Chronic Effects of ACTH and Cortisol Excess on Arterial Pressure in Normotensive and Hypertensive Dogs

THOMAS E. LOHMEIER, PH.D., AND PHILIP R. KASTNER, PH.D.

SUMMARY The chronic effects of ACTH and cortisol on mean arterial pressure (MAP) and related variables were studied in normotensive dogs and, subsequently, in the same dogs after they had been made hypertensive by chronic infusion of angiotensin II (All). MAP was recorded continuously, 24 hours/day, and sodium intake was 71 mEq/day. In both normotensive and hypertensive dogs, 8 to 10 days of ACTH infusions caused natriuresis, kaliuresis, diuresis, hypernatremia, and hypokalemia; additionally, plasma renin activity (PRA) was suppressed to undetectable levels. During ACTH infusion there was a sustained 12-fold increase in plasma cortisol concentration, but only a transient elevation in plasma aldosterone concentration; this steroidogenic response occurred even in dogs with All hypertension where plasma All concentration was maintained at elevated levels by infusion. In normotensive dogs, increases in MAP were not consistently observed during ACTH infusion, whereas, in dogs with All hypertension, ACTH invariably exacerbated the hypertension (ΔMAP = +16 mm Hg). Cortisol infusion, like ACTH infusion, caused a 12-fold increase in plasma cortisol concentration, and negative sodium and water balance; however, cortisol did not produce kaliuresis, hypokalemia, suppression of PRA, or hypertension. In fact, cortisol induced chronic hypotension (ΔMAP = −7 mm Hg) when infused in normotensive dogs, and in dogs with All hypertension there were no detectable changes in MAP during cortisol treatment. Thus, the changes in plasma cortisol concentration and PRA that accompany ACTH infusion do not mediate, but seem actually to oppose, the hypertensive effects of ACTH. Indeed, when ACTH was infused in hypertensive dogs with fixed plasma levels of All, the hypertensive effects of ACTH were manifested. Finally, failure of chronic ACTH administration to maintain an elevated secretion rate of aldosterone cannot be attributed to suppression of PRA. (Hypertension 4: 652-661, 1982)

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

SINCE Harvey Cushing first drew attention to the clinical syndrome that bears his name, the high incidence of hypertension in patients with Cushing's syndrome has become widely recognized. Although it has been almost 50 years since Cushing's original findings, the precise mechanisms whereby ACTH and adrenocortical hormones produce hypertension have not been elucidated. One mechanism usually suggested to contribute to the hypertension of Cushing's syndrome is salt and water retention secondary to enhanced secretion of mineralocorticoid hormones other than aldosterone. The importance of increased mineralocorticoid activity to the pathogenesis of the hypertension has been mainly conjectural.

The role of glucocorticoid excess in the etiology of hypertension in Cushing's syndrome is even more uncertain and controversial. Although pharmacological doses of glucocorticoids produce hypertension in the rat, in man and in other experimental animals high physiological levels of glucocorticoids usually produce little or no change in arterial pressure. Since high plasma levels of glucocorticoids would be expected to exert significant mineralocorticoid activity, this action of glucocorticoids could account for glucocorticoid hypertension. Additionally, the hypertension associated with glucocorticoid excess has been attributed to 1) activation of the renin-angiotensin system due to increased renin substrate production; 2) redistribution of body fluids; or 3) increased vascular reactivity...
to vasoconstrictor substances such as angiotensin II (All) and norepinephrine. At present, however, there is still no definitive evidence that indicates that any of these latter mechanisms are involved in the genesis of glucocorticoid hypertension or in the pathogenesis of hypertension in Cushing's syndrome.

Because of the variable effects of ACTH and adrenocortical hormones on arterial pressure and related variables that have been reported, and because, in general, the mechanisms that are quantitatively important in the pathogenesis of hypertension in Cushing's syndrome are unknown, we have compared the effects of chronic ACTH and cortisol infusion in normotensive dogs. Additionally, since several in vitro and in vivo studies have demonstrated that ACTH and/or adrenocortical hormones enhance the acute vasoconstrictor responses to agents such as norepinephrine and All, and since the hypertensive effects of ACTH and adrenocortical hormones are potentiated in man and in experimental animals with reduced renal excretory capacity, we have also been able to determine whether ACTH or high physiological levels of adrenocortical hormones potentiate the long-term hypertensive effects of All. Finally, to delineate the glucocorticoid effects associated with ACTH excess, cortisol was infused at a rate sufficient to achieve an elevated plasma cortisol concentration comparable to that observed during chronic ACTH infusion. Mean arterial pressure (MAP) was measured continuously 24 hours/day, to monitor precisely the chronic arterial pressure effects associated with long-term infusion of ACTH and cortisol; additionally, careful measurements were made of changes in water and electrolyte balance, plasma renin activity (PRA), and adrenal steroidogenesis.

