Kidney International, Vol. 15 (1979), pp. 669–675

Dissociation of the diurnal variation of aldosterone and cortisol in anephric subjects

C. ROBERT COOKE, PAUL K. WHELTON, MICHAEL A. MOORE, RICHARD A. CAPUTO, TURNER BLEDSOE, and W. GORDON WALKER

Department of Medicine, The Johns Hopkins Hospital and The Johns Hopkins University School of Medicine, Baltimore, Maryland

Dissociation of the diurnal variation of aldosterone and cortisol in anephric subjects. Diurnal variation of plasma aldosterone and cortisol concentration in man was studied in 13 anephric subjects and 7 normal subjects. All subjects were ambulatory and active throughout the study except during an 8-hour sleep period. Six anephric subjects received Kayexalate® (sodium polystyrene sulfonate) during the studies to prevent potassium accumulation and increase in plasma potassium concentration. Diurnal variation of plasma aldosterone concentration with peak and nadir concentrations at 12:00 noon and 12:00 midnight respectively was demonstrated in the studies on normal subjects. Changes in plasma aldosterone concentration were not significantly correlated with changes in plasma cortisol concentration but were highly correlated with changes in PRA ($P < 0.001$). There was a highly significant correlation between plasma aldosterone and potassium concentration in the anephric subjects studied without Kayexalate® administration ($P < 0.001$). In the anephric subjects who received Kayexalate®, plasma aldosterone and potassium concentration remained stable, and no correlation could be demonstrated. No diurnal variation of plasma aldosterone concentration could be demonstrated in either group of anephric subjects, whereas plasma cortisol concentration varied as in the studies on normal subjects. *Conclusion.* Diurnal variation of plasma aldosterone concentration is dependent on continued stimulation by the renin-angiotensin system. Loss of this stimulation has no demonstrable effect on the diurnal variation of plasma cortisol concentration.

Dissociation des variations nycthémérales de l'aldostérone et du cortisol chez les sujets anéphriques. Les variations nycthémérales de l'aldostérone et du cortisol plasmatiques chez l'homme ont été étudiées chez 13 sujets anéphriques et 7 sujets normaux. Tous les sujets étaient ambulatoires excepté pendant une période de sommeil de 8 heures. Six sujets anéphriques recevaient du Kayexalate® (sodium polystyrene sulfonate) afin d'empêcher une accumulation de potassium et une augmentation de la kaliémie. Des variations nycthémérales de l'aldostéronémie avec un pic et un nadir à midi et minuit, respectivement, ont été observées chez les sujets normaux. Les modifications de l'aldostéronémie ne sont pas significativement corrélées avec les modifications du cortisol plasmatique mais très corrélées avec celles de PRA ($P < 0{,}001$). Il existe une corrélation très significative entre l'aldostéronémie et la kaliémie chez les sujets anéphriques étudiés en dehors de l'administration de Kayexalate ($P < 0{,}001$). Chez les sujets anéphriques recevant du Kayexalate l'aldostéronémie et la kaliémie sont stables et aucune corrélation n'est obtenue. Aucune variation nycthémérale de l'aldostéronémie n'a été observé dans les groupes de sujets anéphriques alors que la concentration de cortisol plasmatique varie comme chez les sujets normaux. Il peut être conclu de ces études que les variations nycthémérales de l'aldostéronémie dépendent de la stimulation par le système rénine-angiotensine. La perte de cette stimulation n'a pas d'effet sur la cortisolémie.

At least three factors play a role in the regulation of aldosterone secretion: (*1*) sodium or volume-related stimuli mediated by the renin-angiotensin system, (*2*) potassium, and (*3*) adrenocorticotropic hormone (ACTH). The role of the renin-angiotensin system with regard to volume regulation and the control of aldosterone secretion is well established [1–4]. Modulation of aldosterone secretion by plasma potassium concentration also has been shown clearly in previous studies [5–10]. The role of ACTH is less certain. Stimulation of aldosterone secretion by ACTH has been demonstrated in acute infusion studies [11–14], although often these studies have been performed with greater than physiologic quantities of ACTH. Although observations in such studies may be indicative of the response to acute stress [15], they do not elucidate the role of ACTH in the daily regulation of aldosterone secretion. On the other hand, Kem et al have shown that infusion of ACTH in physiologic quantities increases plasma aldosterone concentration in dexamethasone-suppressed subjects [16]. ACTH infusion also enhanced the response to sodium restriction in these subjects, which suggests that ACTH plays a permissive role in the regulation of aldosterone secretion.

