blood pressure fell and plasma corticosteroids increased further. With the highest dose of nitroprusside, blood pressure returned to the control level and plasma corticosteroid concentration was increased by 4.7 ± 0.9 μg/dl. Thus, these data also demonstrated that AII produces a larger increase in plasma corticosteroid concentration ($P < 0.001$) when the pressor effect of AII is reduced or abolished.

In a second set of experiments, the vasodilator hydralazine was used to reduce the pressor effect of AII infusion. In one group of animals ($n = 8$), a 30-minute infusion of AII alone increased blood pressure by 34 ± 3 mm Hg ($P < 0.001$) and plasma corticosteroid concentration by 2.4 ± 0.8 μg/dl ($P < 0.05$). When hydralazine was administered with AII, blood pressure did not change (3 ± 4 mm Hg; $P > 0.10$), and corticosteroid concentration was increased by 6.6 ± 0.7 μg/dl ($P < 0.001$). Thus, the corticosteroid rise was larger ($P < 0.001$) when AII

TABLE 1
Effect of AII, Saralasin, and Captopril on Baroreflex Function Relationships in Sodium-Replete and -Depleted Conscious Dogs

Protocol	Slope	Intercept	r^2
NP (replete)	−0 25	0 1	0 42
NP + AII (replete)	−0 12*	4 7†	0 35
NP + SAR (replete)	−0 23	0 7	0 43
NP (depleted)	−0.40*	−1.5	0.69
NP + SAR (depleted)	−0 41	−10 2‡	0 73
NP + CAP (depleted)	−0 63	−26 6‡	0 41

Values are slopes and intercepts of the linear equation plasma corticosteroid concentration = slope (change in blood pressure) + intercept The equations were calculated by least squares regression analysis from the individual data points for all dogs All lines have significant slopes with $P < 0.001$ NP = nitroprusside, AII = angiotensin II, SAR = saralasin, CAP = captopril
* $P < 0$ 05 compared to NP (replete) group
† $P < 0$ 001 compared to NP (replete) group
‡ $P < 0$ 001 compared to NP (depleted) group

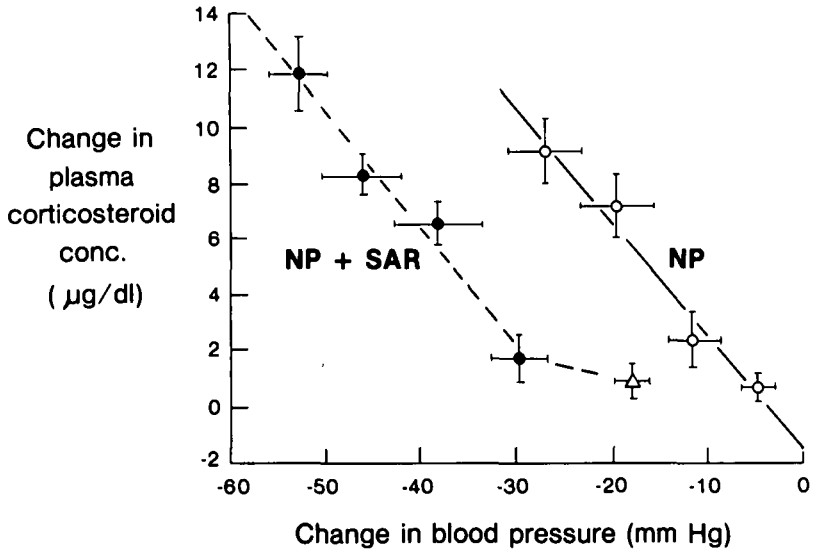

FIGURE 2. *Relationship between the change in blood pressure and the change in plasma corticosteroid concentration in sodium-depleted dogs receiving intravenous infusion of nitroprusside (NP) (n = 6) or nitroprusside and saralasin (NP + SAR) (n = 7). The open triangle represents the mean ± SEM effect of saralasin alone on the change in blood pressure and the change in plasma corticosteroid concentration Control blood pressures were 110 ± 3 (NP) and 108 ± 3 (NP + SAR) mm Hg Control corticosteroid levels averaged 1.9 ± 0 4 (NP) and 2 8 ± 1 1 (NP + SAR) μg/dl n = number of dogs*

was infused with hydralazine compared to the rise following AII alone For comparison, the corticosteroid response to a 30-minute infusion of AII (10 ng/kg per min) or a 30-minute infusion of AII (10 ng/kg per min) and nitroprusside (3 μg/kg per min) was also evaluated. In this group of dogs (n = 5), AII infusion again increased blood pressure by 30 ± 3 mm Hg ($P < 0.001$) and plasma corticosteroid concentration by 1.7 ± 0.6 μg/dl ($P = 0.06$). When nitroprusside was infused along with AII, the blood pressure rise was abolished (1 ± 2 mm Hg, $P > 0.10$), and a larger increase in plasma corticosteroid concentration (5.2 ± 0.7 μg/dl, $P < 0.01$) was produced ($P < 0.05$).

Nitroprusside infusion also enhanced the ACTH response to AII. AII alone increased plasma ACTH levels from 36 ± 6 pg/ml to 48 ± 6 pg/ml ($P < 0.005$, n = 4). In the presence of nitroprusside, AII produced a larger rise in ACTH concentration ($P = 0.05$), increasing it from 44 ± 3 to 81 ± 14 pg/ml ($P < 0.05$, n = 5).