Methods

Five male dogs weighing 22.9 ± 1.1 (se) kg were used in this study. Chronic indwelling catheters made of Tygon tubing (Norton, Akron, Ohio) were placed in the femoral artery and vein. The tip of the femoral artery catheter was advanced into the aorta distal to the region. 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, Statham Laboratories, Inc., Hato Rey, Puerto Rico) 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, Sage Instruments, Cambridge, Massachusetts), and MAP was recorded continuously 24 hours/day from the femoral artery catheter on a Grass polygraph (Model 7D, Grass Instrument Company, Quincy, Massachusetts).

During the experiment, the dogs were given free access to water and maintained on a fixed daily diet of two 15.5 oz cans of h/d prescription diet (Hills Pet Products, Inc., Topeka, Kansas). Two cans of h/d provide less than 5 mEq sodium and 45 to 50 mEq potassium. Isotonic saline was infused at a rate of 460 ml/day (71 mEq sodium/day). When appropriate, ACTH (α 1–24 corticotropin, Cortrosyn, Organon, West Orange, New Jersey), All ([ASP₁-NH₂-Val₃]All, Ciba Pharmaceutical Company, Summit, New Jersey), and cortisol (hydrocortisone sodium succinate, Solu-Cortef, Upjohn Pharmaceutical Company, Kalamazoo, Michigan) 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 obtain accurate measurements of 24-hour urinary sodium and potassium excretion rates, the urinary bladder was catheterized daily using aseptic techniques.

Experimental Protocol

The five dogs were subjected to the following sequence of infusions: saline control (10 to 14 days); ACTH (10 days); saline recovery (10 days); cortisol (10 days); saline recovery (8 days); All (6 days); All + ACTH (8 days); All recovery (5 days); All + cortisol (8 days); All recovery (6 days); and saline recovery (7 days). Hormonal infusion rates were as follows: ACTH, 600 µg/day; cortisol, 45 mg/day; and All, 5 ng/kg/min. At 8–9 a.m., 21 to 22 hours after feeding, 4 to 5 ml blood samples were taken intermittently for measurement of PRA, plasma aldosterone concentration, plasma cortisol concentration, plasma sodium and potassium concentration, plasma protein concentration, and hematocrit. At 11:00 a.m., 24-hour urine collections were made immediately after daily bladder catheterization and just prior to feeding. Daily water consumption was also monitored.

Analytical Methods

Commercially available radioimmunoassay kits were used to measure PRA (Angiotensin I [¹²⁵I] RIA Kit, New England Nuclear, North Billerica, Massachusetts) and plasma cortisol concentration (Cortisol [¹₂⁵I] RIA Kit, New England Nuclear, North Billerica, Massachusetts). PRA is expressed as nanograms of angiotensin I (AI) generated per milliliter of plasma per hour incubation (ng AI/ml/hr). Plasma aldosterone concentration was determined by the radioimmunoassay method of Bühlcr et al. Plasma and urine concentrations of sodium and potassium were determined by flame photometry (IL 343, Instrumentation Laborato-
HYPERTENSION VOL 4, No 5, SEPTEMBER-OCTOBER 1982

ries, Watertown, 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 computer (Digital Equipment Corporation, Maynard, Massachusetts) using an analog-to-digital converter. The analog signal from the Grass recorder was sampled every 60 seconds, and the digitized 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 are 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 mean ± 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

Effects of ACTH in Normotensive Dogs

The effect of ACTH on MAP is shown in figure 1. After 10 days of ACTH infusion, MAP was elevated from a control value of 110 ± 3 to 117 ± 4 mm Hg; however, due to the variability in the arterial pressure response to ACTH, this 7 mm Hg increase in MAP was not statistically significant. In three of five dogs, there was either no measurable change in MAP or only a very small increase in MAP (3 mm Hg, or less), whereas, in another dog, MAP increased as much as 25 mm Hg by the end of the ACTH infusion period.