Received for publication July 20, 1978
and in revised form January 2, 1979

0085-2538/79/0015-0669 $01.40

Diurnal variation of aldosterone secretion and plasma aldosterone concentration has been demonstrated in previously reported studies [17–22]. The possibility that these rhythmic diurnal changes may be ACTH-dependent has been suggested by the similarity of concomitant diurnal changes in plasma cortisol concentration [23, 24]. Diurnal variation of plasma aldosterone concentration, however, also resembles the diurnal variation of PRA [18, 19, 21, 22]. Thus, the diurnal variation of plasma aldosterone and cortisol concentration could be associated with two different control mechanisms with similar rhythmic characteristics, or, alternatively, the effects of ACTH and the renin-angiotensin system on aldosterone secretion could be interrelated in some manner.

To further evaluate these possibilities, we have studied the diurnal variation of plasma aldosterone and cortisol concentration in anephric subjects, thereby excluding the effect of the renin-angiotensin system, and have compared the data from these studies with those obtained from comparable studies on normal subjects. The relationship between plasma aldosterone concentration and plasma potassium concentration in both anephric and normal subjects was also investigated in these studies.

Methods

Thirteen anephric subjects were admitted for studies to the Clinical Research Unit following hemodialysis, which was terminated at approximately 2:00 P.M. on the day of admission in all subjects. Six subjects were females and seven were males; their ages ranged from 21 to 52 years. Total fluid intake was restricted to 500 ml/day to minimize changes in body weight, and dietary sodium and potassium intake were restricted to 20 mEq and 40 mEq/day, respectively. Six subjects, two females and four males, were given Kayexalate® (sodium polystyrene sulfonate), 7.5 g orally at 9:00 P.M. on the day of admission and at 8:00 A.M., 2:00 P.M., and 8:00 P.M. on the following day to prevent potassium accumulation and an increase in plasma potassium concentration during the studies. The other anephric subjects were studied without Kayexalate administration.

Seven normal subjects, all males ranging in age from 27 to 44 years, were admitted for similar studies. Diets and fluid intake were unrestricted; 24-hour urinary sodium excretion was determined as an index of dietary sodium intake. None of the normal subjects received Kayexalate. In other respects, the study protocols for anephric and normal subjects were identical.

On the morning following admission, the subjects were awakened at 7:00 A.M., weighed, and served breakfast. They remained up and active throughout the day and went to bed at 11:00 P.M. to sleep until 7:00 A.M. the following morning. They were awakened again at 7:00 A.M., were weighed, and were out of bed and active within the Clinical Research Unit until the studies were terminated at 9:00 A.M. on day 2. Blood samples for determination of PRA, plasma aldosterone, cortisol, sodium, and potassium concentrations were obtained at 9:00 A.M. on day 1 and every 3 hours through 9:00 A.M. on day 2. All blood samples were drawn through a small indwelling needle in a forearm or antecubital vein, permitting the collection of samples with minimal disturbance of sleeping subjects. All subjects slept in a darkened room, and blood samples obtained during the hours of sleep were drawn in the light of a small bedside lamp. There were no differences in sleep time or brief exposure to light during blood drawing between the studies on normal subjects and the studies on anephric subjects.

Blood for determination of PRA was drawn into chilled syringes containing EDTA and promptly centrifuged at 4° C. All blood samples for determination of plasma aldosterone, cortisol, sodium, and potassium concentrations were collected in heparinized syringes. The methods used in the determination of PRA [25] and plasma aldosterone concentration [9] have been described in previous communications. The lower limit of sensitivity in our assay for PRA using a 3-hour incubation at a pH of 7.4 is 0.1 ng angiotensin I generated/ml/hr. In six replicate determinations performed on purified human renin (1×10^{-4} Goldblatt U) added to anephric human plasma, the mean quantity of angiotensin I generated was 4.6 ± (SD) 0.3 ng/ml/hr. Determinations of plasma aldosterone concentration were performed on 2 ml of plasma following dichloromethane extraction and paper chromatography in a benzene:methanol:water (100:50:50) solvent system. A charcoal-extracted aliquot of the eluted sample was assayed as a "blank" with each determination. This method distinguishes between 0 and 50 pg ($P < 0.01$) and between 25 and 50 pg ($P < 0.05$) of aldosterone added to 5 ml of plasma from an adrenalectomized patient ($N = 20$ samples in each comparison). The relationship between observed and expected concentrations of aldosterone added to plasma from an adrenalectomized patient is linear and highly correlated ($P < 0.001$) over a range be-