Figure 2 illustrates the relationship between blood pressure and plasma corticosteroid concentration in sodium-deprived dogs treated with four doses of nitroprusside. As in sodium-replete dogs, nitroprusside alone decreased blood pressure and increased plasma corticosteroid concentration, and these variables were linearly related (Table 1). Also shown in Figure 2 is the relationship between blood pressure and plasma corticosteroid concentration in sodium-deprived dogs infused with saralasin and nitroprusside. Saralasin alone lowered blood pressure by 18 ± 2 mm Hg ($P < 0.001$) without affecting plasma corticosteroid concentration. However, when blood

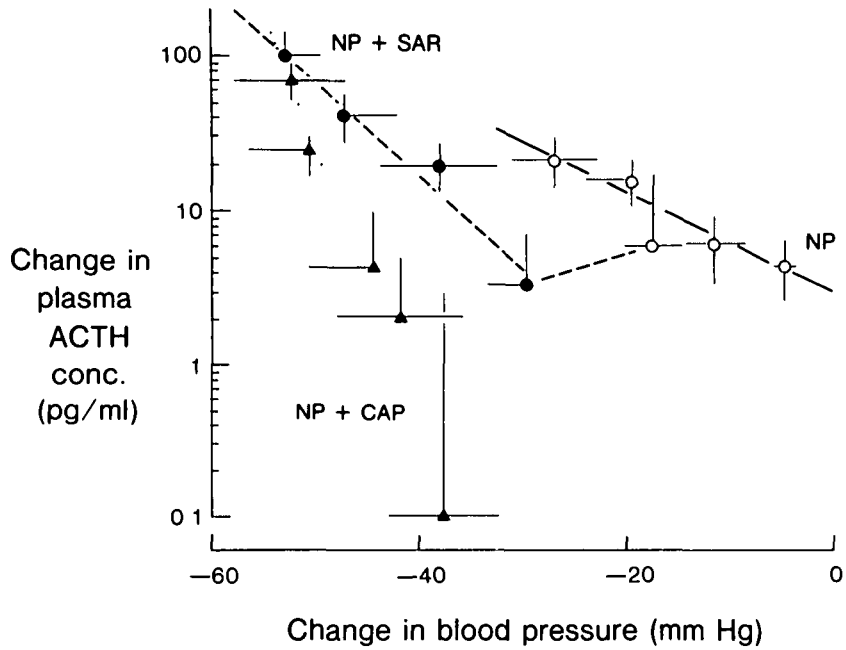

FIGURE 3. *Relationship between the change in blood pressure and log (change in plasma ACTH concentration) in sodium-depleted dogs receiving intravenous infusion of nitroprusside (NP) (n = 6), nitroprusside and saralasin (NP + SAR) (n = 6), or nitroprusside and captopril (NP + CAP) (n = 5). Control blood pressures were 110 ± 3 (NP), 108 ± 3 (NP + SAR), and 107 ± 3 (NP + CAP) mm Hg Control ACTH levels were 31 ± 5 (NP), 44 ± 9 (NP + SAR), and 36 ± 6 (NP + CAP) pg/ml n = number of dogs.*

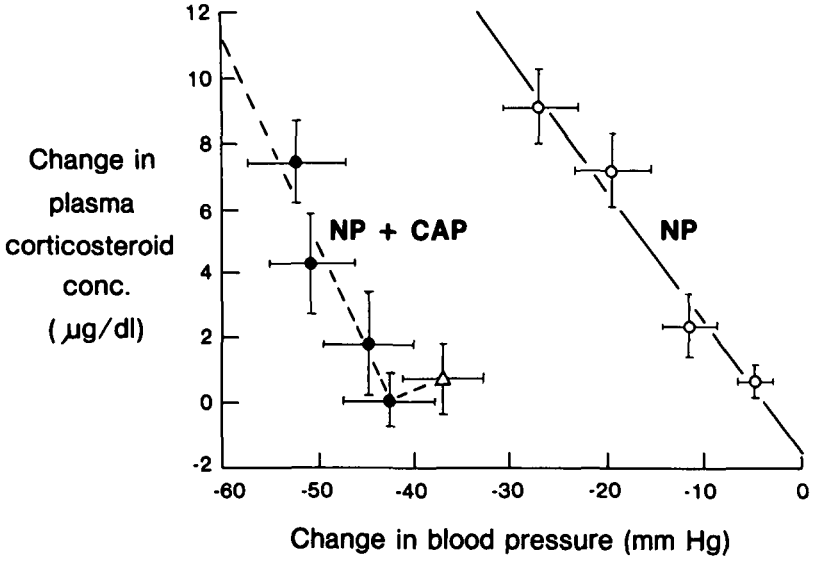

FIGURE 4. *Relationship between the change in blood pressure and the change in plasma corticosteroid concentration in sodium-depleted dogs receiving intravenous infusion of nitroprusside (NP) (n = 6) or nitroprusside and captopril (NP + CAP) (n = 6) The open triangle represents the mean ± SEM effect of captopril alone on the change in blood pressure and the change in plasma corticosteroid concentration Control blood pressures were 110 ± 3 (NP) and 107 ± 3 (NP + CAP) mm Hg. Control corticosteroids averaged 1.9 ± 0 4 (NP) and 3 6 ± 1 4 (NP + CAP) μg/dl n = number of dogs.*

pressure was lowered further with nitroprusside, plasma corticosteroid concentration was increased. During saralasin infusion, the rise in corticosteroids was again linearly related to the blood pressure fall (Table 1), but this line was displaced to the left compared to the line obtained with infusion of nitroprusside alone (Fig. 2; Table 1). Saralasin had a similar effect on the relationship between blood pressure and plasma ACTH concentration (Fig. 3). The relationship between blood pressure and plasma ACTH is exponential, and a linear relationship is produced if ACTH is plotted on a logarithmic scale (Fig. 3). Saralasin shifted the line to the left ($P < 0.05$) without affecting the slope ($P > 0.10$).

Inhibition of AII formation with captopril in sodium-deprived animals produced a similar shift as saralasin in the relationship between blood pressure and plasma corticosteroid concentration (Fig. 4; Table 1) and between blood pressure and log ACTH (Fig. 3). The intercept decreased ($P < 0.01$) without a change in slope ($P > 0.10$). A shift was not observed in sodium replete dogs treated with saralasin (Fig. 5; Table 1). Finally, the relationship between blood pressure and plasma corticosteroid concentration in sodium-replete and -depleted dogs is compared in Figure 6. The slope of the line was slightly but significantly ($P = 0.04$) increased in sodium-depleted dogs, but the intercept was not changed.

