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17-Hydroxylation Deficiency in Man *

EDWARD G. BIGLIERI, MARY ANNE HERRON, AND NORMA BRUST

(From the Medical Services, San Francisco General Hospital, and the Department of Medicine, University of California School of Medicine, San Francisco, Calif.)

The biosynthesis of steroid hormones [1] requires a number of hydroxylating enzymes. Deficiency of these enzymes is demonstrated by increased or decreased amounts of certain steroid metabolites in blood and urine and is best exemplified by the deficiency of 11β-hydroxylase (1) and 21-hydroxylase (2) in patients with congenital adrenal hyperplasia. 17α-Hydroxylase activity is present in these disorders because of the increases in secretion of androgens and excretion of pregnanetriol. In addition, a lack of 3-hydroxysteroid dehydrogenase has also been described (3). 17-Hydroxylation is essential not only to the biosynthesis of cortisol but also to the formation of gonadal hormones (4, 5), the androgenic steroids, androstenedione, testosterone, and, eventually, estrogens (6). Deficiency of this enzyme system should be manifested clinically in both adrenal and gonadal abnormalities if the enzyme is similar in both glands. Furthermore, it is reasonable to assume that lack of 17-hydroxylated steroids would allow uninhibited release of adrenocorticotropin. In such a circumstance in which cortisol secretion is absent, prolonged survival would not be anticipated because mineralocorticoids would be the only adrenal steroids produced. We will describe and discuss a patient with deficiency in 17α-hydroxylase activity with possibly a second defect in production of aldosterone.

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Address requests for reprints to the Editoral Office, Medical Services, San Francisco General Hospital, San Francisco, Calif.

[1] The following trivial names are used in this paper: androstenedione = 4-androsten-3,17-dione; compound S = 11-deoxycortisol = 4-pregnen-17α,21-diol-3,20-dione; dehydroepiandrosterone = 5-androsten-3β-ol-17-one; dexamethasone = 1,4-pregnandien-9-fluoro-16α-methyl-11β,17α,21-triol-3,20-dione; etiocholanolone = 5β-androstan-3α-ol-17-one; pregnanediol = 5β-pregnan-3α,20α-diol; pregnanetriol = 5β-pregnan-3α,11α,20α-triol; stilbestrol = diethylstilbestrol = α,α'diethyl-4,4'stilbenediol; tetrahydroaldosterone = TH aldosterone = 5β-pregnan-3α,11β,21-trihydroxy-20 keto-18-ol; tetrahydrocortisol = THF = 5β-pregnan-3α,11β,17α,21-tetrol-20-one; tetrahydrocortisone = THE = 5β-pregnan-3α,17α,21-triol-11,20-dione; tetrahydrodeoxycorticosterone = THDOC = 5β-pregnan-3α,21-diol-20-one; tetrahydro-11-deoxycortisol = 5β-pregnan-3α,17α,21-triol-20-one; and tetrahydro-18-OH-dehydrocorticosterone = TH-18-OH compound A = 5β-pregnan-3α,18,21-trihydroxy-11,20-dione.

Methods

Case report

The female patient M. H. was the product of a full-term normal pregnancy and weighed 7 pounds at birth. Several severe episodes of bronchitis occurred before 5 years of age. The patient was hospitalized for an influenza-like syndrome when she was 5 years old; the mother (29 years) and one sibling (11 months) died from "influenza" at this time. From 5 to 10 years of age the patient was absent from school about one-third of the time because of infections of the upper respiratory tract. She was hospitalized at age 9 for severe upper respiratory infection, high fever, and unconsciousness. Intravenous glucose therapy promptly restored consciousness, and hypoglycemia was diagnosed but not documented. A similar episode and response to glucose therapy occurred a year later. A tonsillectomy was performed; continued postoperative nausea and vomiting necessitated hospitalization for 1 week.

By 16 years of age the patient was 5 feet 3 inches tall and had not menstruated. Disabling infections of the upper respiratory tract were frequent throughout her adult life. At age 17, the basal metabolic rate and the glucose tolerance test were within normal limits, and a roentgenogram of the skull showed no abnormalities. The patient had grown 4 inches, but menses had not commenced nor had secondary sex characteristics developed. An attempt to effect menses and development of secondary sex characteristics with hormones was made; the breasts developed slightly but menstruation did not occur.