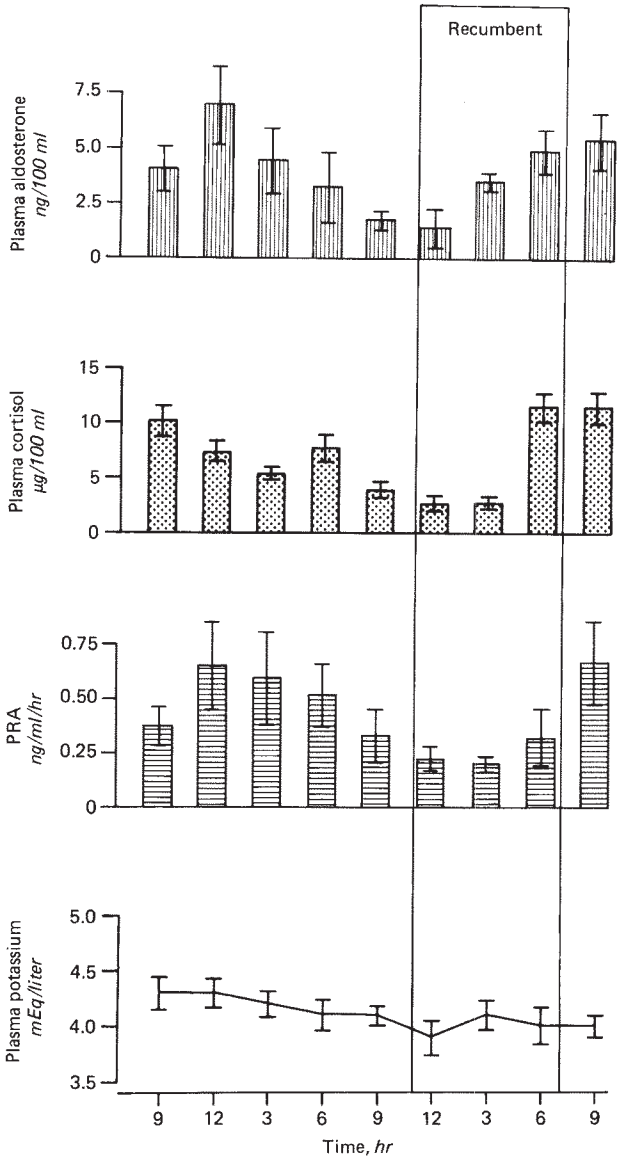

Fig. 1. *Plasma aldosterone and cortisol concentrations, PRA, and plasma potassium concentrations every 3 hours during the 24-hour study period in normal subjects.* Bars represent mean concentrations ± 1 SEM.

tween 0.5 and 5.0 ng/100 ml. Plasma cortisol concentration was measured by the competitive protein-binding radioassay of Hsu and Bledsoe [26]. Interassay and intraassay variation in this assay is 7.2 and 5.1%, respectively. Plasma sodium and potassium concentrations and urinary sodium concentrations in the studies on normal subjects were determined by autoanalyzer flame photometry.

Results

Normal subjects. Plasma aldosterone and cortisol concentrations, PRA, and plasma potassium concentrations every 3 hours beginning at 9:00 A.M. on day 1 and ending at 9:00 A.M. on day 2 are shown in Fig. 1. The relationship between measured values of plasma aldosterone and cortisol concentration and between these and PRA, as well as the relationship between the interval changes in these parameters, was examined statistically. From a peak concentration at 12:00 noon on day 1, plasma aldosterone concentration decreased to significantly lower concentrations at 6:00 P.M. ($P < 0.005$), 9:00 P.M. ($P < 0.005$), and 12:00 midnight ($P < 0.01$) and increased progressively in subsequent intervals through 9:00 A.M. on day 2. Although a positive correlation between measured values of plasma aldosterone and cortisol concentrations could be demonstrated ($r = +0.292$, $P < 0.05$, $N = 60$), changes in plasma aldosterone concentrations were not concordant with the changes in plasma cortisol concentrations ($r = +0.155$, $P > 0.1$, $N = 53$). In contrast, there was a highly significant correlation ($r = +0.441$, $P < 0.001$, $N = 55$) between changes in plasma aldosterone concentrations and changes in PRA (Fig. 2). Measured values of plasma aldosterone concentrations and PRA were also significantly correlated ($r = +0.596$, $P < 0.001$, $N = 62$). No correlation between plasma cortisol concentrations and PRA could be demonstrated.

