Chronic Potentiation of Vasoconstrictor Hypertension by Adrenocorticotropic Hormone

THOMAS E. LOHMEIER, PH.D., AND ROBERT G. CARROLL, PH.D.

SUMMARY The chronic effects of ACTH on mean arterial pressure (MAP) and related variables were studied in dogs with both chronic norepinephrine (NE)- and chronic aldosterone-induced hypertension. MAP was recorded continuously for 24 hours/day, and sodium intake was 71 mEq/day. ACTH was infused for 8 days at a rate that does not increase MAP in normotensive dogs and yet a rate that produces pronounced mineralocorticoid and glucocorticoid effects. Chronic ACTH infusion in dogs with NE hypertension caused natriuresis, kaliuresis, diuresis, hypernatremia, hypokalemia, and suppression of PRA; additionally, there was either no net change in water balance or net water balance was positive. However, in marked contrast to dogs without pre-existing hypertension, in dogs with NE hypertension ACTH produced a pronounced additional increase in MAP of 39 to 63 mm Hg. Although ACTH markedly potentiated NE hypertension, high infusion rates of aldosterone (+6 mm Hg) and cortisol (−7 mm Hg) had relatively weak effects on MAP; further, in dogs with NE hypertension, the increase in MAP associated with simultaneous infusion of high rates of cortisol and aldosterone was equal to only approximately half of that produced by ACTH. In dogs with aldosterone hypertension, the changes in salt and water balance produced by ACTH were comparable to those that occurred when ACTH was administered to dogs with NE hypertension. In dogs with aldosterone hypertension, however, ACTH did not produce kaliuresis, hypernatremia, or hypokalemia; moreover, ACTH did not exacerbate aldosterone hypertension. Thus, the data indicate that the hypertensive effects of ACTH are manifested in conditions of reduced renal excretory capacity such as exist when plasma levels of the potent sodium-retaining hormone NE are inappropriately elevated. Finally, the hypertensive effects of ACTH cannot be accounted for simply on the basis of enhanced mineralocorticoid and glucocorticoid activity.

KEY WORDS • ACTH • cortisol • aldosterone • arterial pressure • norepinephrine • sodium balance • potassium balance • water balance

PRECISE mechanisms that contribute to the hypertension produced by ACTH and adrenocortical hormones are not completely understood. The unresolved nature of ACTH- and adrenocortical-hormone hypertension is perhaps best typified by patients with Cushing's syndrome. In these patients, hypertension is a common finding, but the cause of the hypertension has been mainly conjectural. One hypothesis proposed to account for the hypertension of Cushing's syndrome and one that needs to be evaluated critically is that ACTH and/or adrenocortical hormones enhance the vasoconstrictor response to pressor agents like angiotensin II (AII) and norepinephrine (NE). However, the evidence in support of this hypothesis is not only controversial but, moreover, is based merely on the acute vasoconstrictor responses to these pressor agents. Since it has not been determined whether ACTH or high physiological levels of adrenocortical hormones potentiate the long-term hypertensive effects of AII or NE, the significance of these acute observations to the pathogenesis of hypertension in Cushing's syndrome is purely speculative.

Recently, we found that ACTH did not produce consistent changes in mean arterial pressure (MAP) when infused in normotensive dogs; when administered to dogs with chronic AII hypertension it invariably exacerbated the hypertension (unpublished data). Further, this chronic potentiation of AII hypertension by ACTH could not be reproduced by long-term infusion of high doses of either cortisol or aldosterone. This suggests a hypertensinogenic effect of ACTH other than that mediated via enhanced mineralocorticoid or enhanced glucocorticoid activity. However, the arterial pressure effects of simultaneous...
infusion of cortisol plus aldosterone were not determined. These data would be particularly relevant to our contention that ACTH increases arterial pressure by mechanisms distinct from classical glucocorticoid and mineralocorticoid actions.