Heart Rate

The relationship between blood pressure and pulse interval in dogs treated with nitroprusside or nitroprusside and AII is depicted in Figure 7. Nitroprusside alone decreased blood pressure and decreased pulse interval (heart rate was increased). These variables were linearly related (pulse interval = 0.00025·(blood pressure change) + 0.0144; $r^2 = 0.26$; $P < 0.001$). In the presence of AII, there was again a linear relationship between blood pressure

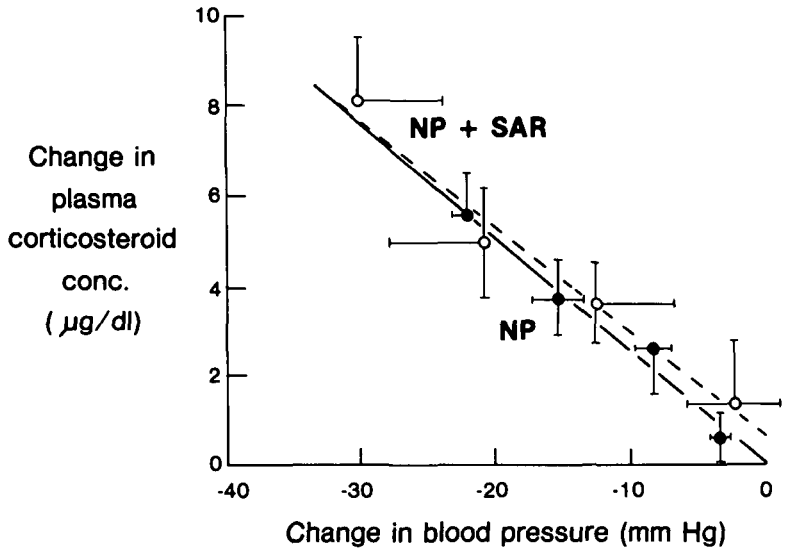

FIGURE 5. *Relationship between the change in blood pressure and the change in plasma corticosteroid concentration in sodium-replete dogs receiving intravenous infusion of nitroprusside (NP, closed circles, solid line) (n = 7) or nitroprusside and saralasin (NP + SAR, open circles, dashed line) (n = 6) Control blood pressures were 109 ± 1 (NP) and 102 ± 4 (NP + SAR) mm Hg Control corticosteroid levels were 1 4 ± 0.2 (NP) and 1 8 ± 0.5 (NP + SAR) μg/dl n = number of dogs*

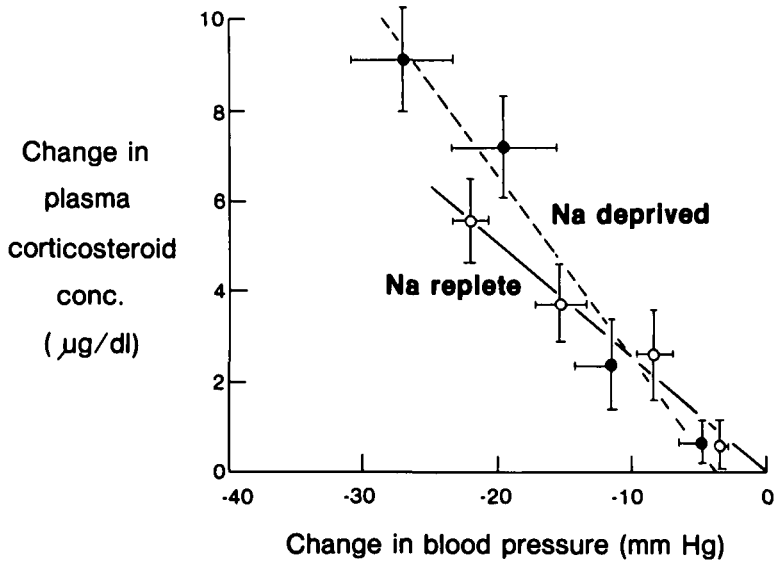

FIGURE 6. *Relationship between the change in blood pressure and the change in plasma corticosteroid concentration in sodium-replete (Na replete) (n = 7) and sodium-deprived (Na deprived) (n = 6) dogs receiving intravenous infusion of four doses of nitroprusside Control blood pressures were 109 ± 1 (sodium-replete) and 110 ± 3 (sodium-deprived) mm Hg. Control corticosteroid levels were 1.4 ± 0 1 (sodium-replete) and 1 9 ± 0 4 (sodium-deprived) μg/dl n = number of dogs*

and pulse interval (pulse interval = 0.00018·(blood pressure change) + 0.0103; $r^2 = 0.26$, $P < 0.001$), but this relationship was displaced to the right ($P < 0.01$) without a change in slope ($P = 0.2$).

In another group of dogs, a 30-minute infusion of AII increased blood pressure from 100 ± 4 to 129 ± 5 mm Hg ($n = 5$, $P < 0.001$), whereas heart rate did not change significantly (61 ± 2 to 71 ± 6 beats/min, $P > 0.05$). When nitroprusside was infused together with AII in the same dogs so that blood pressure did not change (103 ± 2 to 104 ± 2 mm Hg, $P > 0.05$), heart rate increased from 66 ± 2 to 105 ± 12 beats/min ($P < 0.05$). Thus, AII produced a larger increase in heart rate ($P < 0.05$) when the pressor effect was abolished with nitroprusside. Another vasodilator, hydralazine, had a similar effect in a second group of dogs ($n = 8$). AII alone slightly increased heart rate (58 ± 2 to 66 ± 4 beats/min, $P < 0.05$) as it increased blood pressure from 97 ± 3 to 131 ± 3 mm Hg ($P < 0.001$). However, hydralazine eliminated the pressure rise (100 ± 3 to 103 ± 5 mm Hg) and was associated with a larger increase ($P < 0.001$) in heart rate from 58 ± 4 to 122 ± 8 beats/min ($P < 0.001$).

The remaining heart rate results are summarized in Figure 8. Although in all cases, the relationship between blood pressure and pulse interval was not linear, and statistical analyses were not performed, the following observations can be made. Both saralasin and captopril displaced the curve relating pulse interval and blood pressure to the left in sodium-deprived dogs (Fig. 8, A and B). This relationship was not affected by saralasin in sodium-replete dogs (Fig. 8C). Before nitroprusside (zero change in blood pressure), sodium-depleted dogs exhibited an elevated heart rate (smaller pulse interval), compared to sodium-replete dogs ($P < 0.01$); however, nitroprusside produced a similar decrement in pulse interval as blood pressure fell in the replete and depleted dogs (Fig. 8D).