Plasma aldosterone concentrations were not significantly correlated with plasma potassium concentrations, which decreased from 4.3 ± (SEM) 0.13 mEq/liter at 12:00 noon to 3.9 ± 0.16 mEq/liter at

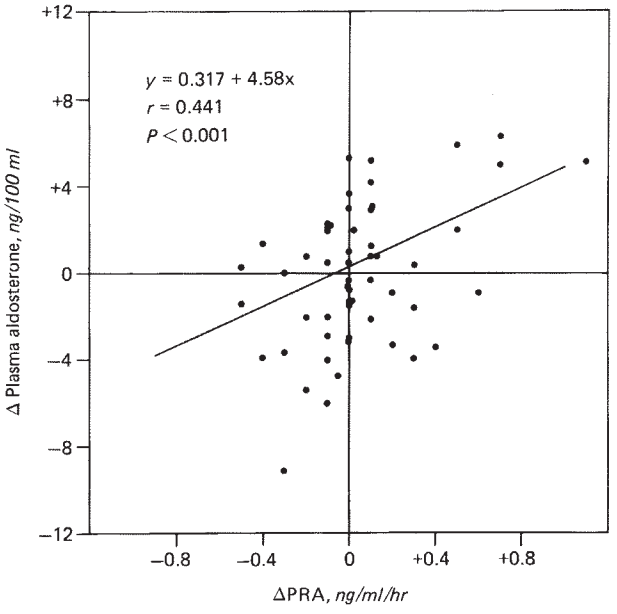

Fig. 2. *Correlation between the changes in plasma aldosterone concentrations and changes in PRA in normal subjects.*

12:00 midnight ($P < 0.001$). There also was no significant correlation between plasma potassium concentrations and plasma cortisol concentrations. No variation could be demonstrated in plasma sodium concentrations; urinary sodium excretion, which served as an index of sodium intakes, ranged from 104 to 265 mEq/24 hours. Body weights were not changed.

Anephric subjects studied without Kayexalate administration. Plasma aldosterone concentrations every 3 hours beginning at 9:00 A.M. on day 1 and ending at 9:00 A.M. on day 2 are shown with plasma cortisol and potassium concentrations in Fig. 3. No PRA could be detected. There were no significant variations in plasma aldosterone concentrations, although plasma cortisol concentrations varied as they did in normal subjects, decreasing from a peak concentration at 9:00 A.M. on day 1, to low concentrations at 12:00 midnight and 3:00 A.M., and increasing later in the morning through 9:00 A.M. on day 2. No correlation between plasma cortisol concentrations and plasma aldosterone concentrations could be demonstrated.

Plasma potassium concentration increased from 4.5 ± (SEM) 0.3 mEq/liter at 9:00 A.M. on day 1 to 5.2 ± 0.2 mEq/liter at 9:00 A.M. on day 2 ($P < 0.001$). Although no correlation between 3-hour interval changes in plasma potassium and aldosterone concentrations could be demonstrated, an effect of plasma potassium on plasma aldosterone concentrations was suggested by the highly significant correlation of the measured concentrations of these parameters ($r = +0.666$, $P < 0.001$, $N = 63$).

Changes in body weight during the studies ranged from −1.1 to +0.2 kg (mean change in body weight, −0.57 ± [SEM] 0.17 kg). Plasma sodium concentrations were not altered.

Anephric subjects who received Kayexalate. Plasma aldosterone, cortisol, and potassium concentrations every 3 hours beginning at 9:00 A.M. on day 1 and ending at 9:00 A.M. on day 2 are shown in Fig. 4. As in the anephric subjects studied without Kayexalate administration, no PRA could be detected. There was no significant change in plasma

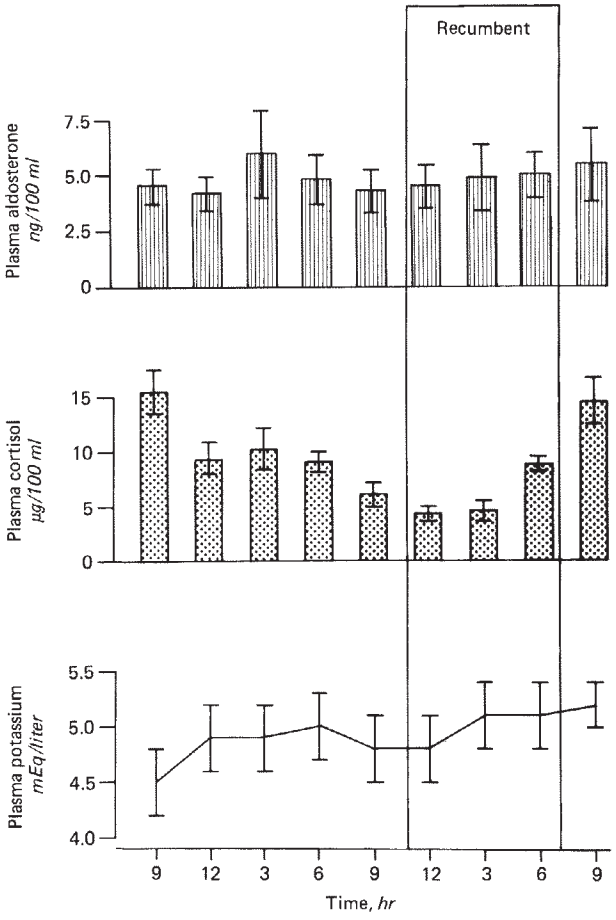

Fig. 3. *Plasma aldosterone, cortisol, and potassium concentrations every 3 hours during the 24-hour study period in anephric subjects studied without Kayexalate administration.* Bars represent mean concentrations ± 1 SEM.