The purpose of the present study was therefore to determine: whether the potentiation of hypertension by ACTH is specific for the renin-angiotensin system or whether it might also apply to other vasoconstrictor hypertensions such as that induced by NE; 2) whether ACTH might also potentiate the hypertension associated with mineralocorticoid excess, and 3) the quantitative importance of glucocorticoid and mineralocorticoid excess in mediating the hypertensive effects of ACTH. The MAP was measured continuously 24 hours/day to monitor precisely the chronic arterial pressure effects associated with long-term infusion of ACTH and adrenocortical hormones in dogs with both NE- and aldosterone-induced hypertension. Additionally, careful measurements were made of changes in water and electrolyte balance, plasma renin activity (PRA), and adrenal steroidogenesis.

**Methods**

In 14 male dogs weighing 22.6 ± 0.7 (SE) kg, chronic indwelling catheters made of Tygon tubing (Norton) were placed in the femoral artery and vein. The tip of the femoral artery catheter was advanced into the aorta distal to the origins of the renal arteries, and the end of the femoral vein catheter was positioned in the vena cava. A Silastic elbow prevented kinking of the catheters in the femoral area. The catheters were tunneled subcutaneously and exteriorized in the posterior thoracic region.

Two weeks after surgery, the dogs were placed in metabolic pens and fitted with an aluminum and canvas backpack housing a Statham arterial blood pressure transducer (Model P23 ID) at heart level. The electrical connections to the transducer and an intravenous infusion line were brought to the top of the cage through a flexible tube attached to the top of the backpack. Continuous intravenous infusions were made through the femoral vein catheter by means of a Sage tubing pump (model 375A), and MAP was recorded continuously 24 hours/day from the femoral artery catheter on a Grass polygraph (Model 7D).

During the experiment, the dogs were given free access to water and maintained on a fixed daily diet of two 15.5-ounce cans of h/d prescription diet (Hills Pet Nutrition, Topeka, Kansas). Two cans of h/d provided less than 5 mEq/sodium and 45-50 mEq/potassium. Isotonic saline was infused at a rate of 460 ml/day (71 mEq/sodium/day). When appropriate, ACTH (al-24 corticotropin; Cortrosyn, Organon, West Orange, New Jersey), NE (norepinephrine bitartrate; Levophed, Breon, New York, New York), cortisol (hydrocortisone sodium succinate; Solu-Cortef, Upjohn, Kalamazoo, Michigan), and aldosterone (d-al-24 corticotropin; Cortrosyn, Organon, West Orange, New Jersey), NE (norepinephrine bitartrate; Levophed, Breon, New York, New York), aldosterone (d-aldosterone, Ciba, Summit, New Jersey) were added to the saline infusion. Body temperature was measured daily, and ampicillin (Principen, E. R. Squibb and Sons, Princeton, New Jersey) and a trimethoprim-sulfamethoxazole combination (Bactrim, Roche Laboratories, Nutley, New Jersey) were given prophylactically. To promote accurate measurements of 24-hour urinary sodium and potassium excretion rates, the urinary bladder was catheterized daily using aseptic techniques.

Blood samples were taken at 8-9 a.m., 21-22 hours after feeding. In all animals, 5 ml blood samples were taken periodically for measurement of PRA, plasma aldosterone concentration, plasma cortisol concentration, plasma sodium and potassium concentration, plasma protein concentration, and hematocrit. Twenty-four-hour urine collections were made at 11:00 a.m., immediately after bladder catheterization and just prior to feeding. Daily water consumption was also monitored.

**Specific Protocols**

**Series 1: ACTH, Cortisol, and Aldosterone Infusion in Dogs with Norepinephrine Hypertension**

Five dogs were subjected to the following sequence of infusions: 1) saline control (10-14 days); 2) NE (6 days); 3) NE plus ACTH (8 days); 4) NE recovery (5 days); 5) NE plus cortisol (7 days); 6) NE recovery (7 days); and 7) NE plus aldosterone (7 days). Hormonal infusion rates were as follows: NE, 0.4 µg/kg/min (free base); ACTH, 600 µg/day; cortisol, 45 mg/day; and aldosterone, 9 µg/kg/day.

**Series 2: ACTH Infusion in Dogs with Aldosterone Hypertension**

Five dogs were infused as follows: 1) saline control (10-14 days); 2) aldosterone (10 days); 3) aldosterone plus ACTH (7 days); 4) aldosterone recovery (7 days); and 5) saline recovery (7 days). The infusion rates of aldosterone and ACTH were 9 µg/kg/day and 600 µg/day, respectively.

