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MINERALOCORTICOIDS IN CONGENITAL ADRENAL HYPERPLASIA

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Summary—While hypertension is observed in only two of the three major subtypes of congenital adrenal hyperplasia (CAH), 11β- and 17α-hydroxylase deficiencies, deoxycorticosterone (DOC) production is increased in all. The elevated zona fasciculata (ZF) DOC produces mineralocorticoid hypertension with suppressed renin and reduced potassium concentrations. The DOC levels in 21-hydroxylase deficiency are in part produced by renin stimulation of the Zona glomerulosa (ZG) along with aldosterone. Assessment of the mineralocorticoid hormones of the ZF and ZF (17-deoxy steroids) provides additional unique characteristics of each subtype. Dissociation of DOC from cortisol is not unique to CAH. This dissociation is seen in other disorders and contrived conditions. There is a strong suggestion of a non-ACTH regulator of 17-deoxy steroids (DOC) that may contribute significantly to DOC production in general and effect DOC levels in CAH.

INTRODUCTION

The mineralocorticoid hormone in hypertensive forms of congenital adrenal hyperplasia (CAH) is deoxycorticosterone (DOC). In the three major forms of CAH, 21-hydroxylase deficiency (21-OHD) [1], 11β-hydroxylase deficiency (11β-OHD) [2] and 17α-hydroxylase deficiency (17α-OHD) [3], DOC production is increased, but hypertension only occurs in the 11β-OHD and 17α-OHD. The secretory mixture of steroids of the 17-deoxy pathway in the zona fasciculata (ZF) is the cause of hypertension in these disorders. CAH is a group of disorders with deficiencies of specific cytochrome *P*-450 hydroxylating enzymes. Of particular interest, but often overlooked, is the diagnostic value of steroid levels distal to the block in the ZF and also the aldosterone levels from a functionally normal zona glomerulosa (ZG) [4].

11β-OHD SYNDROME

The first of the hypertensive syndromes of CAH was described in 1955 by Eberlein and Bongiovanni [5]. The 11β-OHD syndrome was overshadowed by the almost simultaneous identification of an aldosterone producing tumor by Conn [6].

The resultant steroid abnormalities seen in this disorder are shown in Fig. 1. The reduced cortisol levels distal to the block initiate ACTH increases with subsequent elevations in steroid precursors proximal to the deficiency. Characteristically, 11-deoxycortisol is elevated in the 17-hydroxy pathway and DOC is increased in the 17-deoxy pathway. Steroids distal to 11β-hydroxylation (DOC, corticosterone (B) and 18-hydroxyDOC (18-OHDOC), are reduced. They can be useful in further defining the syndrome. With elevated ACTH stimulated levels of 17α-hydroxyprogesterone, B and 18-OHDOC are reduced and fail to normally increase with acute ACTH administration. The increased DOC levels are highest in these hypertensive forms of CAH. Peripheral DOC levels are maintained by the ZF (Table 1). Blood pressure can be severely elevated in this disorder and can vary considerably depending on the degree of the enzyme deficiency. DOC produces a mineralocorticoid excess state and the mechanism of the hypertension is similar to that seen with aldosterone in primary aldosteronism. The high DOC levels cause transient volume dependent hypertension, renal potassium wasting and suppression of aldosterone [7]. A bifunctional 11β-18-hydroxylating enzyme is strongly suggested in this disorder, at least in the ACTH

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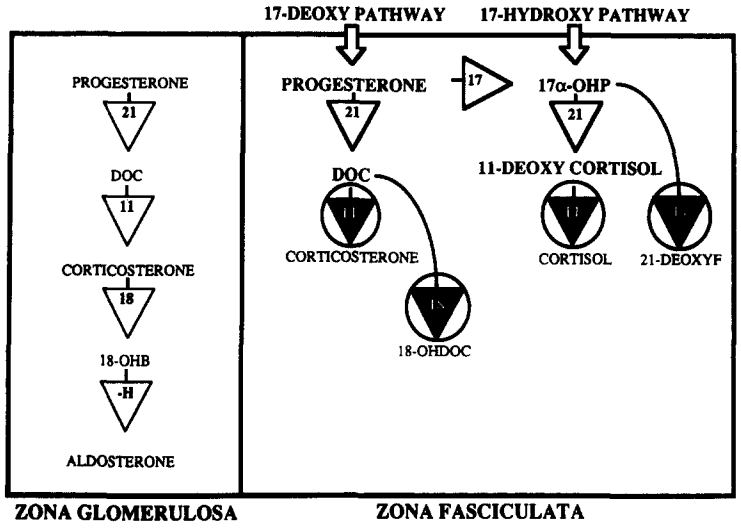