During ACTH infusion, urinary excretion rates of sodium, potassium, and water were elevated significantly (fig. 1). Throughout the 10 days of ACTH infusion, daily sodium and potassium balance was negative, particularly on Day 1. On the last day of the control period, urinary sodium and potassium excretions were 66 ± 2 and 55 ± 1 mEq/day respectively; during the 10-day period of ACTH infusion, urinary sodium excretion averaged 91 ± 4 mEq/day and urinary potassium excretion, 74 ± 4 mEq/day. Thus, after 10 days of ACTH infusion there was a net cumulative loss of approximately 250 mEq sodium and 190 mEq potassium. Urine excretion almost doubled during the first 24 hours of ACTH infusion and increased progressively during the infusion period to approximately six times the control value on Day 10 (control = 824 ± 62 ml/day). Water consumption also increased progressively during ACTH infusion but not as much as urine excretion; consequently, water balance was negative. The greatest daily water deficit was achieved on Day 1 (about 500 ml), and for the entire 10 days of ACTH infusion, cumulative negative water balance was approximately 800 ml.

The changes in PRA and in the plasma concentrations of cortisol, aldosterone, sodium, potassium, and protein that occurred during ACTH infusion are shown in figure 2. As expected, during chronic ACTH infu-

![Figure 1](http://hyper.ahajournals.org/)

**Figure 1.** Effects of chronic ACTH infusion on mean arterial pressure, urinary sodium excretion, urinary potassium excretion, urine excretion, and water consumption. Values are means ± se, n = 5. * indicates p < 0.05 vs Day 0.

![Figure 2](http://hyper.ahajournals.org/)

**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. Values are means ± se, n = 5. * indicates p < 0.05 vs Day 0.
There was a marked and sustained increase in plasma cortisol concentration but only a transient (3 to 5-day) elevation in plasma aldosterone concentration. Control values for plasma aldosterone concentration were 3.3 ± 1.0 and 4.8 ± 2.1 ng/dl, and for plasma cortisol concentration, 1.3 ± 0.4 and 1.4 ± 0.2 µg/dl; after 10 days of ACTH infusion, plasma cortisol concentration was elevated approximately 12-fold (to 15.7 ± 2.4 µg/dl), while plasma aldosterone concentration (5.0 ± 0.4 ng/dl) was not statistically different from control. The changes in PRA, plasma sodium concentration, and plasma potassium concentration that occurred during ACTH infusion were characteristic of mineralocorticoid excess; namely, suppression of PRA, hypernatremia, and hypokalemia. On the last day of ACTH infusion, PRA was suppressed to undetectable levels, plasma sodium concentration was elevated 3 ± 1 mEq/liter, and plasma potassium concentration was reduced 1.1 ± 0.1 mEq/liter; all of these changes were statistically significant. During ACTH infusion, plasma protein concentration increased transiently but then fell to control levels. Hematocrit was unchanged from its control value throughout the infusion period. All variables measured during ACTH infusion returned to control levels by the end of the 10-day recovery period.

Effects of Cortisol in Normotensive Dogs

In contrast to the period of ACTH infusion when MAP was either unchanged or elevated, during the 10-day period of cortisol infusion, MAP fell in every dog (fig. 3). The average fall in MAP after 10 days of cortisol infusion was 7 ± 2 mm Hg, a reduction that was statistically significant.

As when the dogs were infused with ACTH, cortisol infusion was associated with increased water turnover, and negative salt and water balance; in contrast to ACTH infusion, however, kaliuresis was not observed during cortisol infusion (fig. 3). For the 10-day cortisol infusion period, urinary sodium and potassium excretion averaged 81 ± 8 and 58 ± 2 mEq/day. Thus, during the cortisol infusion period, there was a net cumulative loss of approximately 150 mEq sodium; the small increase in urinary potassium excretion was not statistically significant. During the first 24 hours of cortisol infusion, there was an increase in urine excretion comparable to that observed with ACTH (fig. 1); however, in contrast to ACTH infusion, there was no further increase in urine excretion during the remainder of the cortisol infusion period. Water consumption also increased during cortisol infusion but, again, not as much as urine excretion, and, consequently, water balance was negative, particularly on Day 1. For the 10-day cortisol infusion period, cumulative negative water balance was approximately 800 ml.