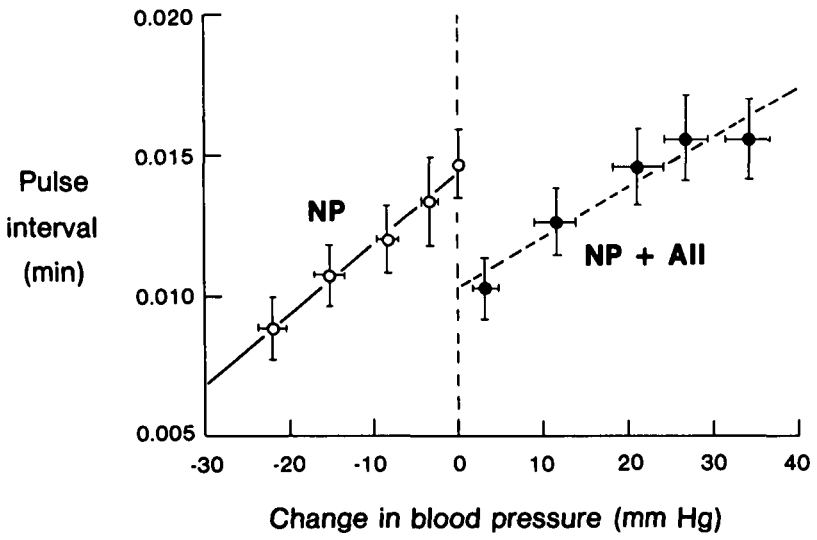

FIGURE 7. *Relationship between the change in blood pressure and pulse interval (inverse of heart rate) in sodium-replete dogs receiving nitroprusside (NP) (n = 7) or nitroprusside and angiotensin II (NP + AII) (n = 7) Control blood pressures as in legend to Figure 1*

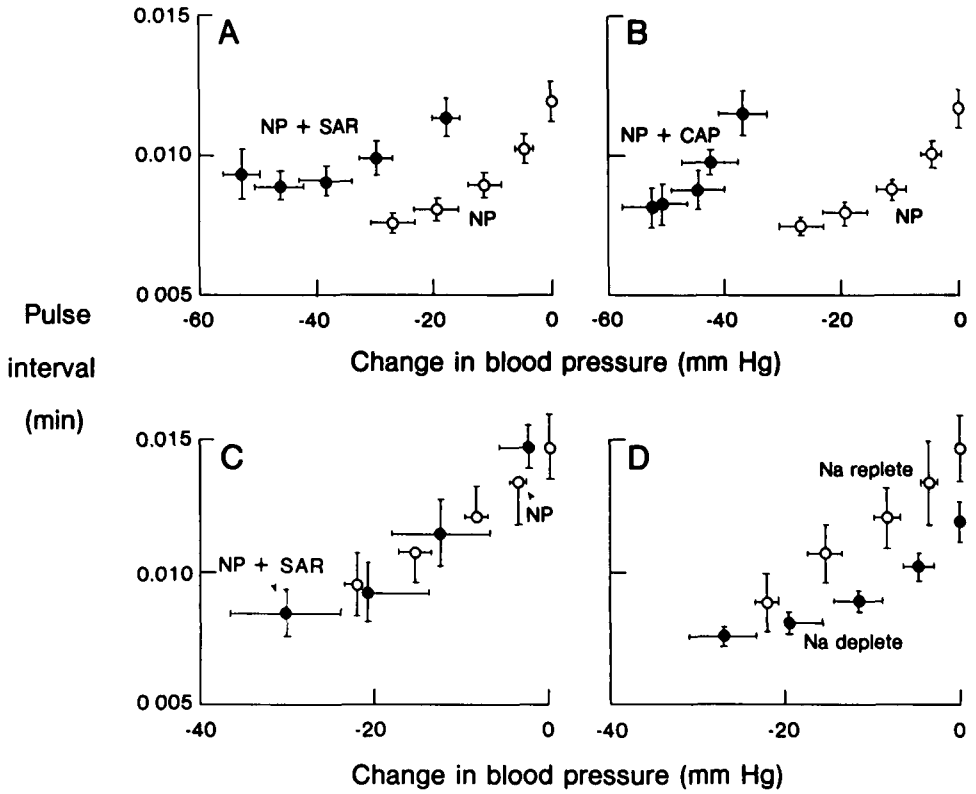

FIGURE 8. *Relationship between the change in blood pressure and pulse interval in (part A) sodium-depleted dogs infused with nitroprusside (NP) (n = 6) or nitroprusside and saralasin (NP + SAR) (n = 7), (part B) sodium-depleted dogs infused with nitroprusside (NP) (n = 6) or nitroprusside and captopril (NP + CAP) (n = 6), (part C) sodium-replete dogs infused with nitroprusside (NP) (n = 7) or nitroprusside and saralasin (NP + SAR) (n = 6), and in (D) sodium-replete (Na replete) (n = 7) and sodium deplete (Na deplete) (n = 6) dogs infused with nitroprusside alone Control blood pressures as in legends to Figures 2, 4, and 5.*

Plasma Renin Activity and Plasma AII Concentration

The effect of infusions of nitroprusside, nitroprusside and AII, nitroprusside and saralasin or captopril, or the saline vehicle on PRA in sodium-replete and -depleted dogs is summarized in Table 2. PRA increased as blood pressure fell with nitroprusside (Table 2). AII infusion suppressed PRA (Table 2), and concurrent nitroprusside infusion did not affect

TABLE 2
Effect of Nitroprusside, Alone or in Combination with AII, Saralasin, or Captopril, on PRA (ng AI/ml per 3 hr) in Conscious, Sodium-Replete, or Sodium-Depleted Dogs