A physical examination at school revealed hypertension; blood pressure ranged between 150/110 and 180/130 mm Hg and remained elevated until age 24. Although the blood pressure was measured frequently between ages 17 and 24, treatment for hypertension was not initiated. At 24 years, Premarin was administered for 3 months after which some vaginal spotting occurred. Small doses of Raudixin were administered to reduce hypertension, but the blood pressure continued to range between 140/100 and 180/110 mm Hg; medication was discontinued after a brief time because of unpleasant side effects. At 26 years of age, the patient was 5 feet 9½ inches tall. At 27, the blood pressure was 180/120 mm Hg, tests for pheochromocytoma were negative, and an intravenous pyelogram showed no abnormalities. At 30, the systolic blood pressure was greater than 200 mm Hg for the first time. At 34, several episodes of marked muscle weakness prompted re-evaluation of the hypertension; low level serum K was discovered electrocardiographically. A Trousseau sign was elicited frequently during measurement of blood pressure; numbness and tingling in the extremities had occurred for many years. In addition, episodes of partial hair loss had occurred since the patient was 24 years old.

Physical examination. At the time of admission to the Clinical Study Center the patient was 35 years old. The blood pressure was 220/140 in the supine position and 194/120 mm Hg on standing. Pulse was 70 beats per minute and regular. Body weight was 75.0 kg. A Trousseau sign was elicited. Funduscopic examination revealed arteriolar narrowing and arteriovenous nicking but no hemorrhage or exudate. The heart was not enlarged and no murmurs were heard. Examination of the lungs and abdomen revealed no abnormalities. No abdominal bruits were detected. The skin was extremely smooth with fine wrinkles at the corners of the mouth and eyes and some fawn-colored freckles on the malar surfaces. The ears were rigid. Axillary and pubic hair were not present, and the breasts were prepubertal in size. Gynecologic examination revealed the following: the clitoris and labia were small, the vagina was pink and nonestrogenized, the cervix was 1 cm in diameter, a tubular structure (2 × 2 cm) was felt in the area of the uterus, no ovaries were felt, and a vaginal smear showed no estrogen effect.

Initial laboratory data. The electrocardiogram showed flattening of the T-waves, U-waves compatible with hypokalemia, and left ventricular hypertrophy. The hematocrit was 40 per 100 ml, and the hemoglobin, 13.5 g per 100 ml. Eosinophils were 2 to 6% of the leukocyte count. Blood urea nitrogen was 12, serum creatinine, 0.8, and serum cholesterol, 233 mg per 100 ml, and protein-bound iodine was 6.7 μg per 100 ml. The following serum electrolyte measurements are based on five determinations: Na, 141 to 147; K, 2.7 to 3.2; CO_2, 29 to 32; and Cl, 95 to 102 mEq per L. Exchangeable K determined by ^{42}K dilution and by the whole body counter was 24 mEq per kg. Serum pH was 7.52. Results of urinalysis included a specific gravity of 1.010 and no evidence of proteinuria, glucose, or casts. The genotype was 46/XX. Steroid values were as follows: urinary excretion of Porter-Silber chromogens (5-ml urine sample) and tetrahydro-11-deoxycortisol, and secretion of cortisol were 0 mg per 24 hours; secretion of aldosterone was 10 μg per 24 hours; and acid-hydrolyzable conjugate of aldosterone was less than 1 μg per 24 hours. A ketosteroid value of 5 mg per 24 hours was obtained but was later considered a result of interference from increased amounts of the metabolites of corticosterone because individual ketosteroids were very low.

All studies were performed in the Clinical Study Center at San Francisco General Hospital periodically over a 2-year period. The patient was put on a constant metabolic diet, which contained 10 mEq Na and 74 mEq K per day by diet analysis. In some studies 6 g NaCl was added to increase Na intake to 122 mEq per day.

All basal steriod measurements were performed while the patient was on 122 mEq Na intake. The administration of corticotropin intramuscularly, 40 U every 12 hours for 5 days, and of angiotensin was also performed on this sodium intake. Pituitary suppression was achieved by administration of dexamethasone and cortisol. Levels of Na and K were measured in the urine daily and in the serum frequently by internal standard flame photometry. Serum chloride was measured by the Cotlove titrimeter technique (7) and serum CO_2 by titrimetric and Van Slyke analysis (8). The Na, K, and N contents were measured after acid digestion of samples of diet and stool.

Steroid measurements

Plasma. Cortisol and corticosterone were measured by a double isotope dilution derivative technique (9). The half-life of corticosterone was determined after the intravenous administration of corticosterone-4-^{14}C (10). Aldosterone was measured by the constant infusion (*d*-aldosterone-1-2-^{3}H) technique of Tait, Tait, Little, and Laumas (11). Progesterone was measured by the double isotope derivative technique (12).[2] Testosterone (13) and androstenedione (14) were determined by the double isotope derivative technique.[3]

Secretion. The methods used to measure secretory rates of cortisol, corticosterone, and aldosterone have been reported previously (15). Cortisol and corticosterone were determined by the double isotope dilution technique and aldosterone by the double isotope derivative technique.