**Series 3: ACTH and Cortisol plus Aldosterone Infusion in Dogs with NE Hypertension**

Four dogs were infused as follows: 1) saline control (10-14 days); 2) NE (6 days); 3) NE plus ACTH (8 days); 4) NE plus aldosterone and cortisol (7 days); and 5) NE plus ACTH recovery (5 days). Hormonal infusion rates were as follows: NE, 0.4 µg/kg/min; ACTH, 600 µg/day; cortisol, 90 mg/day; and aldosterone, 12 µg/kg/day (first 3 days) and 16 µg/kg/day (last 4 days).

**Analytical Methods**

Commercially available radioimmunoassay kits from New England Nuclear (North Billerica, Massachusetts) were used to measure PRA (angiotensin I [125I] RIA kit) and plasma cortisol concentration.
Cortisol 

PRA is expressed as nanograms of angiotensin I (A1) generated per milliliter of plasma per hour incubation (ngA1/ml/hour). Plasma aldosterone concentration was determined by the radioimmunoassay method of Bühler et al. Plasma and urine concentrations of sodium and potassium were determined by flame photometry (Instrumentation Laboratory, IL 343, Lexington, Massachusetts) and plasma protein concentration by refractometry (American Optical, Buffalo, New York).

The MAP was recorded continuously on a Grass recorder and simultaneously on a PDP 11/70 Digital Equipment Corporation (Maynard, Massachusetts) computer using an analog-to-digital converter. The analog signal from the Grass recorder was sampled every 60 seconds and the digitzed information was used by the computer to calculate hourly values for MAP based on 60 sample points per hour. The daily values presented for MAP were calculated from the 960 data points generated during the 16-hour period extending from 4:00 p.m. to 8:00 a.m.

All values presented are means ± the standard error. Control data were compared with experimental data by using Dunnet's paired t test for multiple comparisons. Statistical significance was considered to be p < 0.05.

Results

Series 1: Effects of ACTH, Cortisol, and Aldosterone Infusion in Dogs with Norepinephrine Hypertension

Effects of Norepinephrine Infusion in Normotensive Dogs

The changes in MAP, water consumption, and urinary sodium, potassium, and water excretion that occurred during NE infusion are shown in figure 1. Within 24 hours of NE infusion, MAP increased from 104 ± 2 to 120 ± 2 mm Hg; MAP remained at this hypertensive level during the next 5 days of NE infusion. In contrast to MAP, there were no statistically significant changes in urinary sodium excretion, urinary potassium excretion, urine excretion, or water consumption during Days 1 through 6 of NE infusion with the following exception: sodium and water balance were negative (approximately 37 mEq and 100 ml, respectively) on Day 1 and positive (approximately 10 mEq and 250 ml, respectively) on Day 2 of NE infusion.

As shown in figure 2, there were no statistically significant changes in plasma cortisol concentration, plasma aldosterone concentration, PRA, plasma sodium concentration, plasma potassium concentra-
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Effects of ACTH Infusion in Dogs with Norepinephrine Hypertension

During ACTH infusion in dogs with NE hypertension, there were large increases in MAP, urinary sodium excretion, urinary potassium excretion, urine excretion, and water consumption (fig. 1). Although there was no measurable change in MAP during the first 24 hours of ACTH infusion, by Day 2 of ACTH, MAP was 15-20 mm Hg higher than when NE was infused alone. Subsequently, MAP continued to increase for the duration of the ACTH infusion period, and on the last day of ACTH administration, MAP was 39 ± 4 mm Hg (158 ± 8 mm Hg) above the level achieved with NE infusion alone. Within 48 hours after termination of ACTH, MAP returned to the hypertensive level that existed prior to ACTH infusion. Sodium and potassium balance were negative throughout the ACTH infusion period, and for the 8 days of ACTH administration there was a net loss of 320 mEq of sodium and 200 mEq of potassium. Urine excretion doubled during the first 24 hours of ACTH infusion and then increased progressively throughout the infusion period to approximately 14 times that of control on the last day of ACTH infusion. Water consumption also increased markedly. Although daily water balance was negative during the initial days of ACTH infusion, on subsequent days it was distinctly positive, and, consequently, there was no significant change in net water balance for the 8 days of ACTH infusion.