	Time (min)						
Protocol	15	30	45	60	75	90	*P*
NP (replete) (7)	6 8 ± 0 8	7 0 ± 1 0	9 8 ± 0 7	13 8 ± 1 7	13 6 ± 1 7	19 7 ± 3 5	<0 001
NP + AII (replete) (7)	10 4 ± 1 4	5 7 ± 0 9	3 5 ± 0 6	3 6 ± 0 6	3 6 ± 0 4	3 3 ± 0 4	<0 001
NP + SAR (replete) (6)	7 5 ± 2 1	8 4 ± 2 5	15 7 ± 4 1	34 4 ± 12 6	63 9 ± 21 4	83 7 ± 27 6	<0 001
5% Dextrose (replete) (5)	8 0 ± 1 4	10 5 ± 1 6	11 3 ± 2 2	8 3 ± 1 3	8 0 ± 1 5	8 8 ± 1 4	NS
NP (depleted) (6)	46 ± 6	41 ± 4	59 ± 7	59 ± 7	61 ± 14	79 ± 29	NS
NP + SAR (depleted) (7)	45 ± 8	102 ± 28	213 ± 22	250 ± 23	300 ± 30	250 ± 15	<0 001
NP + CAP (depleted) (7)	32 ± 4	176 ± 34	221 ± 26	262 ± 35	289 ± 67	175 ± 16	<0 001
5% Dextrose (depleted) (4)	38 ± 8	42 ± 6	35 ± 5	36 ± 6	34 ± 7	37 ± 7	NS

Values are means ± SEM of plasma renin activity (ng AI/ml per 3 hr) Nitroprusside infusion was begun after 30-minute sample, 5% dextrose, angiotensin II, saralasin, or captopril infusions were begun after 15-minute sample NP = nitroprusside, AII = angiotensin II, SAR = saralasin, CAP = captopril, PRA = plasma renin activity, NS = not significant ($P > 0$ 10) Numbers in parentheses = number of dogs in each group

TABLE 3
Effect of Nitroprusside, Alone or in Combination with AII, Saralasin, or Captopril, on Plasma AII Concentration (pg/ml) in Conscious, Sodium-Replete, or Sodium-Depleted Dogs

Protocol	Time (min)						P
	15	30	45	60	75	90	
NP (replete) (7)	20 ± 5	17 ± 4	24 ± 4	24 ± 4	26 ± 3	35 ± 4	<0 001
NP + AII (replete) (7)	18 ± 3	185 ± 19	189 ± 10	173 ± 11	180 ± 15	171 ± 7	<0.001
NP + SAR (replete) (5)	45 ± 9	47 ± 6	81 ± 14	178 ± 83	304 ± 119	389 ± 135	<0 01
5% Dextrose (replete) (5)	17 ± 3	20 ± 3	21 ± 3	17 ± 3	17 ± 3	17 ± 3	NS
NP (depleted) (6)	93 ± 11	104 ± 11	123 ± 12	124 ± 8	162 ± 21	174 ± 25	<0 01
NP + SAR (depleted) (7)	93 ± 13	250 ± 61	691 ± 86	832 ± 99	872 ± 89	928 ± 93	<0 001
NP + CAP (depleted) (6)	71 ± 14	23 ± 4	29 ± 5	29 ± 7	32 ± 7	31 ± 7	<0.001
5% Dextrose (depleted) (4)	75 ± 11	82 ± 12	74 ± 11	67 ± 14	67 ± 14	71 ± 14	NS

Values are means ± SEM of plasma angiotensin II concentration (pg/ml). Nitroprusside infusion was begun after 30-minute sample; 5% dextrose, angiotensin II, saralasin, or captopril infusions were begun after 15-minute sample NP = nitroprusside; AII = angiotensin II, SAR = saralasin; CAP = captopril, NS = not significant ($P > 0.10$). Numbers in parentheses = number of dogs in each group.

this suppression (Table 2). The increase in PRA produced by nitroprusside was enhanced by saralasin in both sodium-replete ($P < 0.05$) and -depleted ($P < 0.001$) dogs; captopril also increased the response in sodium-deprived dogs ($P < 0.001$) (Table 2). PRA did not change during saline infusion in either sodium-replete or -depleted dogs (Table 2).

The AII results are summarized in Table 3. In general, changes in plasma AII paralleled the changes in PRA with two notable exceptions. First, plasma AII concentration (Table 3) increased during AII infusion, whereas PRA was decreased (Table 2). Second, captopril treatment decreased plasma AII concentration (Table 3) and increased PRA (Table 2).

Right and Left Atrial Pressures

The effect of the different infusions on right atrial pressure is summarized in Table 4. Neither AII infusion in sodium-replete dogs nor captopril or saralasin infusion in sodium-deprived dogs affected right atrial pressure (Table 4). In contrast, in each group, nitroprusside lowered right atrial pressure below control values (Table 4). However, there was no correlation between the fall in right atrial pressure and the change in plasma corticosteroid concentration in sodium-replete dogs infused with either nitroprusside ($r^2 = 0.12$, $P > 0.05$) or with AII and nitroprusside ($r^2 = 0.12$, $P > 0.05$).

In separate experiments, left atrial pressure was measured in four dogs during AII infusion (10 ng/kg per min), nitroprusside infusion (3 μg/kg per min), and during a combined infusion of AII and nitroprusside. AII increased mean arterial pressure from 100 ± 6 to 128 ± 5 mm Hg ($P < 0.01$) and left atrial pressure from 5.9 ± 0.8 to 9.1 ± 1.1 mm Hg ($P < 0.01$). Conversely, nitroprusside decreased arterial pressure from 103 ± 2 to 76 ± 5 mm Hg ($P < 0.01$) and left atrial pressure from 7.0 ± 1.4 to 2.2 ± 1.2 mm Hg ($P < 0.01$). When AII and nitroprusside were infused simultaneously, neither arterial (100 ± 4 to 101 ± 5 mm Hg; $P > 0.05$) nor left atrial (4.7 ± 1.3 to 4.2 ± 1.3 mm Hg; $P > 0.05$) pressures changed significantly.