The secretory rate of deoxycorticosterone (DOC) was determined as follows: A 3-μc dose of DOC-1-2-^{3}H was administered intravenously, and urine was collected 24 and 48 hours thereafter. During the first 24 hours, 75% of the injected dose was excreted. At most, only an additional 5% was excreted in the subsequent 96 hours. Urine samples were first washed with 2 vol of ethyl ace-

[2] Measurement done by Mr. Richard Underwood, Sears Surgical Laboratory, Boston City Hospital, Boston, Mass.

[3] Determination performed by Dr. Charles Lloyd, Worcester Foundation for Experimental Biology, Shrewsbury, Mass.

TABLE I

*Chromatographic system for isolation of THDOC**

System	Solvent ratios	Time
		hours
I	Cyclohexane 100: benzene 40: methanol 100:water 20	8
II	Decalin 100:nitromethane 50:methanol 50	96
III	Cyclohexane 100:nitromethane 50:methanol 50	28
IV	Methylcyclohexane 100:methanol 100:water 50 (reverse phase)	4
V	Iso-octane system of Pasqualini and Jayle (16)	6
VI	Decalin 100:nitromethane 50:methanol 50	48
VII	Cyclohexane 100:nitromethane 50:methanol 50	12
VIII	Same as IV	

* THDOC = tetrahydrodeoxycorticosterone.

tate, and the pH was adjusted to 4.5 and hydrolyzed with $\frac{1}{10}$ of the volume of the sample with Ketodase. Samples were incubated for 24 hours. The steroid was extracted with CCl_4, washed, and chromatographed in system I (Table I). The THDOC was eluted and chromatographed in systems II and III, then eluted, dried, and acetylated with acetic anhydride-^{14}C for 24 hours. The THDOC diacetate was then chromatographed in systems IV through VIII. The THDOC diacetate of the final chromatogram was eluted, dried, dissolved in toluene with 2,5-diphenyloxazole and 1,4-di-2-phenyloxazole, and ^{3}H and ^{14}C were counted simultaneously in a liquid scintillation spectrometer.

Urinary excretion. Levels of tetrahydrocortisol and tetrahydrocortisone were determined by measurement of Porter-Silber chromogens (17) and those of tetrahydro-11-deoxycortisol, by the technique of Henke, Doe, and Jacobson (18). Tetrahydro-18-hydroxy-11-dehydrocorticosterone was measured (19).[4] Dehydroepiandrosterone, etiocholanolone, androsterone, pregnanetriol, and pregnanediol were measured by gas liquid chromatography.[5] Total biologically active estrogens were determined by the method of Maddock and Nelson (20).[6] Acid-hydrolyzable conjugate of aldosterone and TH aldosterone were measured by the double isotope dilution derivative technique (21). Tetrahydrodeoxycorticosterone excretion was measured by a double isotope dilution derivative technique. Tritium-labeled THDOC was prepared enzymatically from DOC-1-2^{3}-H (21). Approximately 6,000 cpm of THDOC-1-2^{3}-H was added to the urine samples. Portions were extracted, hydrolyzed, acetylated, and chromatographed as described for DOC secretion.

[4] Dr. Stanley Ulick, Veterans Administration Hospital, Bronx, N. Y.

[5] Dr. Roberto Rivera, Syntex Research Laboratory, Palo Alto, Calif.

[6] Dr. C. Alvin Paulsen, University of Washington School of Medicine, Seattle, Wash.

Protein hormone measurements

Blood. Plasma ACTH was measured by the method of Lipscomb and Nelson (22).[7] Renin was determined by a modification of the method of Boucher, Veyrat, De Champlain, and Genest (23).[8] Serum growth hormone was determined by an adaptation of radioimmunoassay technique (24).[9]

Urine. The urine was assayed for follicle-stimulating hormone with the Steelman-Pohley technique (25).

Miscellaneous measurements

Angiotensin sensitivity. The amount of angiotensin II amide required to raise diastolic and systolic blood pressures 20 mm Hg was determined by a technique similar to that of Kaplan and Silah (26).