The changes in PRA and in the plasma concentrations of cortisol, aldosterone, sodium, potassium, and protein that occurred during ACTH infusion in dogs with NE hypertension are shown in figure 2. As expected, during chronic ACTH infusion there was a marked and sustained increase in plasma cortisol concentration (from a control value of 1.1 ± 0.1 to 14.3 ± 1.6 μg/dl). However, unexpectedly, chronic ACTH infusion also produced a sustained (twofold) increase in plasma aldosterone concentration. The changes in PRA, plasma sodium concentration, and plasma potassium concentration that occurred during ACTH infusion are shown in figure 2.

**Figure 2.** Effects of chronic ACTH infusion on plasma cortisol concentration, plasma aldosterone concentration, plasma renin activity, plasma sodium concentration, plasma potassium concentration, and plasma protein concentration in dogs with norepinephrine hypertension. Values are means ± se, n = 5.
Effects of Cortisol and Aldosterone Infusion in Dogs with Norepinephrine Hypertension

In contrast to ACTH, cortisol and aldosterone had relatively weak effects on MAP in dogs with NE hypertension (fig. 3). Additionally, the effects of cortisol on MAP, and sodium and water balance were diametrically opposite to those of aldosterone: cortisol caused sodium depletion, water depletion, and hypotension, whereas aldosterone produced sodium and water retention, and hypertension. MAP decreased significantly during cortisol infusion (7 ± 2 mm Hg); this hypotensive response was associated with a net cumulative loss of 110 mEq of sodium and approximately 1000 ml of water. In contrast to cortisol, aldosterone produced sodium (approximately 350 ml) retention and a small but statistically significant increase in MAP of 6 ± 2 mm Hg. Urine excretion and water consumption increased significantly during both cortisol and aldosterone infusion. Similarly, both hormones increased urinary potassium excretion, particularly during the first 24 hours of hormone infusion; however, only the cumulative urinary loss of potassium induced by cortisol infusion (30 mEq/potassium) was statistically significant.

The effects of cortisol and aldosterone on plasma cortisol concentration, plasma aldosterone concentration, PRA, plasma sodium concentration, plasma potassium concentration, and plasma protein concentration in dogs with NE hypertension are shown in figure 4. Cortisol and aldosterone had opposite effects on these variables, and, in general, the changes produced by aldosterone were similar to those induced by ACTH. During cortisol infusion, there was a four-fold increase in plasma cortisol concentration but no measurable change in plasma aldosterone concentration, PRA, or plasma sodium concentration. Additionally, cortisol produced a significant increase in plasma potassium concentration (0.2 ± 0.1 mEq/liter) and plasma protein concentration (0.6 ± 0.1 g/dl), and a significant decrease in hematocrit (3% ± 1%).

When aldosterone was infused in dogs with NE hypertension, plasma aldosterone concentration increased about fourfold while plasma cortisol concent-
tation was unchanged. Further, aldosterone failed to reproduce the arterial pressure effects of ACTH, but the changes in PRA, plasma sodium concentration, plasma potassium concentration, and hematocrit that occurred during aldosterone infusion were similar both qualitatively and quantitatively to those produced by ACTH with one exception: the fall in PRA associated with aldosterone administration was greater than that produced by ACTH. However, in contrast to both ACTH and cortisol, aldosterone significantly decreased plasma protein concentration (0.5 ± 0.1 g/dl), which increased plasma protein concentration.

Series 2: Effects of ACTH Infusion in Dogs with Aldosterone Hypertension

Effects of Aldosterone Infusion in Normotensive Dogs

The effects of aldosterone were similar quantitatively to those observed in one of our earlier studies where the same rate of aldosterone was infused chronically in dogs maintained on a comparable sodium and potassium intake. The effects of aldosterone infusion on MAP, urinary sodium excretion, urinary potassium excretion, urine excretion, and water consumption are shown in figure 5. During the initial 10 days of aldosterone infusion, MAP increased progressively to 14 ± 3 mm Hg above control on Day 10. Aldosterone-induced hypertension was associated with net sodium (73 mEq) and water (675 ml) retention, and a cumulative urinary loss of 35 mEq of potassium. After an initial period of water retention, urine excretion gradually increased throughout the aldosterone infusion period to almost two times control on Day 10; simultaneously, water consumption increased progressively during the initial 10 days of aldosterone administration.