TABLE 4
Effect of Nitroprusside, Alone or in Combination with AII, Saralasin, or Captopril, on Right Atrial Pressure (mm Hg) in Conscious, Sodium-Replete, or Sodium-Depleted Dogs

Protocol	Time (min)						P
	15	30	45	60	75	90	
NP (replete) (5)	0 4 ± 1 7	0 0 ± 1 6	−1 2 ± 1 6	−1 7 ± 1 7	−1 8 ± 1 5	−2.0 ± 1 4	<0.01
NP + AII (replete) (6)	0 8 ± 1 5	0 9 ± 1 5	−0.7 ± 1 6	−1 3 ± 1 7	−2 7 ± 1 8	−3 1 ± 1 6	<0 001
NP (depleted) (6)	−1 3 ± 1 7	−1.4 ± 1 7	−3 8 ± 1 6	−4 3 ± 1.4	−4 6 ± 1 5	−4.5 ± 1 7	<0.001
NP + SAR (depleted) (5)	0 3 ± 1 3	0.5 ± 1.5	−1 2 ± 1 1	−1 0 ± 1 3	−0 8 ± 1 2	−0.8 ± 1.3	<0.05
NP + CAP (depleted) (4)	−1 5 ± 1 6	−2.4 ± 2 1	−3 6 ± 2 0	−3 8 ± 1.9	−4 1 ± 1 5	−4.4 ± 1 2	<0.001

Values are means ± SEM of right atrial pressure (mm Hg) Nitroprusside infusion was begun after 30-minute measurement; angiotensin II, saralasin, and captopril infusions were begun after 15-minute measurement. NP = nitroprusside; AII= angiotensin II; SAR = saralasin, CAP = captopril. Numbers in parentheses = number of dogs in each group.

Discussion

AII and ACTH Secretion

ACTH secretion is increased during hypotensive hemorrhage (Gann et al., 1981) or vasodilator infusion (Rose et al., 1982; Fig. 3) and the logarithm of plasma ACTH concentration is linearly related to the blood pressure fall (Gann et al., 1981; Fig. 3). Because plasma corticosteroid concentration is linearly related to the logarithm of the plasma ACTH concentration (Wood et al., 1982), the relationship between plasma corticosteroid concentration and blood pressure is linear (Fig. 1).

There is evidence that the increase in ACTH and corticosteroid secretion during hypotension is mediated by arterial and atrial mechanoreceptors (Gann et al., 1981). These responses may, in turn, be mediated via corticotropin-releasing factor (CRF), vasopressin, or AII, since these factors are increased by hypotension (Plotsky et al., 1985; Brooks et al., 1986; Table 3) and have been shown to increase ACTH secretion (Ramsay et al., 1978; Rivier et al., 1982). The current studies do not support a major role for AII in sodium-replete animals because angiotensin II receptor blockade with saralasin did not diminish the increase in corticosteroid concentration produced by nitroprusside-induced hypotension. On the other hand, recent studies suggest that both CRF and vasopressin may be necessary for hemorrhage-induced ACTH secretion, since blockade of these factors with either pharmacological inhibitors or a specific antiserum reduced the ACTH response (Carlson and Gann, 1984; Plotsky et al., 1985).

A major finding of the present study was that intravenous AII infusion causes a shift in the relationship between blood pressure and plasma corticosteroid concentration to a higher pressure level or "setpoint." These results suggest that baroreflex control of ACTH secretion is altered in the presence of AII. The slope of the baroreflex curve was slightly decreased in the presence of AII, but this may be because baroreflex function curves are sigmoid, and a different pressure range was studied during AII infusion.

The mechanism of the shift with AII is not clear, but there are three possibilities. First, there is evidence that arterial baroreceptors adapt to changes in arterial pressure (Coleridge et al., 1981; Munch et al., 1983; Heesch et al., 1984). Because AII infusion increases blood pressure, it is possible that the shift in baroreflex curves produced by AII was simply due to the pressor effect. The following observation suggests this is not the case. When the pressor effect of AII was reduced by infusion of increasing doses of nitroprusside, plasma corticosteroid concentration was increased by 4.7 ± 0.9 μg/dl with the highest dose of nitroprusside, which returned pressure to control values. When the highest dose of nitroprusside was administered simultaneously with AII and blood pressure was not altered, the same rise in plasma corticosteroid concentration (5.2 ± 0.7 μg/dl) was observed. These results suggest that the ability of AII to increase corticosteroid concentration and reset the baroreflex is independent of its pressor effect.

A second possible mechanism for the shift may be that AII acts on the brain or pituitary to stimulate ACTH release. During concurrent nitroprusside infusion, blood pressure falls and initiates an additional stimulation of ACTH release that is mediated via the baroreceptors. Thus, at any given blood pressure, ACTH secretion in the presence of AII would be higher and the relationship between blood pressure and ACTH secretion would be displaced to the right.

Another possibility is that AII acts within the baroreflex loop to alter reflex control of ACTH secretion. A finding that favors this hypothesis is that AII causes a similar shift in the relationship between blood pressure and plasma vasopressin concentration (Brooks et al., 1986), between blood pressure and heart rate, and between blood pressure and lumbar sympathetic activity (Guo and Abboud, 1984; Schmid et al., 1985). Thus, AII may act by a common mechanism to affect baroreflex control of heart rate, sympathetic activity, ACTH, and vasopressin secretion. If this is the case, an effect early in the baroreflex arc could explain the similar action of AII on these variables. However, there is evidence that AII does not directly affect activity from either the carotid sinus or aortic arch during changes in pressure (McCubbin et al., 1957; Lumbers et al., 1979; Guo and Abboud, 1984). It is likely, therefore, that AII acts at an area of the brain which is accessible to bloodborne AII and which interacts with medullary cardiovascular control centers. A likely candidate is the area postrema, a circumventricular organ that lacks a blood-brain barrier and that is located in close proximity to and communicates with the nucleus tractus solitarius. The area postrema has been shown to have specific AII receptors (Van Houten et al., 1980) and to mediate some of the cardiovascular effects of AII (Joy and Lowe, 1970).

In these experiments, it was assumed that corticosteroid concentration is a reliable index of ACTH secretion. This assumption appears to be justified because, in some cases, plasma ACTH concentration was also measured and was found to mimic changes in plasma corticosteroid levels. In addition, we have recently reported that the corticosteroid response to AII is blocked by pretreatment with dexamethasone, a steroid that inhibits ACTH secretion (Brooks et al., 1984). These results suggest that ACTH is necessary for the rise in plasma corticosteroids provoked by AII and that plasma corticosteroid concentration is a good index of ACTH secretion.