Fig. 1. 11β-OHD. Steroids in bold type are increased, others are normal or reduced; 17-OHP, 17α-hydroxyprogesterone; S, 11-deoxycortisol; 21-deoxyF, 21-deoxycortisol; F, cortisol; 18-OHB, 18-hydroxycorticosterone.

dependent ZF. Basally, 18-OHDOC and B are reduced with increased plasma DOC levels (Fig. 2). Both 18-OHDOC and B show impaired responses to acute and continued ACTH stimulation. After prolonged ACTH suppressive treatment, the renin–aldosterone system returns to normal basal values of aldosterone and 18-OHB resume normal dynamics to potassium, angiotensin II and ACTH stimulation. Both 18-OHDOC and B remain subnormal suggesting alternate 18-hydroxylating mechanisms in the ZG [8].

Management of this disorder consists primarily of adequate glucocorticoid treatment to

Table 1. Basal steroid levels in untreated patients with 11-OHD and 17-OHD

Patient	F (μg/dl)	DOC (μg/dl)	B (μg/dl)	18-OHDOC (μg/dl)	Aldo (μg/dl)	18-OHB (μg/dl)	17-OHP (μg/dl)	S (μg/dl)
				11-OHD				
1	1.6	279	13	1.5	1.0	5.5	435	4840
2	1.1	350	13	1.5	1.0	6.9	195	3669
3	0.3	1095	13	1.5	1.0	3.0	670	15000
4	0.2	851	13	1.5	1.0	3.0	163	8000
5	0.2	1175	13	1.5	1.0	3.0	476	14000
6	3.9	1710	100	6.1	5.4	11.5	275	19000
Mean	1.2	910	28	2.3	1.7	5.5	369	10752
SEM	0.6	220	14	0.8	0.7	1.4	79	2512
				17-OHD				
1	0.2	277	11600	172	4.7	247	—	—
2	0.2	136	8000	141	5.1	386	—	—
3	0.2	360	20600	350	11.0	755	—	—
4	0.2	478	24600	427	8.0	407	—	—
5	0.2	145	7300	57	0.6	69	0.5	8.0
6	0.5	73	782	17	1.6	38	22.1	13.9
7	4.5	28	8800	109	1.3	115	21.5	15.8
8	3.8	77	11100	225	1.3	79	41.0	25.7
9	2.6	24	10900	270	2.4	300	24.8	8.8
10	0.2	240	23000	383	—	2200	—	—
11	0.2	360	5800	3	2.0	142	—	—
12	0.2	143	4100	123	5.3	113	—	—
13	0.5	233	—	—	0.5	—	—	—
14	0.4	286	26700	541	0.9	387	0.6	4.0
15	0.2	173	12800	183	8.8	145	—	—
16	0.2	244	10000	141	2.0	86	—	—
Mean	0.9	205	12405	209	3.7	365	18.4	12.7
SEM	0.4	31	1827	37	0.8	128	15.1	1.8
Normal	10.4	5.1	148	3.8	9,7	24.9	115	32.5
SEM	0.7	0.4	25	0.7	1.1	2.5	5	9.0

Abbreviations used: F, cortisol; Aldo, aldosterone; 18-OHB, 18-hydroxycorticosterone; 17-OHP, 17-hydroxyprogesterone; S, 11-deoxycortisol.

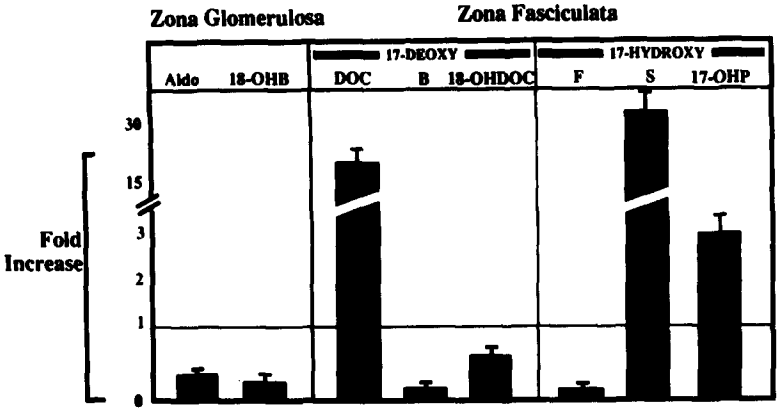

Fig. 2. 11β-OHD. Fold changes compared to normal control value.

reduce the 17α-hydroxyprogesterone and DOC levels to near normal. It is often difficult to completely suppress DOC into the normal range but it is sufficiently reduced to cause correction of the potassium wasting and the hypertensive process. Care is advised, not only in this form of CAH, but in the 17α-OHD syndrome patient when starting glucocorticoid therapy. The ZG is severely suppressed and may take months or years to fully recover. A transient period of mineralocorticoid replacement with fludrocortisone may be necessary to prevent or correct a hypovolemic crisis.