Insulin sensitivity. Insulin sensitivity was assessed after intravenous administration of .05 kg crystalline insulin 16 hours after fasting by measuring blood sugar (27) and levels of free fatty acids and glycerol in plasma.[10]

Results

C-21 steroids derived from progesterone. The concentration of progesterone in plasma was 0.21 μg per 100 ml (normal is 0.11 to 1.04), and that of pregnanediol in urine ranged from 2 to 11 mg per 24 hours (normal is 2 to 5) in three consecutive 24-hour collections. Urinary THDOC was 500 μg per 24 hours (normal is 7 to 25), and secretion of DOC was 4.0 mg per 24 hours (normal is 0.050 to 0.160). The concentration of corticosterone in plasma ranged from 21 to 31 μg per 100 ml (normal is < 1) and showed a diurnal rhythm (25 at 8 a.m. and 9.1 μg per 100 ml plasma at 6 p.m.). The secretory rate of corticosterone was 112 to 124 mg per 24 hours (normal is 0.9 to 4.4). The TH-18-OH compound A in urine was 675 μg per 24 hours (normal is $< 5 \times$ TH aldosterone). No aldosterone was detected in plasma (normal is < 0.01 μg per 100 ml plasma). The secretory rate of aldosterone ranged from 10 to 18 μg per 24 hours on four occasions (normal is 60 to 168). Urinary levels of acid-hydrolyzable con-

[7] Dr. E. M. Gold, Veterans Administration Hospital, Los Angeles, Calif.

[8] Determination done in the laboratories of Dr. J. W. Conn, University of Michigan Medical Center, Ann Arbor, Mich.

[9] Dr. G. Grodsky, Metabolic Unit, University of California Medical Center, San Francisco, Calif.

[10] Free fatty acids and glycerol were measured by Dr. Richard Havel, University of California Medical Center, San Francisco, Calif.

jugate of aldosterone were always < 1 μg per 24 hours (normal is 5 to 20), and those of TH aldosterone ranged from 0 to 5 μg per 24 hours (normal is 15 to 60).

C-21 steroids derived from 17α-OH-progesterone. None of the C-21 steroids derived from 17α-OH-progesterone were detected in blood and urine. The secretory rate of cortisol was 0 (normal is 10 to 30 mg per 24 hours).

C-19 steroids and estrogens derived from 17α-OH-progesterone and 17α-OH-pregnanolone. Urinary dehydroepiandrosterone, androsterone, and etiocholanolone levels were 0.11 to 0.17 (normal is 1.34), 0.13 to 0.24 (normal is 3.12), and 0.20 to 0.40 (normal is 1.0 to 3.0) mg per 24 hours, respectively. Plasma testosterone was 0.014 μg per 100 ml (normal is 0.037), and androstenedione was 0.068 μg per 100 ml (normal is 0.140). The total amount of biologically active estrogens in urine was < 0.2 μg-Eq estradiol benzrate per 24 hours (normal is 0.4 to 0.7).

Protein hormone measurements. Plasma levels of ACTH were 2.0 at 8 a.m. and 1.6 mU per 100 ml at 6 p.m. No plasma renin activity was detected after 4 days of 10 mEq Na intake and 4 hours of standing. The amount of angiotensin II amide required to produce a 20 mm Hg blood pressure increase was only 2.7 mμg per kg per minute (normal is 5 to 11). The level of follicle-stimulating hormone was 138 international units (IU) per 24 hours (highest normal is 20). Serum growth hormone levels were normal at 0.5 mU per ml.

Infusion of corticosterone-4-^{14}C. The biological half-time of infused corticosterone-4-^{14}C was 50 minutes (normal is 60 minutes). The pool size was 8.2 mg (normal is .3).

Effect of continued administration of ACTH (Figure 1). Administration of ACTH gel, 40 U every 12 hours, for 5 days produced no significant change in the secretory rates of corticosterone and aldosterone. The control rates of secretion of corticosterone and aldosterone were 112 mg and 10 μg per 24 hours, respectively.

SECRETORY RATES	CORTICOSTERONE mg/24 HR	ALDOSTERONE ug/24 HR
CONTROL	112.0	10.5, 8.3
5TH DAY * CORTICOTROPIN	116.0	15.6

*CORTICOTROPIN 40 UNITS I.M. EVERY 12 HOURS FOR 5 DAYS

FIG. 1. RESPONSE TO CONTINUED ADMINISTRATION OF CORTICOTROPIN. Note little change in aldosterone and corticosterone secretion.