Although exogenous AII administration stimulates ACTH release, it is not clear if AII is a physiologically important regulator of ACTH secretion. In a previous report, we evaluated the physiological

significance of AII in the control of ACTH secretion by determining whether doses of AII that produce plasma concentrations within the physiological range are sufficient to stimulate ACTH (Reid et al., 1982). We found that supraphysiological levels were necessary, arguing against an important role for AII. It is possible, however, that large doses of exogenous AII were necessary to increase ACTH secretion because the pressor effect of AII, which would be expected to inhibit ACTH release (Ganong et al., 1967; Raff et al., 1983), counteracts a direct stimulatory action of AII. The present experiments favor this hypothesis, since it was found that intravenous AII infusion produced larger increases in plasma corticosteroid and ACTH concentration when the pressor response to AII was abolished by concurrent infusion of the vasodilator, nitroprusside. In circumstances such as hemorrhage and sodium depletion, endogenous AII levels are increased without an increase in blood pressure. The present results indirectly suggest that AII may provide an important input to ACTH secretion in such situations.

It is possible that nitroprusside infusion enhanced the stimulatory effect of AII on ACTH by some action other than by lowering arterial blood pressure. This seems unlikely, however, since an agent which relaxes vascular smooth muscle by another mechanism, hydralazine, was also effective in increasing the corticosteroid response. Furthermore, we have found that there is no corticosteroid response to nitroprusside infusion in dogs with chronic denervation of both high pressure (carotid sinus and aortic arch) and low pressure (cardiopulmonary) baroreceptors. In intact dogs, nitroprusside increased corticosteroid concentration from 2.2 ± 0.5 to 9.7 ± 1.1 μg/dl ($P < 0.01$, $n = 4$), but had no significant effect (2.8 ± 0.9 to 3.8 ± 1.2 μg/dl; $P > 0.10$, $n = 3$) in denervated dogs (Brooks, Quillen, Klingbeil, and Reid, unpublished results). Thus, nitroprusside appears to increase ACTH and corticosteroid levels by activating the baroreceptor reflex. It is also possible that nitroprusside acted to enhance the corticosteroid response to AII by lowering blood pressure and further increasing PRA and plasma AII levels to cause additional stimulation of ACTH. However, plasma AII levels were not increased to higher levels when nitroprusside was infused concurrently with AII. Finally, since there is evidence that atrial stretch receptors affect ACTH release (Gann et al., 1981), it is possible that nitroprusside caused a larger increase in ACTH secretion during AII infusion by decreasing pressure in either atrium below control levels. Although AII infusion had no effect on right atrial pressure, pressure was decreased below control values during nitroprusside infusion and during AII and nitroprusside. However, the smallest dose of nitroprusside tended to decrease right atrial pressure to the lowest level, and in neither case was the fall in pressure correlated with the rise in plasma corticosteroid concentration. This is in sharp contrast to the significant correlation observed between mean arterial pressure and corticosteroid levels. Although the possibility that decreases in right atrial pressure contributed to the enhanced ACTH response to AII during nitroprusside infusion cannot be definitely ruled out, the lack of a correlation between atrial pressure and plasma corticosteroid concentration seems to suggest, first, that decreases in right atrial pressure may not significantly influence ACTH secretion and, second, that the increased corticosteroid response to AII during nitroprusside infusion was not due to the fall in right atrial pressure. In contrast to right atrial pressure, changes in left atrial pressure tended to parallel changes in arterial pressure. Thus, AII may act to inhibit ACTH secretion by increasing left atrial and arterial pressure. When AII and nitroprusside were infused simultaneously, elevated left atrial pressures were decreased to control values, suggesting that nitroprusside may act to increase ACTH secretion by lowering left atrial pressure and by lowering arterial pressure.

A second purpose of the present experiments was to investigate why ACTH secretion does not rise when saralasin decreases blood pressure in sodium-deprived dogs. One hypothesis is that baroreflex function is altered by some aspect of sodium depletion. The reflex tachycardia elicited by carotid occlusion is diminished in sodium-depleted animals (Rocchini et al., 1977; Szilagyi et al., 1981), and the reflex increase in renal nerve activity induced by hypotension is reduced (Takishita and Ferrario, 1982). To examine whether baroreflex control of ACTH and corticosteroid secretion is also affected, we compared the relationship between blood pressure and plasma corticosteroid concentration in sodium-replete and sodium-deprived conscious dogs. The finding that the corticosteroid response to a given decrease in blood pressure was not depressed in sodium-deleted dogs suggests that the reduced corticosteroid response to saralasin-induced hypotension was not the result of sodium depletion affecting baroreflex control of ACTH secretion.

Another possibility is that AII blockade interferes with baroreflex control of ACTH secretion so that the reflex increase in ACTH secretion induced by hypotension is not obtained. The present experiments favor this hypothesis, since both saralasin and captopril caused a shift to the left in the relationship between blood pressure and plasma corticosteroid concentration to a lower blood pressure level or "setpoint." Because endogenous AII levels are elevated in sodium-depleted animals, it might be expected that these animals would exhibit elevated plasma corticosteroid levels, as well as baroreflex function curves that are displaced to the right of curves generated in sodium-replete animals. However, corticosteroid levels and baroreflex curves are similar in replete and depleted dogs (Fig. 6). Furthermore, AII blockade with saralasin does not

alter baroreflex function in sodium-replete dogs (Fig. 5). These results suggest that some factor, perhaps related to the decreased blood volume, displaces the baroreflex curves to a lower pressure in sodium-depleted animals. The elevated levels of AII appear to act to maintain a normal relationship between blood pressure and ACTH by shifting the curves back to a normal pressure level. This is similar to the vasoconstrictor action of the elevated AII levels to maintain a normal, rather than an increased pressure, during sodium depletion.