The changes in plasma cortisol concentration, plasma aldosterone concentration, PRA, plasma sodium concentration, plasma potassium concentration, and plasma protein concentration observed during aldosterone infusion can be seen in figure 6. As expected, the infusion rate of aldosterone employed increased plasma aldosterone concentration to approximately 4 to 5 times the control level but did not change plasma cortisol concentration. Additionally, after 10 days of aldosterone infusion, plasma sodium concentration was elevated 4 ± 1 mEq/liter, plasma potassium concentration was reduced 1.4 ± 0.2 mEq/liter, and PRA was suppressed to undetectable levels; all of these changes were statistically significant. Plasma protein concentration and hematocrit were unchanged during aldosterone administration.

![Figure 4. Effects of chronic cortisol and chronic aldosterone infusion on plasma cortisol concentration, plasma aldosterone concentration, plasma renin activity, plasma sodium concentration, plasma potassium concentration, and plasma protein concentration in dogs with norepinephrine hypertension. Values are means ± SE, n = 5.](http://hyper.ahajournals.org/doi/fig)
**Effects of ACTH Infusion in Dogs With Aldosterone Hypertension**

The effects of ACTH infusion on MAP, urinary sodium excretion, urinary potassium excretion, and water consumption in dogs with aldosterone hypertension are shown in figure 5. In contrast to the marked potentiation of norepinephrine-induced hypertension by ACTH (fig. 1), ACTH failed to increase the severity of hypertension associated with aldosterone infusion. In fact, MAP actually decreased significantly (6 ± 2 mm Hg) during the first 24 hours of ACTH infusion in dogs with aldosterone hypertension; subsequently, MAP increased progressively to the hypertensive level achieved prior to ACTH infusion. In spite of the initial hypotensive response to ACTH, urinary sodium excretion increased during the first 24 hours of ACTH infusion in dogs with aldosterone hypertension; subsequently, MAP increased progressively to the hypertensive level achieved prior to ACTH infusion. In spite of the initial hypotensive response to ACTH, urinary sodium excretion increased during the first 24 hours of ACTH infusion; and on all subsequent days except Day 2, urinary sodium excretion exceeded sodium intake. Consequently, as in dogs with NE hypertension, net sodium balance was distinctly negative (310 mEq) during the ACTH infusion period. Although urine excretion increased to almost four times the level achieved with aldosterone infusion alone, water consumption also increased during ACTH administration, and for the 8-day ACTH infusion period, there was no significant change in net water balance. In contrast to the marked potassium depletion induced by ACTH in dogs with NE hypertension, ACTH failed to produce a significant change in cumulative potassium balance in dogs with aldosterone hypertension.

Of the variables measured in the plasma, only plasma cortisol concentration changed significantly during ACTH infusion in dogs with aldosterone hypertension (fig. 6). The increase in plasma cortisol concentration achieved by ACTH infusion was comparable in dogs with aldosterone- and NE-hypertension (fig. 2).

**Series 3: Effects of Cortisol Plus Aldosterone Infusion in Dogs with Norepinephrine Hypertension**

During the initial 6 days of NE infusion and during the subsequent 8 days of NE plus ACTH infusion, the changes in all measured variables were comparable to those observed in Series 1 animals given NE plus ACTH (figs. 1 and 2) with the following exceptions. In the present series, when ACTH was infused in dogs with NE hypertension, cumulative water balance was more positive (approximately 1,000 ml), PRA was suppressed to a greater degree (to undetectable levels), and the potentiation of NE hypertension was more severe (54 vs 39 mm Hg in Series 1 animals).