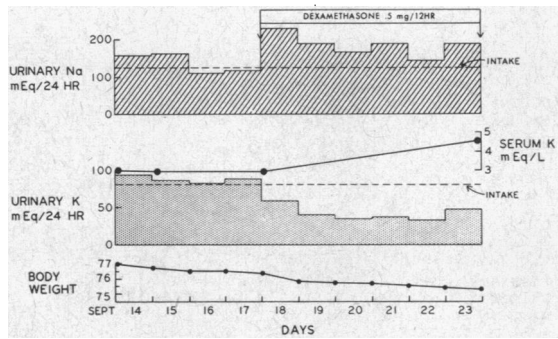

FIG. 2. EFFECT OF PITUITARY SUPPRESSION DURING 122 MEQ NA INTAKE. Note that dexamethasone produced Na diuresis, K retention with correction of hypokalemia, and weight loss.

Effect of pituitary suppression on Na, K, and aldosterone excretion, serum K, and body weight during 122 mEq Na intake (Figure 2). Administration of dexamethasone, 0.5 mg every 12 hours, for 6 days effected prompt Na diuresis, decrease in urinary K, increase in serum K from 2.9 to 4.5 mEq per L, and loss of weight. Cumulative Na excretion was 372 mEq and cumulative K retention, based on measurements made in urine, was 242 mEq per L. There was no change in aldosterone excretion; values were < 1 μg per 24 hours.

Effect of restricted Na intake and pituitary suppression on electrolyte balance, steroids, and body weight (Figure 3). A 4-day control study after equilibration on 122 mEq Na intake was carried out. Potassium balance was slightly negative, and serum K levels were low. Corticosterone secretion was 124 mg per 24 hours, and plasma level was 20 μg per 100 ml. Aldosterone excretion was 1 μg per 24 hours, and secretion on day 1 was 10 μg per 24 hours. On day 4, THDOC was 500 μg per 24 hours.

At the end of the control period added NaCl was removed from the diet. Renal sodium conservation on the sodium-limited diet was accomplished in the first 2 days of the 9-day study (even though a mild gastroenteric disorder and fever produced a brief negative Na and K balance on day 6. Potassium was retained, and serum K increased slightly. Aldosterone excretion remained at 1 μg per 24 hours, and after 9 days THDOC