The changes in PRA and in the plasma concentrations of cortisol, aldosterone, sodium, potassium, and protein that occurred during cortisol infusion are shown in figure 4. As intended, the plasma cortisol levels achieved during cortisol infusion were comparable to those observed during ACTH. During cortisol
Effects of ACTH in Dogs with Angiotensin II Hypertension

The changes in MAP, water consumption, and urinary sodium, potassium, and water excretion that occurred during ACTH infusion in dogs with All hypertension are shown in figure 5. Prior to infusion of ACTH, MAP increased from 108 ± 3 to 132 ± 4 mm Hg during the first 24 hours of All infusion, and to 137 ± 4 mm Hg after 6 days of All. Retention of sodium (approximately 50 mEq) and water (approximately 450 ml) occurred on Days 1 and 2 of All infusion, and, subsequently daily salt and water balance was achieved. There were no statistically significant changes in urinary potassium excretion, urine excretion, or water consumption during the initial 6 days of All infusion. These results with All infusion are quantitatively similar to those reported in one of our earlier studies in which dogs were subjected to the same infusion rate of All and maintained on a comparable sodium and potassium intake.

Infusion of ACTH in dogs with All hypertension, in contrast to ACTH infusion in normotensive dogs (fig. 1), consistently increased MAP (fig. 5). For the group, the average increase in MAP during ACTH infusion was 16 ± 3 mm Hg above that achieved with All infusion alone. Within 2 days after termination of ACTH, MAP returned to the hypertensive level observed prior to ACTH infusion.

As in normotensive dogs, ACTH infusion in dogs with All hypertension caused natriuresis, kaliuresis, diuresis, polydipsia, and negative sodium, potassium, and water balance (fig. 5). Quantitatively, the effects of ACTH on water and electrolyte metabolism were approximately equal in normotensive and All hypertensive dogs with one notable exception: the kaliuresis and negative potassium balance induced by ACTH were less severe in the hypertensive dogs.

The hormonal, electrolyte, and protein changes that occurred in the plasma during All and All + ACTH infusion are shown in figure 6. After 6 days of All infusion, plasma aldosterone concentration was elevated approximately four-fold to 12.3 ± 2.8 ng/dl, PRA was suppressed to undetectable levels, and plasma potassium concentration was reduced 0.2 ± 0.1 mEq/liter; in contrast, there were no statistically significant changes in plasma cortisol, aldosterone, plasma sodium concentration, plasma protein concentration, or hematocrit. These changes observed during All infusion are quantitatively similar to those reported in one of our earlier studies in which dogs were subjected to the same infusion rate of All and maintained on a comparable sodium and potassium intake.

In the presence of chronically elevated plasma levels of All, the aldosterone response to ACTH was enhanced acutely but not chronically. As in normotensive dogs, when dogs with All hypertension were given ACTH, there was only a transient (Day 1) increase in plasma aldosterone concentration, in spite of the fact that in the hypertensive dogs there was probably little change in plasma All concentration during ACTH infusion because of the fixed infusion rate of All. In fact, the ACTH infusion actually decreased plasma aldosterone concentration to about 25% of the level achieved with All infusion alone. Further, as shown in figures 2 and 6, plasma aldosterone concentration was actually less during chronic All + ACTH infusion (2.9 ± 0.4 ng/dl) than when ACTH alone was infused in dogs without preexisting All hypertension (5.5 ± 0.9 ng/dl). The plasma cortisol response was similar in dogs infused with ACTH and All + ACTH.

The hypokalemic response to ACTH was greatly attenuated in dogs with All hypertension; chronic infusion of ACTH was associated with a decrease in plasma potassium concentration to only 4.1 ± 0.1 mEq/liter in dogs with All hypertension, whereas plasma potassium concentration fell to 3.2 ± 0.2 mEq/liter when All was not infused simultaneously with the ACTH (fig. 2). Plasma sodium concentration and PRA
Effects of Cortisol in Dogs with Angiotensin II Hypertension

Changes in MAP, urinary sodium excretion, urinary potassium excretion, urine excretion, and water consumption that occurred during cortisol infusion in dogs with All hypertension are shown in figure 7. In dogs infused with All, the effects of cortisol on water and electrolyte metabolism were similar to those observed during cortisol infusion alone (fig. 3), namely, natriuresis, diuresis, polydipsia, and negative water balance. In dogs infused with All simultaneously with cortisol, however, net losses of sodium and water were attenuated. Accordingly, in contrast to the hypotensive response observed in normotensive dogs, cortisol failed to produce a detectable change in MAP in dogs with All hypertension.