The changes in MAP, plasma cortisol concentration, plasma aldosterone concentration, PRA, plasma sodium concentration, and plasma potassium concentration associated with ACTH and cortisol plus aldosterone...
terone in dogs with NE hypertension can be seen in figure 7. When the infusion of ACTH was terminated and replaced immediately by cortisol plus aldosterone, MAP fell dramatically (30-35 mm Hg) within 1 to 2 hours. For the entire 7 days of cortisol plus aldosterone infusion, MAP remained 20-25 mm Hg below the hypertensive level achieved with ACTH (Day 14) in spite of the fact that: 1) plasma cortisol concentration and PRA were comparable to that achieved with ACTH infusion; and 2) plasma aldosterone concentration was very high (about 10 times control levels). In fact, the plasma electrolyte data indicate that a greater mineralocorticoid effect was achieved during infusion of cortisol plus aldosterone than during ACTH. When cortisol plus aldosterone infusion was terminated on Day 24 and ACTH initiated once again, MAP increased 15-20 mm Hg within 1-2 hours. Over the subsequent 5 days of ACTH infusion, MAP increased progressively to 30 mm Hg above the level associated with cortisol plus aldosterone infusion, and to 63 mm Hg above the level achieved with norepinephrine infusion alone (Day 6).

During the 7 days of cortisol plus aldosterone infusion, daily urinary sodium, potassium, and water excretion averaged 106 ± 8 mEq, 53 ± 3 mEq, and 5415 ± 310 ml, respectively. These values were comparable to those observed during the two ACTH infusion periods with the exception of urinary potassium excretion (43 ± 4 mEq) during the second ACTH infusion period. On the last two days of the initial ACTH infusion period (Days 7 and 8), daily water balance was distinctly positive (averaging approximately +600 ml per day). During the subsequent cortisol plus aldosterone and ACTH infusion periods, water balance remained positive but the retention of water was greatly attenuated, averaging approximately a total of 200-300 ml for each of the two infusion periods.

Discussion

A most important finding in this study is that ACTH markedly potentiates the long-term hypertensive effects of NE but not those of aldosterone. However, this hypertensive response to chronic ACTH excess is not specific for NE hypertension; it also occurs in dogs with AIH hypertension (unpublished data). In contrast, ACTH does not produce hypertension when administered over comparable periods of time in dogs without pre-existing hypertension (unpublished data).9 Thus, our recent findings indicate that the hypertensive effects of ACTH are manifested when there is reduced renal excretory capacity such as exists when plasma levels of the potent sodium-retaining hormones, AIH, and NE are inappropriately elevated. In corroboration of this hypothesis is the observation that ACTH-induced hypertension is potentiated in
Figure 7. Effects of chronic ACTH and cortisol plus aldosterone infusion on mean arterial pressure, plasma cortisol concentration, plasma aldosterone concentration, plasma renin activity, plasma sodium concentration, and plasma potassium concentration in dogs with norepinephrine hypertension. Values are means ± SE, n = 4.

Sheep with surgical reduction of renal mass. Also, the observation that an increase in arterial pressure is much more likely to occur during the administration of high doses of glucocorticoids (doses which exhibit mineralocorticoid effects) in patients with renal disease than in patients without renal disease is also consistent with this hypothesis.

The present study also provides some insight into the mechanisms that contribute to the long-term hypertensive effects of ACTH. First, although ACTH produced marked and sustained increases in plasma cortisol concentration, enhanced glucocorticoid activity apparently cannot account for the hypertensive effects of ACTH. In fact, our data in the dog indicate that cortisol is a hypotensive agent by virtue of its renal actions that favor salt and water depletion. In the present study, when high rates of cortisol were infused in dogs with NE hypertension, MAP actually decreased. Further, chronic hypotension also occurred when high rates of cortisol were infused in normotensive dogs; and, in dogs with AII hypertension, cortisol did not increase the severity of the hypertension (unpublished data). It should be emphasized that the high infusion rates of cortisol employed in these studies were apparently devoid of mineralocorticoid activity, yet they produced large increases in plasma cortisol concentration comparable to those achieved with ACTH. Others have also found that chronic administration of high physiological doses of cortisol or cortisone in experimental animals produces little or no hypertension. These findings in experimental animals, taken together with the observation that there is a low incidence of hypertension during glucocorticoid therapy in patients without renal disease, suggest that excess glucocorticoid activity is not importantly involved in mediating ACTH hypertension or in the pathogenesis of hypertension in Cushing’s syndrome.