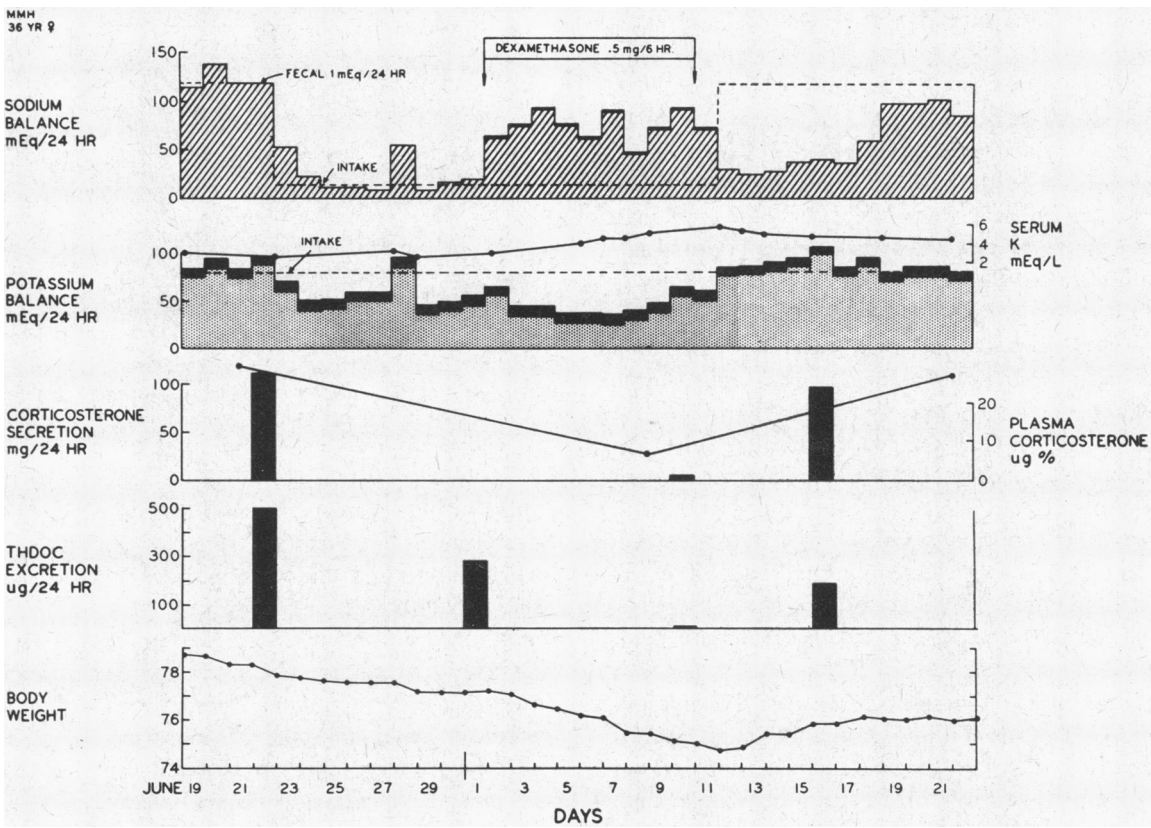

FIG. 3. EFFECT OF RESTRICTED Na INTAKE AND PITUITARY SUPPRESSION ON ELECTROLYTE BALANCE AND STEROID MEASUREMENTS. THDOC = tetrahydrodeoxycorticosterone.

was 285 μg per 24 hours. Blood pressure was unaffected during this period.

Sodium restriction was continued, and dexamethasone, 0.5 mg every 6 hours, was administered for 9 days. Negative Na balance occurred and K retention increased. Serum K gradually increased to 5.5 mEq per L. Secretion of corticosterone decreased to 4.4 mg per 24 hours and plasma corticosterone to 6 μg per 100 ml. The secretory rate of DOC was 44 μg per 24 hours, and THDOC was 7.0 Aldosterone excretion was still reduced at 1 μg per 24 hours. Blood pressure fell and was 120/80 mm Hg on day 8 of the suppression period. The patient lost a total of 2.2 kg body weight.

After dexamethasone was discontinued, NaCl was added again to the diet. Sodium balance was progressively positive, K balance was negative, and serum K gradually decreased from 5.5 to 4.0 mEq per L. Corticosterone secretion increased to 99 mg per 24 hours; plasma corticosterone, to 22 μg per 100 ml; and THDOC excretion, to 180 μg per 24 hours.

Effect of DOC and metyrapone on electrolytes and steroids (Figure 4). During the 2 days of treatment with DOC acetate (20 mg per 24 hours) Na retention was 114 mEq. There was little change in K balance, although serum K decreased from 3.5 to 3.2 mEq per L.

During the 3 days of metyrapone administration, Na excretion fluctuated slightly, but a negative urinary K balance of 40 mEq was noted. Excretion of THDOC on the third day was 4,850 μg per 24 hours. The concentration of corticosterone in plasma decreased on the fourth day from the control level of 35.4 to 18.9 μg per 100 ml; in the subsequent 4 days after discontinuance of metyrapone the concentration increased to 27.8 μg per 100 ml.

Nitrogen and carbohydrate metabolism. Although corticosterone secretion was approximately 60 times the normal rate, N balance was slightly

positive, 0.2 to 2.0 g per 24 hours over a 30-day period. Levels of blood glucose were within normal limits, and sensitivity to insulin was normal. Levels of free fatty acids and glycerol in plasma were considerably elevated at 1.51 and 0.252 μmoles per ml, respectively, but decreased normally in response to insulin. Measurements of growth hormone in serum were within normal limits and increased to 3.5 mU per ml after administration of insulin.

Course of treatment (*Figure 5*). After the studies had been completed, the patient was treated during the first 12 weeks with dexamethasone, 0.5 mg each 12 hours, orally. Blood pressure was maintained within the normal range, but the level of serum K began to rise and salt craving was noted by the patient. She increased the NaCl intake to 12 to 16 g per day. When the serum potassium level reached 6.7 mEq per L, 9α-fluorohydrocortisone, 100 μg per day, was given orally; serum K returned to normal levels, but a marked gain in weight occurred. Plasma corticosterone gradually decreased to a normal level (0.8 μg per 100 ml). Dexamethasone and 9α-fluorohydrocortisone therapy were discontinued; the concentration of plasma corticosterone rose to 20 μg per 100 ml, and the level of serum K dropped to 3.8 mEq per L.

