Modulation of Plasma Aldosterone Concentration by Plasma Potassium in Anephric Man in the Absence of a Change in Potassium Balance

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Abstract In studies on seven anephric patients, glucose and insulin administration before hemodialysis produced a significant reduction in plasma potassium concentration (mean reduction = 1.3, 1.7, and 1.4 meq/liter at 60, 120, and 180 min, respectively) which was accompanied by a significant and sustained reduction in plasma aldosterone concentration. There was a significant correlation between plasma aldosterone and plasma potassium concentration ($r = +0.74$, $P < 0.001$) and between changes in the concentration of plasma aldosterone occurring in individual patients and the corresponding changes in plasma potassium concentration ($r = +0.52$, $P < 0.01$). There was no significant change in plasma sodium concentration, and plasma corticoid concentration, which was monitored as an index of ACTH elaboration, was reduced at 60 min but increased subsequently as symptoms attributable to hypoglycemia were observed.

These studies demonstrate that plasma aldosterone concentration can be modulated acutely by transitory changes in plasma potassium concentration without a change in potassium balance. The effect of glucose and insulin administration on intracellular potassium in the adrenal cortex is uncertain, and although increased net movement of potassium into cells is the presumptive mechanism of the reduction in plasma potassium concentration, whether the potassium content of the adrenal cortex may have increased or decreased or remained essentially unchanged, cannot be inferred from our data.

INTRODUCTION

Previous studies have shown that aldosterone production can be markedly influenced by changes in potassium (1–5). It is still uncertain, however, whether the modulating effect of potassium is dependent upon gross changes in potassium balance or whether it may also occur in response to changes in plasma potassium concentration independently of changes in potassium balance. Large changes in aldosterone secretion were observed by Cannon, Ames, and Laragh in association with changes in potassium balance that were accompanied by relatively minor variations in plasma potassium concentration (6). Since plasma potassium concentration *per se* appeared to be a poor determinant of aldosterone secretory activity in these studies, these investigators postulated that aldosterone secretion may be regulated by variations in zona glomerulosa potassium accumulation resulting from cumulative changes in potassium balance. However, studies by Dluhy, Axelrod, Underwood, and Williams have shown that plasma aldosterone concentration can be increased acutely by intravenous potassium administration regardless of the previous dietary potassium intake (7). Similarly, aldosterone secretion by the isolated adrenals of dogs (3) and sheep (8) can be stimulated acutely by direct intra-arterial potassium administration. While these observations suggest that aldosterone secretion is indeed responsive to abrupt increments in plasma potassium concentration, they do not specifically answer the question of whether changes in plasma potassium concentration, decreases as well as increases, may alter aldosterone secretion in the absence of a change in potassium balance.

Previous studies on anephric patients have indicated that aldosterone secretion may be regulated predominantly by potassium in the absence of the renin-angiotensin system (9, 10). To determine whether changes in plasma potassium concentration may alter aldosterone secretion in anephric patients in the absence of a change in potassium balance, we administered glucose and insulin in-

Received for publication 19 April 1973 and in revised form 10 August 1973.

TABLE I

Plasma Potassium, Aldosterone, and Corticoid Concentrations before and after Glucose and Insulin Administration

Patient	Plasma potassium				Plasma aldosterone				Plasma corticoids			
	Pre-inf.	60 min	120 min	180 min	Pre-inf.	60 min	120 min	180 min	Pre-inf.	60 min	120 min	180 min
	meq/liter				*ng/100 ml*				*μg/100 ml*			
W. F.	6.0	3.5	2.5	3.6	16.2	1.8	1.8	5.4	16.0	7.0	8.1	11.4
I. F.	5.7	5.5	4.6	4.5	11.1	10.8	1.5	3.0	10.5	4.9	4.1	5.7
M. S.	6.1	4.1	3.8	4.5	9.6	4.2	3.6	5.1	6.0	4.0	15.3	10.7
T. G.	5.3	4.2	4.0	3.8	15.3	3.0	9.6	5.7	5.8	4.6	11.7	33.8
J. S.	7.3	6.6	6.5	6.6	34.8	24.3	6.0	14.4	10.7	10.6	10.5	5.6
B. C.	4.6	3.9	3.7	3.9	6.6	6.6	3.9	8.4	14.8	—	12.7	10.1
J. W.	6.2	4.1	4.1	4.5	7.5	3.3	7.8	4.2	9.1	5.1	12.3	11.4
Mean	5.9	4.6	4.2	4.5	14.4	7.7	4.9	6.6	10.4	6.0	10.7	12.7
SEM	±0.3	±0.4	±0.5	±0.4	±3.7	±3.0	±1.2	±1.4	±1.5	±1.0	±1.4	±3.6