Our studies also indicate that enhanced mineralocorticoid activity contributes to the hypertension associated with ACTH infusion. However, additional factors are also importantly involved in mediating the hypertensive effects of ACTH. When aldosterone was infused at high rates in dogs with NE hypertension and plasma aldosterone concentration increased to approximately four times normal (Series 1), mineralocorticoid effects comparable to those produced by ACTH were achieved, but the hypertension produced by aldosterone was quite modest in comparison to ACTH (7 vs 39 mm Hg). Similarly, infusion of aldosterone at this same elevated rate in dogs with AII hypertension produced marked mineralocorticoid effects but no further increase in MAP. In contrast, when ACTH was infused in dogs with AII hypertension, MAP increased an additional 16 mm Hg (manuscript submitted for publication). Additionally, in the present study, dogs with NE hypertension were infused with very high rates of aldosterone simul-
taneously with enough cortisol to increase plasma cortisol concentration to levels comparable to those achieved with ACTH. Even though plasma aldosterone concentration increased to approximately 10 times normal and produced mineralocorticoid effects greater than those achieved during ACTH administration, the increase in arterial pressure associated with enhanced mineralocorticoid and enhanced glucocorticoid activity was equal to only approximately half of that produced by ACTH. Thus, the hypertensive effects of ACTH cannot be accounted for simply by enhanced glucocorticoid and enhanced mineralocorticoid activity.

Theoretical and experimental evidence indicates that a prerequisite for sustained chronic hypertension is a reduction in renal excretory capacity such that a higher arterial pressure level is required to achieve fluid balance. Indeed, fluid balance was much more positive and the hypertension was much more severe when ACTH was administered to dogs with NE hypertension than when infused in dogs without pre-existing hypertension. In the present study, there was either no net change in water balance or water balance was positive during the 8 days of ACTH in fusion in dogs with NE hypertension. In contrast, when ACTH was infused at the same rate for 10 days in normotensive dogs maintained on a comparable sodium intake, water balance was distinctly negative and arterial pressure was unchanged (unpublished data). However, in spite of the negative sodium and water balance, extracellular fluid volume was expanded (unpublished data). Thus, in normotensive dogs infused with ACTH, some of the fluid shifted from the intracellular space (due to cortisol excess) is retained in the extracellular fluid compartment. Presumably, since dogs with NE hypertension did not exhibit negative water balance during ACTH administration, more of the fluid shifted from the intracellular space was retained in the extracellular fluid compartment, resulting in a marked increase in arterial pressure.

Unfortunately, our experiments provide little information regarding the extra mineralocorticoid and glucocorticoid factor that is responsible for producing the alterations in renal function that contribute to the hypertension associated with ACTH infusion. One interesting observation, however, was the rapid changes in arterial pressure that occurred in dogs with NE hypertension when the ACTH and aldosterone plus cortisol infusions were interchanged (Series 3). When the ACTH infusion was terminated and immediately replaced by an infusion of high rates of aldosterone plus cortisol, MAP decreased dramatically by 30–35 mm Hg within 1–2 hours. Similarly, when the aldosterone plus cortisol infusion was switched to ACTH, MAP increased 15–20 mm Hg within 1–2 hours. One possible explanation for these rapid changes in arterial pressure is that ACTH stimulates the secretion of a vasoconstrictor agent. Since PRA was suppressed to undetectable levels and since plasma catecholamine concentration was very high throughout these infusion changes, it is tempting to suggest that vasopressin (particularly in the light of current interest in vasopressin as a hypertensive hormone) might be that vasoconstrictor agent. Alterations in plasma vasopressin concentration might account not only for the rapid changes in arterial pressure observed when ACTH infusion was terminated and initiated but also high plasma vasopressin levels might contribute to the chronic fluid retention associated with ACTH infusion in dogs with NE hypertension. Additionally, it has been reported that vasopressin potentiates the pressor effects of NE. On the other hand, we have recently concluded from long-term infusions of high rates of vasopressin in normotensive dogs and in dogs with both AII- and aldosterone-induced hypertension, that vasopressin is not an important long-term hypertensive hormone.