17α-OHD SYNDROME

17α-OHD also produces a hypertensive mineralocorticoid state not unlike that seen in 11β-OHD. The mineralocorticoid hormone produced in excess is DOC. The schema for the steroid patterns is displayed in Fig. 3. All the steroids originating from the ZG and the steroids of the ZF 17-hydroxy pathway are impaired. The only steroids produced in excess are those of the 17-deoxy pathway (Fig. 4). The key location of 17α-OHD prevents side chain cleavage (and may actually be the same enzyme) and gonadal steroid production. A single gene controls the enzyme both in the gonads and in the adrenals. Clinically, these individuals present in the male as pseudohermaphrodites and in the female with primary amenorrhea and eunuchoid habitus. No virilizing steroids are produced as is seen in the other forms of CAH. Again, with the cortisol deficiency, ACTH drives primarily the steroids of the 17-deoxy-

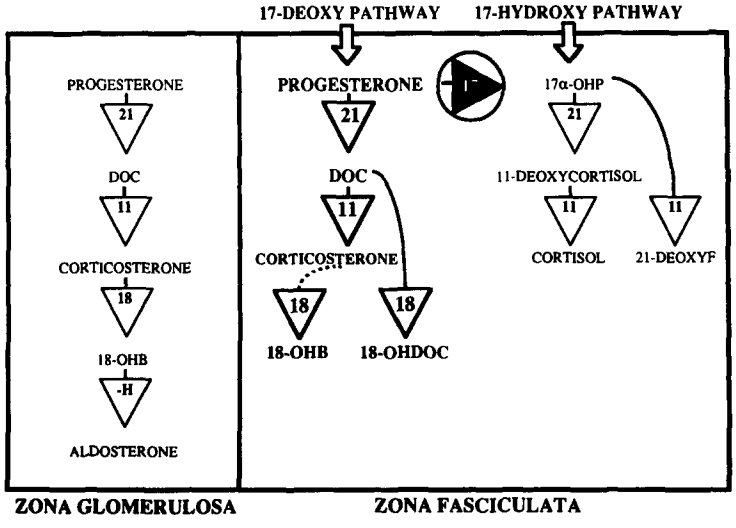

Fig. 3. 17α-OHD. Steroids in bold type are increased, others are normal or reduced.

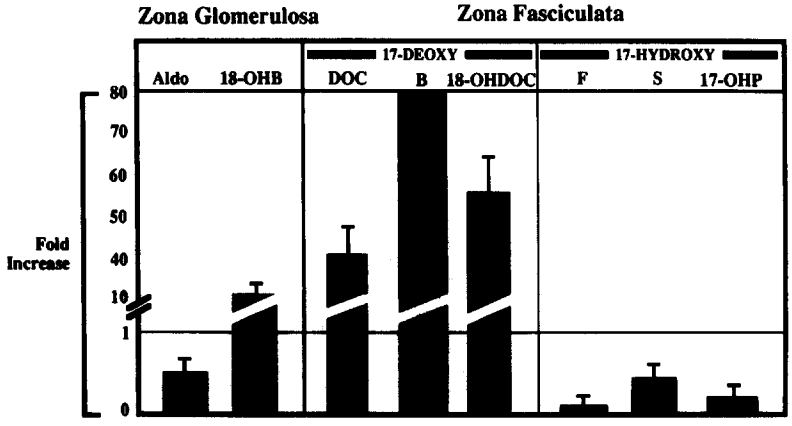

Fig. 4. 17α-OHD. Fold changes after normal control value.

pathway. DOC is produced in quantities sufficient to suppress the renin–aldosterone system and cause hypokalemia. The other steroids of this pathway do have varying degrees of mineralocorticoid activity. B can reach concentrations greater than 20 mg/dl where both glucocorticoid and mineralocorticoid properties can be expressed. Cortisol levels are extremely low in all our patients. Higher levels could be ascribed to a milder deficiency and the glucorticoid effect of B on central release and production of ACTH. It is important to stress that in our experience, it is very rare to find measurable levels of aldosterone.