After 6 weeks cortisol, 30 mg per day, was given orally for 10 weeks. The concentration of plasma corticosterone fell to 3 μg per 100 ml, and

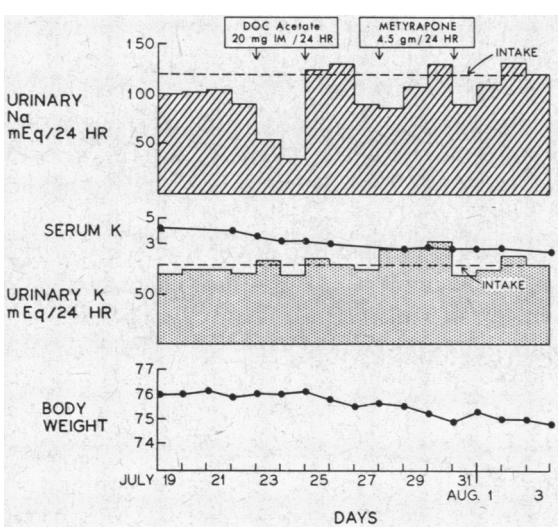

FIG. 4. EFFECT OF DEOXYCORTICOSTERONE (DOC) ACETATE AND METYRAPONE ON URINARY Na AND K.

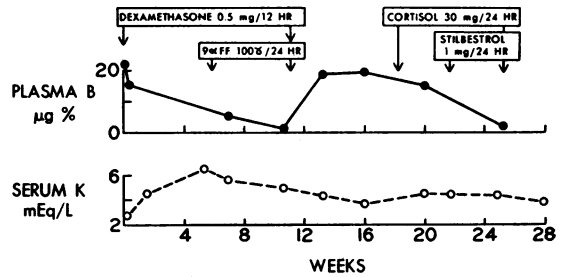

FIG. 5. COURSE OF TREATMENT. 9αFF = 9α-fluorohydrocortisone; B = corticosterone.

the level of serum K increased to 4.5 mEq per L and remained there. Blood pressure again returned to the normal range. Stilbestrol, 1 mg per day, was administered for 4 weeks; all measurements remained the same except the level of serum corticosterone, which was three times higher than that observed during administration of dexamethasone by itself. When cortisol and stilbestrol were discontinued, the level of corticosterone in plasma promptly rose to 25 μg per 100 ml. During the course of treatment upper respiratory infections and oral mucosal sores did not develop and stamina increased.

Discussion

A marked deficiency of adrenal 17α-hydroxylase activity is indicated by the absence of C-21 steroids derived from 17α-OH-progesterone and the minimal amounts of C-19 steroids derived from 17α-OH-progesterone and 17α-OH-pregnenolone. Furthermore, the negligible estrogen production, manifested clinically by the absence of secondary sex characteristics, the lack of estrinization, and the negligible amount of estrogens in urine, indicates additional evidence of diminished 17-hydroxylation in the ovary. The only steroids detected were those not dependent on this enzymatic process, namely, progesterone, DOC, corticosterone (B), and TH-18-OH compound A. Secretory rates of these steroids were greater than normal, permitting survival of the patient. The minimal amount of aldosterone secreted in the presence of increased secretion of B and excretion of TH-18-OH compound A may also indicate a second biosynthetic defect either in the conversion of 18-OH-B to aldosterone because of lack of dehydrogenase activity or in the conversion of angular methyl group of B to an aldehyde.

The secretory rates of B and DOC were far greater than rates observed after infusion of ACTH (10). Plasma levels of B were continually elevated and varied diurnally, and the pool size was much greater than normal. Metabolism of B was normal, indicated by the normal half-life. Corticosterone is not generally considered a mineralocorticoid, but the amounts secreted in this patient readily explain the presence of hypokalemic alkalosis, hypertension, and eosinophilia. Conn, Fajaris, and Louis demonstrated that similar amounts produce Na retention, K loss, and serum K reduction (28). Corticosterone does not affect the circulatory eosinophil count or the excretion of ketosteroids and cortisol metabolites. Short-term administration of B has no apparent effect on blood pressure, but continued and excessive secretion of this mineralocorticoid would be expected to cause hypertension eventually. The increased production of DOC also contributed to hypertension and hypokalemia. Mineralocorticoids have little, if any, effect on release of ACTH, as previously suggested, by failure to alter the urinary metabolites of cortisol (28). However, because such large amounts of B are secreted there appears to be some control exerted on ACTH secretion in the absence of cortisol. Pigmentation did not increase in this patient. Plasma ACTH was slightly above the normal range and fluctuated diurnally. The adrenal glands were already responding maximally to endogenous ACTH judged by the lack of increase in secretion of corticosterone after 5 days of exogenous ACTH administration. The levels of ACTH observed, including the persistent diurnal pattern, are quite similar to those in patients with congenital adrenal hyperplasia (29).