The changes that occurred in plasma cortisol concentration, plasma aldosterone concentration, PRA, plasma sodium concentration, plasma potassium concentration, and plasma protein concentration during cortisol infusion in dogs with All hypertension are shown in figure 8. The most dramatic change that occurred during cortisol infusion was an increase in plasma cortisol concentration to a level comparable to that observed during cortisol, ACTH, and All + ACTH infusion (figs. 2, 4, and 6). Chronic cortisol infusion appeared to increase plasma aldosterone concentration but the plasma aldosterone concentration achieved was no greater than either the All control value on Day 6 (fig. 6) or the All recovery value on Day 33 (fig. 8). Thus, it is unlikely that cortisol influenced aldosterone secretion. Values for PRA, plasma sodium concentration, plasma potassium concentration, and hematocrit that were achieved during cortisol infusion were not statistically different from those observed just prior to cortisol infusion (Day 19); however, plasma potassium concentration and plasma protein concentration were significantly greater during cortisol infusion than during the subsequent All recovery.
by guest on September 23, 2017 http://hyper.ahajournals.org/ Downloaded from

The relative importance of mineralocorticoid excess versus glucocorticoid excess in the pathogenesis of hypertension in Cushing's syndrome has not been resolved. Our present findings indicate that, at least in the dog, cortisol is not a hypertensive agent when present in high physiological concentrations that do not possess significant mineralocorticoid activity. On the contrary, in the present study, when cortisol was infused in normotensive dogs and high plasma concentrations of cortisol were achieved, comparable to those observed during chronic ACTH stimulation, arterial pressure actually decreased. Also, in dogs with All hypertension, cortisol infusion failed to increase the severity of the hypertension. Similarly, others have found that chronic administration of high physiological doses of cortisol or cortisone in experimental animals produces very 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 may not be important in the pathogenesis of hypertension in Cushing's syndrome. It is also relevant that hypertension is more likely to occur in patients treated with ACTH than in patients treated with glucocorticoids.

Since it is well established that chronic ACTH excess is associated with prolonged hypersecretion of mineralocorticoids other than aldosterone, it may appear somewhat incongruous that hypertension was not consistently manifested during the 10-day infusion of ACTH in dogs without preexisting hypertension. The changes in plasma electrolyte concentration that occurred during ACTH infusion were indicative of pronounced mineralocorticoid effects. Further, in an earlier study, we observed within 7 days a 10 to 15 mm Hg increase in MAP in dogs maintained on a comparable sodium and potassium intake and infused with enough aldosterone to increase plasma aldosterone concentration to 3 to 4 times normal. Although the fall in PRA was undoubtedly one of several compensatory mechanisms that acted to minimize increases in arterial pressure during ACTH infusion, the data also suggest that the relative plasma concentrations of mineralocorticoids (favoring hypertension) and glucocorticoids (favoring hypotension) may be of paramount importance in determining the final arterial pressure level achieved during ACTH
excess. In corroboration of this hypothesis is the finding that the administration of metyrapone (an inhibitor of adrenocortical 11-β-hydroxylase activity) consistently produces hypertension in dogs within 7 days. During metyrapone treatment, cortisol synthesis is impaired and, as a result, chronic endogenous ACTH overdrive leads to increases in deoxycorticosterone secretion. High plasma levels of deoxycorticosterone, in turn, cause salt and water retention, and, consequently, hypertension. In contrast to metyrapone administration, during ACTH infusion, elevated secretion rates of cortisol as well as deoxycorticosterone exist. Apparently, the hypercortisolism, which favors salt and water depletion, attenuates the fluid retention and, thus, the hypertension induced by mineralocorticoid excess.