travenously and performed serial determinations of plasma potassium, sodium, aldosterone, and corticoid concentrations before hemodialysis. This enabled us to study the effect of changes (mainly reduction) in plasma potassium concentration on aldosterone secretion, as reflected in the changes in plasma aldosterone concentration, without adding or removing potassium from the body.

METHODS

Studies were performed on seven anephric patients, three males and four females ranging in age from 18 to 52 yr, before hemodialysis. All of the studies were begun at approximately 8:00 a.m. The patients were supine throughout the studies, and after venous blood samples were obtained for determinations of plasma potassium, sodium, aldosterone, and corticoid concentration, and plasma renin activity (PRA),[1] 500 ml of 10% glucose in water containing 20 U of crystalline zinc insulin was administered intravenously over a period of 30 min. Venous blood samples were obtained 60, 120, and 180 min after the infusion was begun for repeat determination of plasma potassium, sodium, aldosterone, and corticoid concentration. Preinfusion blood samples for determination of PRA were collected in chilled syringes containing EDTA and promptly centrifuged at 4°C. All blood samples for determination of plasma aldosterone and plasma corticoid concentration were collected in heparinized syringes. Four patients developed mild symptoms of hypoglycemia between 90 and 120 min after the glucose and insulin infusions were discontinued, and were given additional glucose (10–50 g) intravenously. The total volume of fluid administered to each patient did not exceed 1,000 ml. After the completion of the studies, each patient was hemodialyzed for 7 h, and blood samples were obtained 1 h postdialysis for determination of plasma glucose concentration. Blood samples obtained at the time of suspected hypoglycemia were also subsequently analyzed for plasma glucose concentrations.

PRA in preinfusion blood samples were determined by a modification of the radioimmunoassay described by Haber, Koerner, Page, Kliman, and Purnode (11). Plasma aldosterone concentration was determined by a modification of the radioimmunoassay described by Bayard, Beitins, Kowarski, and Migeon (12) utilizing ammonium sulfate precipitation of bound antigen in the assay as described by Mayes, Furuyama, Kem, and Nugent (13). The accuracy of this method at low plasma aldosterone concentrations was investigated by determining the recovery of aldosterone added to 5 ml of plasma from an adrenalectomized patient in concentrations of 0.5, 1.0, 2.0, and 5.0 ng/100 ml. Mean recovery ($n = 40$ samples) was 114, SEM±8.2%. The relationship between observed and expected concentrations in this range was linear and significantly correlated ($r = +0.73$, $P < 0.001$). This method also distinguishes between 0 and 50 pg (1.0 ng/100 ml) and between 25 and 50 pg (0.5 ng/100 ml difference) of aldosterone added to 5 ml of plasma from an adrenalectomized patient with P values < 0.01 and < 0.05, respectively ($n =$ 20 samples in each comparison). Plasma corticoid concentration was measured by the competitive protein-binding radioassay of Hsu and Bledsoe (14).