In the hypertensive models studied, variations in plasma vasopressin concentration (induced by infusion) were associated with rather pronounced acute effects on MAP, but the long-term changes in MAP produced by vasopressin were either minimal or non-existent. However, the chronic arterial pressure effects of vasopressin in dogs with NE hypertension have not yet been studied.

It is of great interest that the Australian group from the Howard Florey Institute have also concluded from their extensive studies that the hypertensive effects of ACTH and adrenocortical hormones are not simply related to enhanced mineralocorticoid or glucocorticoid activity. In the sheep, where ACTH infusion alone produces chronic hypertension, simultaneous infusion of cortisol, corticosterone, 11-deoxycorticisol, deoxytrycortisone, and aldosterone at rates that produce plasma concentrations similar to those observed with ACTH infusion produces an increase in arterial pressure equal to only approximately 50% of that achieved with ACTH. Additionally, these investigators have identified two additional steroids, 17a-hydroxyprogesterone and 17a, 20a-dihydroxyprogesterone, from the adrenal venous blood of ACTH hypertensive sheep. Infusion of these two additional steroids, together with the above-mentioned steroids, reproduced the effects of ACTH on arterial pressure. However, 17a-hydroxyprogesterone and 17a, 20a-dihydroxyprogesterone apparently exert their hypertensive effects by mechanisms distinct from classical glucocorticoid and mineralocorticoid actions. It will be particularly interesting to determine whether the hypertensive effects of ACTH in dogs with NE hypertension are entirely adrenal dependent.

In light of our recent data, the fact that ACTH did not potentiate the hypertension associated with aldosterone excess was not too surprising. First, one would not expect this hypertensive mechanism to be very potent in dogs with already high plasma levels of aldosterone since enhanced mineralocorticoid activity contributes significantly to the hypertensive effects of ACTH. Second, our data indicate that impaired renal excretory capacity is a prerequisite for the manifestation of ACTH-induced hypertension in the dog. Since aldosterone has less capacity to produce alterations in renal function that favor hypertension than do AII and NE, one might predict less hypertension with
ACTH in dogs with aldosterone hypertension than in dogs with the vasoconstrictor hypertensions. Finally, in the dog, suppression of PRA and plasma NE concentration are important compensatory responses to ACTH excess which apparently oppose the hypertensive effects of ACTH. When these compensatory responses cannot function appropriately, such as during chronic AII and NE infusion, the hypertensive effects of ACTH are amplified. In contrast, suppression of mineralocorticoid activity is not a compensatory response to ACTH infusion, but enhanced mineralocorticoid secretion actually contributes to the hypertension induced by ACTH. Thus, ACTH infusion in dogs with aldosterone hypertension did not increase the severity of the hypertension. In fact, transient hypotension was observed, probably secondary to increased cortisol secretion.

In summary, we found that chronic infusion of ACTH at a rate that does not increase MAP in normotensive dogs markedly potentiates the hypertension associated with chronic NE infusion but does not increase the severity of aldosterone-induced hypertension. Further, although ACTH produced pronounced mineralocorticoid and glucocorticoid effects, mineralocorticoid and glucocorticoid excess could account for, at best, only approximately half of the hypertension achieved with ACTH administration. Additionally, we found no evidence that the hypercortisolism associated with chronic ACTH excess contributes to ACTH-induced hypertension. In fact, it appears that cortisol excess favors hypotension by virtue of its renal actions that favor natriuresis and diuresis. Thus, our data indicate that the hypertensive effects of ACTH are manifested in conditions of reduced renal excretory capacity such as exist when plasma levels of the potent sodium-retaining hormones, AII and NE, are inappropriately elevated.

Therefore, subtle alterations in renal function may predispose one to the development of severe hypertension during ACTH and/or adrenocortical hormone excess. Further, renal functional status may be an important determinant of the severity of hypertension in patients with Cushing's syndrome. Finally, the hypertensive effects of ACTH cannot be accounted for simply on the basis of enhanced mineralocorticoid and enhanced glucocorticoid activity.

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References


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