Three patients with presumed aldosterone levels in the low normal range were recently referred to our laboratory. In each instance we found the measurements to be inaccurate and aldosterone levels were virtually absent. The Japanese literature reported low or normal aldosterone levels in patients with presumed 17α-OHD that were suppressed with dexamethasone or glucocorticoid therapy. While the methodology seems adequate in this complex array of steroids, isolation of individual steroids is essential before one draws a conclusion that aldosterone is present [9]. Theoretically, it is possible that the renin–angiotensin system may not be completely suppressed due to a mild deficiency and the low cortisol levels may have less of an inhibiting effect or present less pseudosubstrate to interfere with the late steps in aldosterone biosynthesis. There is a direct reciprocal relationship between cortisol production and aldosterone levels in many disorders of ACTH excess [10]. In Cushing's syndrome and the ectopic ACTH syndrome aldosterone levels can be extremely low even though renin levels are normal [11].

A feature of this disease which is not appreciated is the sensitivity of the ZG to ACTH therapy after ACTH suppressive therapy has been withheld for 1–2 weeks for essential diagnostic studies. When glucocorticoid therapy is stopped there is a surge of aldosterone production reaching levels that may be three times normal basal values. These elevated levels occur when the renin system is still suppressed, presumably due to the ACTH surge. The levels of all detectable steroids of the ZG and ZF do have a circadian rhythm that is ACTH dependent. It takes 7–10 days for the aldosterone levels to return to normal as the renin–angiotensin system recovers [12] (Fig. 5). Thus, in many situations, if this is not taken into account, these patients may have certain characteristics of dexamethasone suppressible hyperaldosteronism, in that the dexamethasone corrects steroid abnormalities and maintains the correction of the hypokalemia and hypertension.

The search for heterozygotes with 17α-OHD is often difficult since there is no linkage with the HLA system as observed in the 21-OHD and 17α-OHD types. In the study of several families there has been slightly exaggerated responses of DOC and B to ACTH stimulation. In a family studied in our laboratory [12], the obligate heterozygotes had normal ACTH increases in cortisol and 17-deoxy steroids. Aldosterone did not increase. The ratio of 18-hydroxycorticosterone from the ZF and aldosterone from the ZG is elevated. Another useful technique has been to establish the ratio of total urinary metabolites of B (C-21, 17-deoxy steroids) to the total metabolites of cortisol (C-21, 17-hydroxy steroids).

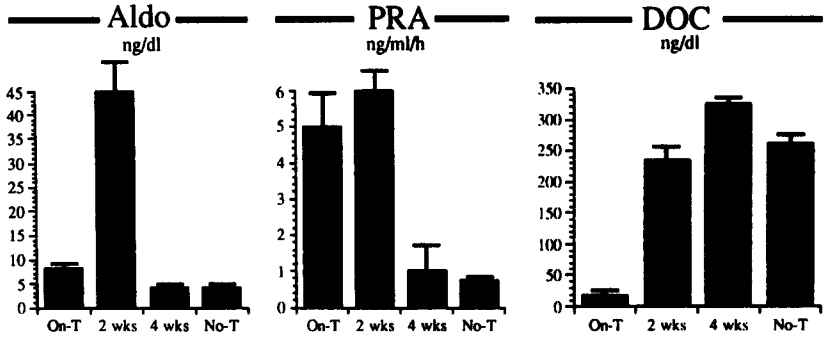

Fig. 5. 17α-OHD, after dexamethasone withdrawal. PRA, plasma renin activity.

This ratio was elevated (0.36, 1.43, 0.52) in the heterozygotes with no overlap with the normal control value of $0.21 \pm .012$. The ratio of the sum of urinary androsterone and etiocholanolone to total B and cortisol metabolites (C-21 steroids), again was found to be abnormally low in obligate heterozygotes [12].

Treatment is similar to 11β-OHD syndrome. Glucocorticoid therapy is given to suppress ACTH and the 17-deoxy steroids. Blood pressure and potassium wasting is usually effectively corrected and though the DOC levels do not completely return to normal values, they are at levels where there are no clinical effects of the DOC excess. When a patient is first treated with glucocorticoid suppressive therapy hypovolemic crisis may occur. This should be corrected by volume replacement and by fludrocortisone. The ZG eventually recovers but it make take 2 years before this event is realized. The index patient of this disorder has now been on small maintenance doses for 25 years. Blood pressure is controlled but occasional potassium supplements are needed. Antihypertensive drugs are not required. Treatment with estrogen has generally been accepted by most patients and reconstructive surgery in some of the female patients. However, there remains the unusual observation that bone density has not been affected in the index patient who has never received any estrogen therapy.