Several theoretical analyses, as well as experimental studies, indicate that chronic increases in renal excretory capacity, such as those observed during cortisol infusion, could result in sustained reductions in arterial pressure. It is well established that glucocorticoid excess is associated with a decrease in renal vascular resistance, an increase in GFR, and salt and water depletion. Thus, in spite of the fact that glucocorticoid excess causes a shift in fluid from the intracellular space to the extracellular space, chronically this fluid is not retained in the extracellular compartment if the glucocorticoid does not possess significant mineralocorticoid activity. Indeed, in our present study there was a striking loss of salt and water, and a decrease in MAP during cortisol infusion. Accordingly, we have observed in our laboratory (and unpublished data) that chronic infusion of high levels of either cortisol or methylprednisolone (a glucocorticoid with virtually no mineralocorticoid activity) is associated with a decrease in extracellular fluid volume as well as a reduction in arterial pressure. In contrast to cortisol infusion, however, we have observed that chronic ACTH infusion in dogs is associated with an increase in extracellular fluid volume in spite of negative salt and water balance (unpublished data). This response is consistent with the fact that ACTH stimulates the secretion of mineralocorticoid hormones, in addition to cortisol, and, therefore, some of the fluid shifted to the extracellular compartment is apparently retained. Consequently, over the long term, extracellular fluid volume is increased, PRA is decreased, and typically there is a very modest increase in arterial pressure. It is likely that mobilization of sodium from depots in bone contributes to the natriuresis associated with ACTH administration.

There are numerous reports that ACTH, mineralocorticoid hormones, and/or glucocorticoid hormones potentiate, in both experimental animals and human subjects, the acute blood pressure response to pressure agents such as norepinephrine and angiotensin II. It is disconcerting, however, that there are also numerous reports that deny such an effect. Nonetheless, because of the positive findings, it has been postulated that ACTH, mineralocorticoid hormones, and/or glucocorticoid hormones might potentiate the blood pressure effects of AII and norepinephrine, and this might be an important mechanism in the pathogenesis of hypertension in Cushing's syndrome. Be this hypothesis has never been evaluated under long-term conditions, and since an increase in arterial pressure is much more likely to occur during glucocorticoid treatment in patients with renal disease than in patients without renal disease, we infused ACTH and cortisol in dogs with AII hypertension to determine whether ACTH excess or cortisol excess might potentiate the long-term hypertensive effects of AII. Our data demonstrate very clearly that high plasma levels of ACTH, which do not consistently increase MAP in normal dogs, invariably exacerbate the hypertension associated with long-term AII infusion.

Although the precise mechanisms whereby ACTH produces hypertension remain to be elucidated, our experiments provide insight relating to the importance of excessive glucocorticoid activity and excessive mineralocorticoid activity in mediating the hypertensive effects of ACTH in dogs with AII hypertension. First, although chronic cortisol infusion produced increases in plasma cortisol concentration comparable to those observed with long-term infusion of ACTH, MAP was unchanged in dogs with AII hypertension; thus, hypercortisolism alone cannot account for the hypertensive effects of ACTH. Second, in an earlier study in which high rates of aldosterone were infused in dogs with AII hypertension (induced by long-term AII infusion), prominent changes in electrolytes occurred (indicative of mineralocorticoid excess) that were associated with elevations in plasma aldosterone concentration 6 to 7 times above normal; however, during aldosterone infusion there were no detectable changes in MAP from the hypertensive level achieved with AII infusion alone. It is unlikely, therefore, that mineralocorticoid excess alone can account for the exacerbation of AII hypertension observed during chronic ACTH infusion. Since we have not determined the arterial pressure effects of simultaneous infusion of large amounts of cortisol and aldosterone, it is possible that high plasma levels of these two adrenocortical hormones in combination could mimic the hypertensive effects of ACTH. It is of interest, however, that, at least in the sheep where ACTH infusion alone produces chronic hypertension, simultaneous infusion of cortisol, corticosterone, 11-deoxycorticosterone, and aldosterone at rates producing plasma concentrations similar to those observed with ACTH infusion increases arterial pressure to only approximately 50% of that achieved with ACTH. Further, the Australian group has concluded from 10 years of extensive studies of this model of hypertension in the sheep that the hypertensive effects of adrenocortical hormones are not simply related to their mineralocorticoid or glucocorticoid activity.