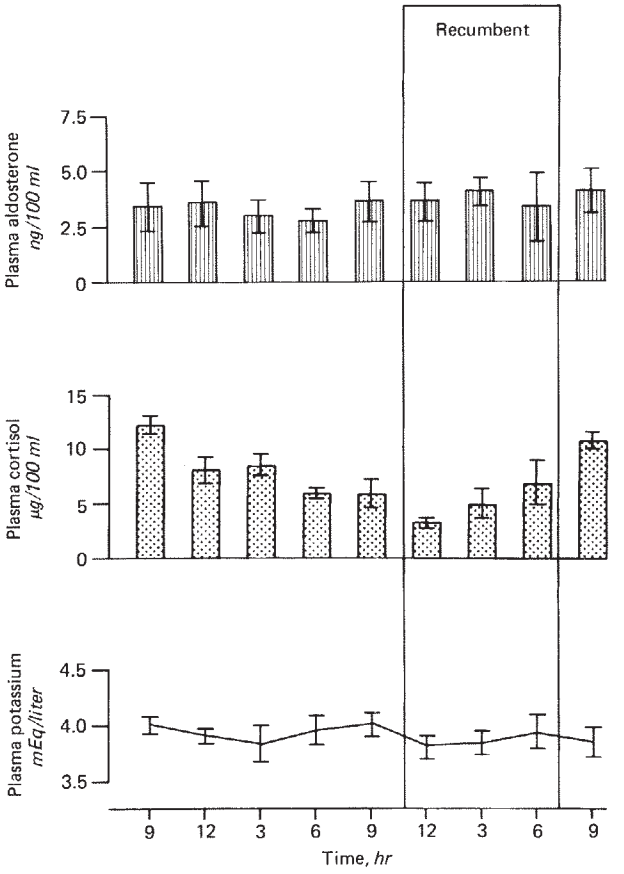

Fig. 4. *Plasma aldosterone, cortisol, and potassium concentrations every 3 hours during the 24-hour study period in anephric subjects who received Kayexalate.* Bars represent mean concentrations ± 1 SEM.

aldosterone concentrations, which remained stable throughout the studies despite the changes in posture and activity of the subjects. Mean plasma aldosterone concentration during the studies was 3.4 ± (SEM) 0.3 ng/100 ml, whereas the mean plasma aldosterone concentration in the anephric subjects who did not receive Kayexalate was 4.9 ± (SEM) 0.4 ng/100 ml ($P < 0.005$).

There was no increase in plasma potassium concentration which was 4.0 ± (SEM) 0.1 mEq/liter at 9:00 A.M. on day 1 and 3.9 ± (SEM) 0.1 mEq/liter at 9:00 A.M. on day 2. Under these conditions, the correlation of plasma aldosterone with plasma potassium concentrations was not demonstrated.

Diurnal variation of plasma cortisol concentrations persisted without change. No significant differences in plasma cortisol concentrations between anephric subjects who received Kayexalate and those who did not could be demonstrated. There were no correlations between plasma cortisol concentrations and either plasma potassium or plasma aldosterone concentrations.

Mean change in body weight was +0.68 ± (SEM) 0.14 kg. No change occurred in plasma sodium concentration.

Discussion

Diurnal variation of plasma aldosterone concentration resembling the diurnal variation of plasma cortisol concentration and PRA was demonstrated in our studies on normal subjects. Similar observations were reported by Grim et al who also found that plasma aldosterone concentration in normal ambulatory subjects increased to a peak level at 12:00 noon and decreased progressively from 12:00 noon through 12:00 midnight [22]. A similar pattern, but with an early morning peak, was observed in studies on recumbent subjects by Grim et al [22] and Kunita et al [21]. Katz, Romfh, and Smith found that plasma aldosterone concentrations in recumbent subjects increased during sleep and reached their highest concentrations in the late sleep and early awake hours [19]. In these studies, plasma aldosterone concentrations correlated with both plasma cortisol concentrations and PRA. The early morning increases in plasma aldosterone concentrations and PRA, however, persisted in dexamethasone-suppressed subjects, but the increases in plasma cortisol concentrations were abolished. In studies on sodium-restricted recumbent subjects, Vagnucci et al found that plasma aldosterone concentrations increased in the early hours of sleep, whereas plasma cortisol and corticosterone concentrations increased in the terminal portion of the sleep period [18]. Similar dissociation of the changes in plasma aldosterone and cortisol concentrations during sleep was observed in our studies. In addition, the various 3-hour interval changes in plasma aldosterone concentrations were correlated with changes in PRA but not with concurrent changes in plasma cortisol concentrations.