The mechanism by which captopril and saralasin act to affect baroreflex control of ACTH secretion in sodium-depleted dogs is not clear, but the inhibitors may act by blocking the actions of AII described earlier. First, it was found that when blood pressure was decreased with nitroprusside infusion alone in sodium-depleted dogs, plasma AII levels increased to levels of 174 ± 25 pg/ml. It is possible that these elevated levels of AII, via an action on the brain or pituitary, directly stimulated ACTH release. When either captopril or saralasin was infused along with nitroprusside, this action of AII would be inhibited and a smaller ACTH response for a given decrease in blood pressure would be produced. The result would be a shift to the left in the relationship between blood pressure and ACTH. In this regard, it is interesting that plasma AII levels were increased to only 35 ± 4 pg/ml in sodium-replete dogs, and saralasin infusion did not affect the relationship between blood pressure and corticosteroid concentration in these animals.

Another possible mechanism for the shift produced by AII blockade is that AII acts somewhere within the baroreflex loop to maintain normal reflex control of ACTH secretion in sodium-depleted dogs, and that saralasin and captopril block this effect. Evidence that supports this hypothesis is that saralasin and captopril have been reported to also affect the relationship between blood pressure and vasopressin secretion (Brooks et al., 1986) and between blood pressure and heart rate. This suggests that saralasin and captopril may act by blocking a common action of angiotensin II to alter baroreflex control of heart rate, ACTH, and vasopressin secretion.

Finally, it is emphasized that the effect of AII blockade to displace the baroreflex curves does not appear to be secondary to the hypotensive effect of saralasin or captopril. As shown in Figure 2, a 15-minute infusion of nitroprusside (1.5 μg/kg per min) decreased arterial pressure by almost 20 mm Hg and increased plasma corticosteroid concentration by 7 μg/dl. In contrast, a 15-minute infusion of saralasin lowered blood pressure by almost the same amount, and plasma corticosteroid concentration was unaltered. Thus, angiotensin blockade and nitroprusside infusion have very different effects on plasma corticosteroid concentration, even though they both lower blood pressure. The results of the present experiments suggest that the different effects are due to AII blockade resetting the baroreflex to a lower pressure level while blood pressure is decreased so that ACTH secretion is not stimulated by the hypotension, whereas normal reflex increases in ACTH are produced when blood pressure is reduced with nitroprusside.

In summary, the present experiments provide evidence that AII alters baroreflex control of ACTH secretion by causing a shift in the relationship between blood pressure and plasma corticosteroid concentration to a higher blood pressure level. This effect may be physiologically significant, since blockade of the renin-angiotensin system in sodium-deprived dogs produces an opposite shift. This suggests that endogenous AII is involved in the long-term maintenance of normal baroreflex control of ACTH secretion during sodium depletion. The mechanism of this action is unknown, but may result from either a direct effect of AII to stimulate ACTH release or an action of AII within the baroreflex loop. Finally, exogenous AII produced a greater increase in ACTH release when the pressor effect of AII was abolished. This suggests that infusions of exogenous AII may underestimate the ability of endogenously formed AII to increase ACTH secretion, since AII is normally produced in vivo without an increase in pressure.

AII and Control of Heart Rate

The present results confirm reports that AII infusion alters baroreflex control of the heart (Ismay et al., 1979; Guo and Abboud, 1984). This study further demonstrates that AII acts by displacing the relationship between cardiac pulse interval and blood pressure to the right or by increasing the "setpoint" of the baroreflex, rather than by altering the slope or sensitivity. The present results also confirm a previous report by Hatton et al. (1981) that captopril and saralasin cause a shift in the relationship between blood pressure and pulse interval to a lower blood pressure level in conscious, sodium-depleted dogs. Because the shift is not observed in sodium-replete dogs, this suggests that endogenous AII is involved in baroreflex control of the heart during sodium depletion.

In the study by Hatton et al. (1981), baroreflex function was examined according to the method of Smyth et al. (1969), in which pulse injections of either phenylephrine or nitroglycerine were used to alter blood pressure and pulse interval. A beat-to-beat relationship between these two variables was generated. The effect of AII blockade on this relationship was examined by infusing a converting enzyme inhibitor and, up to 30 minutes later, reassessing baroreflex function. Because AII blockade decreases blood pressure in sodium-depleted dogs, it could be argued that the resetting of the baroreflex in this earlier study was due to a nonspecific resetting of the stretch receptors resulting from the hy-

potension. In the present study, however, the shift in the baroreflex curves does not appear to be secondary to the hypotensive effect of captopril or saralasin administration. Each experiment depicted in Figure 8A was begun with a 15-minute reduction in arterial pressure. In dogs receiving nitroprusside alone, a sustained decrease in pulse interval was associated with the decrease in blood pressure. In dogs given saralasin for 15 minutes, pulse interval did not change. Baroreflex curves generated during saralasin infusion were displaced to a lower blood pressure, whereas the same time interval of nitroprusside-induced hypotension did not have a similar effect. Similarly, in experiments with AII, the effect of AII to alter the baroreflex was not due indirectly to the pressor effect, since similar increases in heart rate were observed when AII was given simultaneously with nitroprusside, and blood pressure was not altered, compared to when nitroprusside was infused 15 minutes or more after the AII infusion was begun. This finding is in agreement with other studies which demonstrated that the effect of AII to reset reflex control of the heart is not dependent on the pressure rise (Guo and Abboud, 1984; Lee et al., 1980).

AII and Plasma Renin Activity

The present results confirm that small decreases in blood pressure stimulate renin secretion in conscious dogs, and that the renin-releasing effect of decreases in blood pressure is enhanced in sodium-depleted dogs (Farhi et al., 1983). In addition, it was demonstrated that AII blockade in sodium-depleted dogs increases PRA, and that this blockade enhances the PRA response to hypotension (Keeton and Campbell, 1980). A new finding in the present study sheds light on the mechanism by which AII decreases renin secretion. At least two possibilities have been proposed (Freeman and Davis, 1979; Keeton and Campbell, 1980). AII may act directly within the kidney to inhibit renin secretion, or indirectly by increasing blood pressure. In the present study, it was found that reducing the pressor effect of AII with nitroprusside infusion did not alter the inhibitory action of AII on PRA. Thus, these results suggest that the pressor response of AII is not needed for the inhibitory action of AII on renin secretion.

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INDEX TERMS. Brain • Renin-angiotensin system • Blood pressure • Corticosteroids • Nitroprusside • Saralasin • Captopril