RESULTS

No PRA could be detected in the preinfusion blood samples from any of these patients. Plasma potassium, aldosterone, and corticoid concentrations in the preinfusion blood samples and at 60, 120, and 180 min after the infusions of glucose and insulin were begun are shown in Table I. There was a significant and sustained reduction in the plasma potassium concentration beginning with the samples obtained at 60 min ($P < 0.005$)[2] and extending through those obtained at 120 min ($P <$ 0.0025) and 180 min ($P < 0.0025$). Concomitantly, the plasma aldosterone concentration decreased from the preinfusion concentrations to levels that were significantly reduced at 60 min ($P < 0.02$), 120 min ($P <$

[1] *Abbreviations used in this paper:* MCR, metabolic clearance rate; PRA, plasma renin activity.

[2] t test for paired variates.

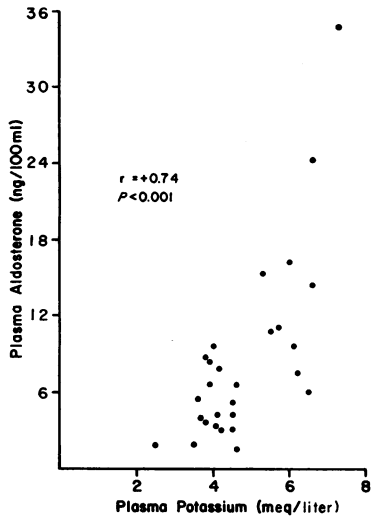

FIGURE 1 Relationship between plasma aldosterone and plasma potassium concentration before and after glucose and insulin administration.

0.025), and 180 min ($P < 0.025$). In contrast, the plasma corticoid concentration was significantly reduced at 60 min ($P < 0.025$), but returned to the preinfusion concentration at 120 min. The plasma corticoid concentration at 180 min was substantially lower than the concentration at 60 min in only one patient (J. S.) who did not manifest symptoms of hypoglycemia and whose plasma glucose concentration at 120 min was 168 mg/100 ml. Plasma glucose concentrations in three of the four patients who exhibited symptoms that were attributed to hypoglycemia fell to 58 (I. F.), 36 (M. S.) and 36 (T. G.) mg/100 ml. Hypoglycemia in the fourth patient (W. F.) was not documented before the administration of additional glucose intravenously. The mean plasma corticoid concentrations at 120 and 180 min were not significantly different, and neither differed significantly from the preinfusion concentration. The plasma sodium concentration was not significantly altered; the preinfusion plasma sodium concentration was 137.1, SEM±2.0 meq/liter and the concentrations at 60, 120, and 180 min were 136.0, SEM±1.7 meq/liter, 135.5, SEM±1.7 meq/liter, and 134.1±1.5 meq/liter, respectively.

There was a highly significant correlation ($r = +0.74$, $P < 0.001$) between individual plasma aldosterone concentrations and plasma potassium concentrations (Fig. 1). Furthermore, changes in the concentration of plasma aldosterone occurring in individual patients after glucose and insulin administration (Fig. 2) could be significantly correlated with the corresponding changes in plasma potassium concentration ($r = +0.52$, $P < 0.01$).

After seven h of hemodialysis (dialysate glucose concentration = 200 mg/100 ml), none of these patients had abnormally reduced plasma glucose concentrations.

DISCUSSION

These studies demonstrate a relationship between glucose and insulin-induced changes in plasma potassium concentration and changes in the concentration of plasma aldosterone which suggests an exquisitely sensitive control mechanism for the regulation of aldosterone secretion. 60 min after the infusion of glucose and insulin was begun, the mean plasma aldosterone concentration was 46% less than the preinfusion concentration. At the same time, there was a 22% reduction in the plasma potassium concentration (1.3 meq/liter). Neither of these changes can be attributed to a dilutional effect of intravenous fluid administration, which produced less than 1% reduction in the plasma sodium concentration. The maximal reduction in plasma aldosterone concentration (66%) and plasma potassium concentration (29%) occurred at 120 min after the infusion of glucose and insulin was begun. If one assumes that the volume of distribution and metabolic clearance rate (MCR) of aldosterone remained constant, this reduction in plasma aldosterone concentration is indicative of a 66% reduction in the aldosterone production and/or secretion rate (15). The effect of glucose and insulin administration on either the volume of distribution or the MCR of aldosterone is unknown. However, a two-fold increase in either parameter would be required to reduce the plasma aldosterone concentration by the amount noted in these studies.