No diurnal variation of plasma aldosterone concentration could be demonstrated in the studies on anephric subjects. In the subjects who were studied without Kayexalate administration, slight increases in plasma aldosterone concentrations were observed in the latter half of the study period. These increases, although not statistically significant, coincided with progressive increases in plasma potassium concentrations. Vetter et al also observed increases in plasma aldosterone concentrations in the early morning hours between 2:00 A.M. and 6:00 A.M. in studies on recumbent anephric subjects [27]. Although changes in plasma potassium concentrations were small in these studies by Vetter et al, our earlier studies on anephric subjects [9] and studies reported by McCaa, McCaa, and Guyton [10] suggest that they were large enough to account for increases in plasma aldosterone concentrations.

In our studies without Kayexalate, plasma aldosterone concentrations and plasma potassium concentrations were significantly correlated. This correlation was abolished in the anephric subjects who received Kayexalate, by maintaining their plasma potassium concentrations at constant levels throughout the studies. Differences in plasma aldosterone concentrations between the anephric subjects who received Kayexalate and those who did not can also be attributed to the differences in plasma potassium concentrations in the two groups. Mean plasma aldosterone concentration was 4.9 ± (SEM) 0.4 ng/100 ml in the anephric subjects studied without Kayexalate administration and 3.4 ± 0.3 ng/100 ml in those who received Kayexalate. Lower values were reported by Sealey et al [28], but the anephric subjects in their studies were usually hemodialyzed with potassium-free dialysate, whereas the dialysate potassium concentration used routinely in the hemodialysis of our subjects was 2.0 mEq/liter. Plasma aldosterone concentrations similar to those reported by Sealey et al [28] were observed by Weidmann et al in anephric subjects who were studied following hemodialysis with either potassium-free dialysate or 1.0 mEq/liter dialysate potassium concentration [29]. Mean plasma aldosterone concentration in ten anephric subjects whose plasma potassium concentrations ranged from 2.7 to 4.0 mEq/liter in these studies was 1.18 ng/100 ml. This evidence of regulation of plasma aldosterone concentration by potassium in the anephric subject

is consistent with our previously reported observations [8, 9] which suggest that potassium is the primary regulator of plasma aldosterone concentration in the absence of the renin-angiotensin system.

Plasma aldosterone concentrations in the anephric subjects who received Kayexalate, although lower than they were in the anephric subjects studied without Kayexalate administration, were higher than the nadir concentrations in normal subjects at 9:00 P.M. and 12:00 midnight ($P < 0.05$). This cannot be attributed to a difference in plasma potassium concentrations, which, in this group of anephric subjects, were almost identical to the concentrations observed in the normal subjects at these times. It is possible, however, that the sensitivity of aldosterone secretion to potassium is increased in the anephric subject, either because of the absence of other stimuli or due to repeated elevations of plasma potassium concentrations between dialyses. It should be noted in this regard that plasma aldosterone concentrations similar to those occurring at 9:00 P.M. and 12:00 midnight in our studies on normal subjects were observed by Sealey et al [28] and Weidmann et al [29] in their studies on anephric subjects with low plasma potassium concentrations.

Plasma aldosterone concentrations in the anephric subjects who received Kayexalate were also lower ($P < 0.05$) than were the peak concentrations which occurred in the normal subjects at 12:00 noon. This failure of plasma aldosterone concentrations in the anephric subjects to increase to the midday concentrations observed in normal subjects is consistent with either the loss of stimulation that produces rhythmic diurnal changes in plasma aldosterone concentrations in normal subjects or decreased responsiveness to this stimulation. Clearly, the mechanism responsible for the diurnal variation of plasma cortisol concentrations remains intact in anephric subjects.

Although these studies suggest that the mechanism responsible for diurnal variation of plasma aldosterone concentrations in normal subjects could be different from that responsible for the diurnal variation of plasma cortisol concentrations, they do not exclude the possibility that the mechanisms are interrelated in some manner. It could be argued, for example, that the response of aldosterone secretion to ACTH is dependent on continued stimulation by the renin-angiotensin system. Studies by several investigators have shown previously that the response of aldosterone secretion to ACTH administration, as shown by the degree of change in plasma aldosterone concentration, is reduced in anephric subjects [29–32]. Several factors, however, in addition to loss of stimulation by the renin-angiotensin system, may influence the response of aldosterone secretion to ACTH in anephric subjects. One of these factors, as shown by the studies of Weidmann et al, is plasma potassium concentration [29]. These investigators found that ACTH administration produced little or no change in plasma aldosterone concentrations in anephric subjects whose plasma potassium concentrations were low (2.5 to 4.0 mEq/liter) due to prior hemodialyses with low-potassium or potassium-free dialysate. Hemodialyses with higher dialysate potassium concentrations resulted in higher plasma potassium concentrations and marked enhancement of the plasma aldosterone response to ACTH.