The levels of corticosterone secretion might be expected to affect carbohydrates and protein metabolites. However, growth was normal throughout life. Negative N balance was not detected during a 1-month study. Administration of B prevents hypoglycemia after fasting in patients with Addison's disease and decreases carbohydrate tolerance in normal subjects (28). The blood glucose levels after fasting, the oral glucose tolerance test, and the insulin sensitivity test were normal in this patient. Thus, some glucocorticoid activity could be ascribed to the large quantities of corticosterone secreted. The frequency and severity of upper respiratory infections and the persistence of oral sores can be attributed to lack of cortisol and to minimal glucocorticoid activity of corticosterone. This is supported by the symptomatic improvement after dexamethasone and cortisol therapy. Levels of free fatty acids and glycerol in plasma were elevated in the presence of normal carbohydrate tolerance. The reason for this abnormality is not clear. It is unlikely that increased production of ACTH is responsible because ACTH levels were not particularly elevated. Lack of cortisol, normal amounts of growth hormone, and greater than normal amounts of B may be factors involved in this observation. Because B and DOC have little or no effect on release of ACTH and because circulating cortisol is absent, minimal inhibition of ACTH secretion could be a major factor in this disorder. Evidence for ACTH as the cause of the increased secretion of B and DOC, the hypertension, and the hypokalemia was effectively demonstrated by the correction of these abnormalities during slight pituitary suppression with dexamethasone and cortisol. Treatment with dexamethasone for 12 weeks effected the same response, but it was apparent that no mineralocorticoid activity was present, since serum K increased, salt craving occurred, and aldosterone was absent in the urine. These responses did not occur with comparable doses of cortisol for the same period of time, although blood pressure and plasma corticosterone levels were essentially the same. During the 4 weeks in which stilbestrol was administered in addition to cortisol all measurements remained the same except plasma corticosterone levels. The increase in B in plasma from 0.8 to 3 μg per 100 ml might be attributed to the effect of estrogens on steroid-binding globulin (30).

A second biosynthetic defect may also be present. The diminished secretion and excretion of aldosterone remained essentially unchanged during the continued administration of ACTH and the 9 days of Na restriction and after the marked natriuresis that occurred with dexamethasone therapy. The negligible aldosterone secretion and excretion in this patient are similar to those observed after unilateral adrenalectomy for an aldosterone-producing tumor (31). In these patients

the reduced aldosterone secretion is a consequence of prolonged suppression of renin secretion (32). The absence of plasma renin in this patient most likely results from excessive secretion of DOC and B, but whether or not this explains the lack of aldosterone secretion is not known at this time (33). Before a second biosynthetic defect can be implicated, measurement of aldosterone secretion during more prolonged suppression of ACTH production is necessary. Precedence for such an abnormality can be found in patients with an aldosterone biosynthetic defect, with Na loss, with extensively increased secretion of 18-OH-B, and with slight increases in B secretion. Treatment with DOC and a high Na diet reduce the secretory rates of 18-OH-B and corticosterone in these patients (34).

Whether or not "escape" from salt-retaining hormones occurred in this patient is not clear. Hypervolemia was not present. Excessive Na retention and K depletion were demonstrated by the diuresis of Na and retention of K during suppression of DOC and B and by the extremely low total body K. However, escape may not have occurred because administration of DOC acetate for 3 days produced further retention of Na and slight decrease in serum K.

Metyrapone, an 11β-OH inhibitor, reduced the concentration of corticosterone in plasma by 50% and increased DOC production but had little effect on urinary electrolytes. The amount of corticosterone present during these two periods may have modified the Na response to exogenous and endogenous DOC.

17-Hydroxylation of steroids occurs only in the adrenal glands and the gonads. The absence of secondary sex characteristics and the negligible excretion of estrogens strongly suggest that the demonstrated 17-hydroxylase deficiency in the adrenal glands also occurs in the ovaries. In addition, the level of follicle-stimulating hormone was pathologically increased in this estrogen-deficient patient. The presence of a similar enzymatic defect in both the ovary and the adrenal gland suggests that the enzyme may be determined by a single gene. We do not know whether a similar defect was present in the sibling who died at 11 months of age or whether a partial defect was present in the mother.

Summary

A patient with deficiency of 17-hydroxylation activity in the adrenal glands is reported. A similar defect in the ovary is suggested. Corticosterone and deoxycorticosterone in excess produce a mineralocorticoid excess syndrome characterized by hypertension and hypokalemic alkalosis. The virtual absence of aldosterone secretion may represent a second biosynthetic defect. The importance of 17-hydroxylation in steroid biosynthesis is demonstrated *in vivo*. Amenorrhea, hypertension, and hypokalemic alkalosis are the indicators of a 17-hydroxylation deficiency.

Acknowledgment

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