The reduction in plasma corticoid concentration noted at 60 min after glucose and insulin administration was

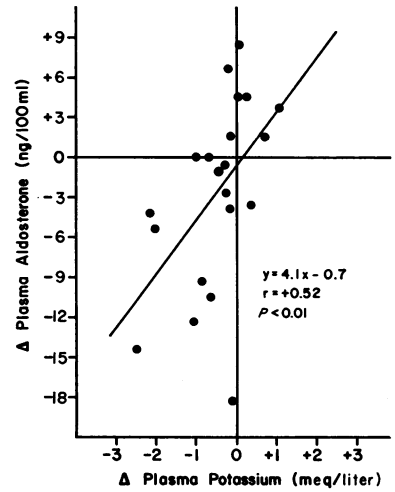

FIGURE 2 Relationship between the changes in plasma aldosterone concentration and plasma potassium concentration in individual patients at 60, 120, and 180 min after glucose and insulin administration was begun.

begun may reflect the normal fall in ACTH and cortisol secretory activity which follows the early morning peak levels (16–18). However, the subsequent increase in plasma corticoid concentration at a time (9:30 a.m. to 11:30 a.m.) when the diurnal rhythm of adrenal cortical secretory activity should have produced either a continued reduction or episodic increments in plasma corticoid concentration of smaller magnitude (19) suggests that ACTH secretion was being stimulated during the studies and that a reduction in ACTH effect on aldosterone production was not the basis for the sustained reduction in plasma aldosterone concentration. The most likely stimulus to ACTH secretion in these studies is the development of hypoglycemia (18) as shown by the low plasma glucose concentrations in three patients and the occurrence of agitation, weakness, and profuse sweating in a fourth patient, which coincided with the increase in plasma corticoid concentration.

The studies of Baumber, Davis, Johnson, and Witty (20) and the in vitro studies of Cushman (21) have indicated that aldosterone production can be directly related to the intracellular potassium content of the adrenal cortex. There are no available data on the effect of glucose and insulin administration on adrenal cortical potassium. However, the reduction in plasma potassium concentration induced by glucose and insulin administration can be primarily attributed to an increase in the net movement of potassium into the liver in association with glycogen deposition (22, 23). Data from studies on forearm skeletal muscle have yielded contradictory results. Andres, Baltzan, Cader, and Zierler observed an increase in the net uptake of potassium by forearm muscle after insulin administration (24), and Grob, Liljestrand, and Johns noted similar changes in potassium uptake after oral glucose loading (25). However, the latter investigators also observed a net *loss* of potassium from forearm skeletal muscle when insulin was administered intra-arterially 2 h after glucose loading, which they attributed to increased potassium uptake in another site, presumably the liver. Thus, although further elucidation of the changes in tissue potassium that occur during glucose and insulin administration is needed, it is possible that the cells of the adrenal cortex do not share in the augmented cellular influx of potassium and that the potassium content of the adrenal cortex may have decreased in our studies as the plasma potassium concentration decreased. It is also possible, on the basis of our data, that glucose and insulin administration produces no change in the net flux of potassium in the adrenal cortex and that changes in plasma potassium concentration alone may alter aldosterone secretion.

It is evident from the correlation between the changes in plasma aldosterone and plasma potassium concentration that even minor transitory changes in plasma potassium concentration in the absence of a change in potassium balance may alter aldosterone secretion in the anephric state. Although heightened sensitivity to potassium in the absence of the renin-angiotensin system cannot be excluded as a factor in these responses, the importance of plasma potassium concentration in the regulation of aldosterone secretion is clearly established by these studies.

ACKNOWLEDGMENTS

This work was supported in part by U. S. Public Health Service Research Grant HL-03303 and Clinical Research Center Grant RR-35.

Dr. Moore was supported by U. S. Public Health Service Training Grant no. 5 TOI AM 05655 and Dr. Horvath by a fellowship from the Heart Association of Maryland.

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