Plasma potassium concentrations in our studies, especially in the subjects studied without Kayexalate administration, were such that the sensitivity of aldosterone secretion to ACTH should not have been reduced on this basis. The only discernible factor accounting for the loss of diurnal variation of plasma aldosterone concentration in the anephric subjects in our studies is the lack of stimulation by the renin-angiotensin system. Whether the loss of diurnal variation of plasma aldosterone concentrations in these subjects is a reflection of decreased sensitivity to ACTH or indicates that the renin-angiotensin system rather than ACTH is responsible for the diurnal variation of plasma aldosterone concentrations in normal subjects is uncertain. These studies show, however, that diurnal variation of plasma aldosterone concentrations depends on continued stimulation by the renin-angiotensin system, whereas loss of this stimulation has no demonstrable effect on diurnal variation of plasma cortisol concentrations.

Acknowledgments

These studies were supported in part by USPHS Research Grant HL 03303 and Clinical Research Centers Grant RR 0035. Dr. Moore was supported by USPHS Training Grant AM 05655.

Reprint requests to Dr. C. R. Cooke, 1011 Blalock, The Johns Hopkins Hospital, 601 North Broadway, Baltimore, Maryland 21205, USA

References

1. DAVIS JO, CARPENTER CCJ, AYERS CR, HOLMAN JE, BAHN RC: Evidence for secretion of an aldosterone-stimulating hormone by the kidney. *J Clin Invest* 40:684–696, 1961
2. DAVIS JO, AYERS CR, CARPENTER CCJ: Renal origin of an

aldosterone-stimulating hormone in dogs with thoracic caval constriction and in sodium-depleted dogs. *J Clin Invest* 40:1466–1474, 1961