In the present study the finding that chronic ACTH infusion suppressed PRA (to undetectable levels) is consistent with the findings of others in dogs, in other experimental animals, and in humans. Thus, in spite of our findings that ACTH potentiates the long-
term arterial pressure effects of AI, it is questionable whether the renin-angiotensin system has an important role in the pathogenesis of ACTH-induced hypertension. This contention is further supported by the observations of the Australian group. These investigators administered the converting enzyme inhibitor, SQ 14,225, in sheep with chronic ACTH-induced hypertension and observed no greater reduction in MAP in hypertensive sheep than in normotensive sodium-replete sheep.39 These observations, however, do not discount the possibility that the renin-angiotensin system might contribute importantly to the hypertension of Cushing’s syndrome in conditions where there is an inappropriately high renin level, as in some forms of renal disease.41 Further, a renin component to the hypertension might become more likely in the advanced states of the disease since arteriosclerosis and nephrosclerosis are not uncommon in patients with Cushing’s syndrome. Thus, in spite of the fact that ACTH treatment decreases PRA in human subjects, the fact that PRA is not suppressed in all patients with Cushing’s syndrome5 10 would indicate, particularly in light of the present data, that elevated or even normal plasma levels of AI, when present, might contribute significantly to the hypertension. Finally, although in the present study ACTH chronically potentiated AI hypertension, our data do not necessarily indicate that this effect of ACTH is specific for the renin-angiotensin system. In more general terms, the present findings may simply indicate that the hypertensive effects of ACTH are more prominent when there is reduced renal excretory capacity such as when plasma AI levels are inappropriately elevated. Corroborating this hypothesis is the observation that ACTH-induced hypertension is potentiated in sheep with surgical reduction of renal mass.18 Further studies relating to the hypertensive effects of ACTH in other models of hypertension are needed.

Finally, although ACTH acutely stimulates aldosterone secretion and although physiological levels of ACTH are required to maintain normal adrenal glomerulosa cell function, it is also well established that prolonged ACTH administration causes only a transient rise in aldosterone secretion. The cause of this decline in aldosterone secretion to basal levels or below basal levels after several days34, 42, 43 has been the subject of much debate. One of the more popular hypotheses is that adrenocortical hormones such as deoxycorticosterone, corticosterone, and 18-hydroxydeoxycorticosterone possess significant mineralocorticoid activity and the sustained secretion causes salt and water retention with consequent hypervolemia and suppression of PRA.38, 43, 44 The fall in PRA leads to decreased sensitivity of the zona glomerulosa and, consequently, to a decline in aldosterone secretion.38, 43, 44 Although the fall in PRA with ACTH treatment is consistent with this hypothesis, failure of ACTH to produce a sustained increase in aldosterone secretion in dogs with AI hypertension (and fixed plasma levels of AI) indicates that other mechanisms besides suppression of PRA play a more dominant role in mediating the chronic aldosterone response to ACTH. Consistent with our findings is the observation that a rise followed by a decline in aldosterone secretion during ACTH treatment also occurs in patients with primary aldosteronism who have low to undetectable levels of PRA.45 In fact, in the present study, although chronically elevated plasma levels of AI enhanced the acute aldosterone response to ACTH, the chronic aldosterone response to ACTH was suppressed by elevated plasma levels of AI. Since plasma potassium concentration is a particularly important long-term controller of aldosterone secretion,46 the hypokalemia that occurs concomitantly with ACTH treatment may be significant in mediating the fall in aldosterone secretion occurring during chronic ACTH excess; on the other hand, there may be other important mechanisms than alterations in potassium balance.46, 47

In summary, we found no evidence that the hypercortisolism associated with chronic ACTH excess contributes to ACTH-induced hypertension. On the contrary, it appears that the elevated plasma levels of cortisol exert hypotensive effects by virtue of their renal actions which favor natriuresis and diuresis. In addition, since PRA fell to undetectable levels during chronic ACTH infusion, the present data do not support the contention that the renin-angiotensin system is typically involved in the pathogenesis of ACTH-induced hypertension. In fact, suppression of PRA during ACTH excess appears to be an important compensatory response that ameliorates the hypertensive effects of ACTH. Indeed, when ACTH was infused in hypertensive dogs with fixed plasma levels of AI, the hypertensive effects of ACTH were manifested. Finally, failure of chronic ACTH administration to maintain an elevated secretion rate of aldosterone cannot be attributed to suppression of PRA.

Acknowledgments

We are extremely grateful to Thomas A. Walker for his technical assistance with the animals, and to Barbara McLenore and Philip Rushing for their work in the radioimmunoassay laboratory. We thank the National Institute of Arthritis, Metabolism, and Digestive Diseases for providing the aldosterone antiserum used for radioimmunoassay of aldosterone, and Upjohn Company for donating the Solu Cortef.

References

Chronic effects of ACTH and cortisol excess on arterial pressure in normotensive and hypertensive dogs.
T E Lohmeier and P R Kastner

Hypertension. 1982;4:652-661
doi: 10.1161/01.HYP.4.5.652

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1982 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/4/5/652.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/