3. BLAIR-WEST JR, COGHLAN JP, DENTON DA, GODING JR, WINTOUR M, WRIGHT RD: The control of aldosterone secretion. *Recent Progr Hormone Res* 19:311–363, 1963
4. GANONG WF, BIGLIERI EG, MULROW PJ: Mechanisms regulating adrenocortical secretion of aldosterone and glucocorticoids. *Recent Progr Hormone Res* 22:381–430, 1966
5. DAVIS JO, URQUHART J, HIGGINS JT JR: The effects of alterations of plasma sodium and potassium concentration on aldosterone secretion. *J Clin Invest* 42:597–609, 1963
6. BOYD JE, PALMORE WP, MULROW PJ: Role of potassium in the control of aldosterone secretion in the rat. *Endocrinology* 88:556–565, 1971
7. DLUHY RG, AXELROD L, UNDERWOOD RH, WILLIAMS GH: Studies of the control of plasma aldosterone concentration in normal man: II. Effect of dietary potassium and acute potassium infusion. *J Clin Invest* 51:1950–1957, 1972
8. COOKE CR, RUIZ-MAZA F, KOWARSKI A, MIGEON CJ, WALKER WG: Regulation of plasma aldosterone concentration in anephric man and renal transplant recipients. *Kidney Int* 3:160–166, 1973
9. COOKE CR, HORVATH JS, MOORE MA, BLEDSOE T, WALKER WG: Modulation of plasma aldosterone concentration by plasma potassium in anephric man in the absence of a change in potassium balance. *J Clin Invest* 52:3028–3032, 1973
10. MCCAA RE, MCCAA CS, GUYTON AC: Role of angiotensin II and potassium in the long-term regulation of aldosterone secretion in intact conscious dogs. *Circ Res* 36–37 (suppl 1): I-57–67, 1975
11. LIDDLE GW, DUNCAN LE, BARTTER FC: Dual mechanism regulating adrenocortical function in man. *Am J Med* 21:380–386, 1956
12. TUCCI JR, ESPINER EA, JAGGER PI, PAUK GL, LAULER DP: ACTH stimulation of aldosterone secretion in normal subjects and in patients with chronic adrenocortical insufficiency. *J Clin Endocrinol Metab* 27:568–575, 1967
13. NEWTON MA, LARAGH JH: Effect of corticotropin on aldosterone excretion and plasma renin in normal subjects, in essential hypertension and in primary aldosteronism. *J Clin Endocrinol Metab* 28:1006–1013, 1968
14. BIGLIERI EG, SCHAMBELAN M, SLATON PE JR: Effect of adrenocorticotropin on desoxycorticosterone and aldosterone excretion. *J Clin Endocrinol Metab* 29:1090–1101, 1969
15. LLAURADO JG: Aldosterone excretion following hypophysectomy in man: Relation to urinary Na/K ratio. *Metabolism* 6:556–563, 1957
16. KEM DC, GOMEZ-SANCHEZ C, KRAMER NJ, HOLLAND OB, HIGGINS JR: Plasma aldosterone and renin activity response to ACTH infusion in dexamethasone-suppressed normal and sodium-depleted man. *J Clin Endocrinol Metab* 40:116–124, 1975
17. KATZ FH, ROMFH P, SMITH JA: Episodic secretion of aldosterone in supine man: Relationship to cortisol. *J Clin Endocrinol Metab* 35:178–181, 1972
18. VAGNUCCI AH, MCDONALD RH JR, DRASH AL, WONG AKC: Intradiem changes in plasma aldosterone, cortisol, corticosterone and growth hormone in sodium restriction. *J Clin Endocrinol Metab* 38:761–776, 1974
19. KATZ FH, ROMFH P, SMITH JA: Diurnal variation of plasma aldosterone, cortisol and renin activity in supine man. *J Clin Endocrinol Metab* 40:125–134, 1975
20. KOWARSKI A, DE LACERDA L, MIGEON CJ: Integrated concentration of plasma aldosterone in normal subjects: Correlation with cortisol. *J Clin Endocrinol Metab* 40:205–210, 1975
21. KUNITA H, OBARA T, KOMATSU T, HATA S, OKAMOTO M: The effects of dietary sodium on the diurnal activity of the renin-angiotensin-aldosterone system and the excretion of urinary electrolytes. *J Clin Endocrinol Metab* 43:756–759, 1976
22. GRIM C, WINNACKER J, PETERS T, GILBERT G: Low renin, "normal" aldosterone and hypertension: Circadian rhythm of renin, aldosterone, cortisol and growth hormone. *J Clin Endocrinol Metab* 39:247–256, 1976
23. KRIEGER DT, ALLEN W, RIZZO F, KRIEGER HP: Characterization of the normal temporal pattern of plasma corticosteroid levels. *J Clin Endocrinol Metab* 32:266–284, 1971
24. GALLAGHER TF, YOSHIDA K, ROFFWARG HD, FUKUSHIMA DK, WEITZMAN ED, HELLMAN L: ACTH and cortisol secretary patterns in man. *J Clin Endocrinol Metab* 36:1058–1068, 1973
25. WALKER WG, HORVATH JS, MOORE MA, WHELTON P, RUSSELL RP: Relation between plasma renin activity, angiotensin, and aldosterone and blood pressure in mild untreated hypertension. *Circ Res* 38:470–476, 1976
26. HSU TH, BLEDSOE T: Measurement of urinary free corticoids by competitive protein-binding radioassay in hypoadrenal states. *J Clin Endocrinol Metab* 30:443–448, 1970
27. VETTER W, ZARUBA K, ARMBRUSTER H, BECKERHOFF R, RECK G, SIEGENTHALER W: Control of plasma aldosterone in supine anephric man. *Clin Endocrinol* 3:411–419, 1974
28. SEALEY JE, WHITE RP, LARAGH JH, CASE DB, RUBIN AL: Studies of plasma aldosterone in anephric people: Evidence for the fundamental role of the renin system in maintaining aldosterone secretion. *J Clin Endocrinol Metab* 47:52–60, 1978
29. WEIDMANN P, HORTON R, MAXWELL MH, FRANKLIN SS, FICHMAN M: Dynamic studies of aldosterone in anephric man. *Kidney Int* 4:289–298, 1973
30. WILLIAMS GH, BAILEY GL, HAMPERS CL, LAULER DP, MERRILL JP, UNDERWOOD RH, BLAIR-WEST JR, COGHLAN JP, DENTON DA, SCOGGINS BA, WRIGHT RD: Studies on the metabolism of aldosterone in chronic renal failure and anephric man. *Kidney Int* 4:280–288, 1973
31. MCCAA RE, READ VH, COWLEY AW JR, BOWER JD, SMITH GV, MCCAA CS: Influence of acute stimuli on plasma aldosterone concentration in anephric man and kidney allograft recipients. *Circ Res* 33:313–322, 1973
32. GOODWIN TJ, JAMES VHT, PEART WS: The control of aldosterone secretion in nephrectomized man. *Clin Sci Mol Med* 47:235–248, 1974