21-OHD SYNDROME

The 21-OHD syndrome with the classical simple virilizing and the non-classical virilizing syndrome do not have hypertension but they do have increased levels of DOC (Fig. 6). They also have secondary hyperaldosteronism because of the renin–angiotensin system activation, presumably by salt-losing steroids such as progesterone and 17α-hydroxyprogesterone (Fig. 7). The increased production of DOC and aldosterone prevents marked sodium wasting in most.

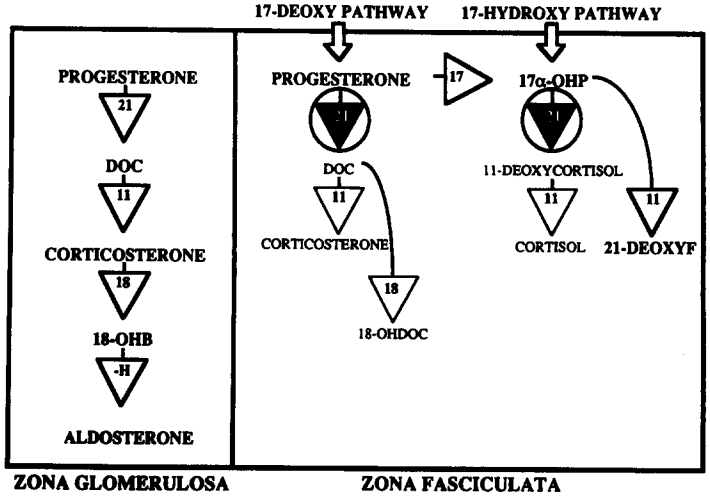

Fig. 6. 21-OHD. Steroids in bold type are increased, others are normal or reduced.

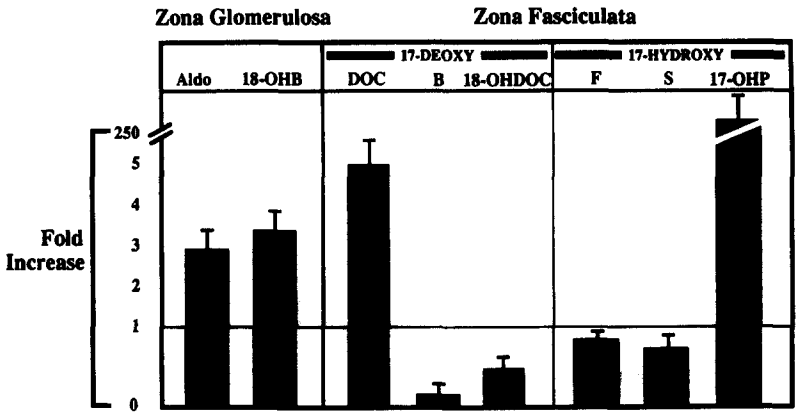

Fig. 7. 21-OHD. Fold changes from normal values.

The DOC levels can be raised to levels that contribute salt-retaining properties. However, the origin of DOC in the 21-OHD cannot originate in the ZF because it is distal to 21-hydroxylation [10]. Peripheral conversion of progesterone could not solely account for these levels [13]. Presumably then, the DOC must be originating from the ZG under the drive of the renin–angiotensin system. Additional evidence supports that it is originating from the ZG by the increase with upright posture, and to angiotensin II infusions, and has dynamics similar to aldosterone. The steroids distal to the block in the 17-deoxy pathway of the ZF (B and 18-OHDOC) are extremely low. The ratio of stimulated 17-hydroxyprogesterone to that of stimulated 18-OHDOC can prove to be useful. Since 18-OHDOC is distal to the deficiency, it virtually does not respond to ACTH whereas 17α-hydroxyprogesterone does. In a series of 14 obligate heterozygotes, the increased ratio was extremely useful in identifying heterozygosity [14]. Even though DOC and aldosterone are elevated, they do not produce hypertension, presumably due to counter-regulatory forces and events that would tend to produce blood pressure lowering. An intact ZG is essential for the classical simple virilizing type.

In both the simple virilizing and non-classical form of CAH, aldosterone and DOC levels are elevated. However, with continued ACTH stimulation, cortisol levels in the partially deficient state can be increased to near normal levels by the 3rd day. At that particular time, aldosterone production is reduced to normal levels. This has provided further evidence of the effect of cortisol as possibly a pseudosubstrate or another form of an enzyme inhibitor on the late steps of aldosterone synthesis and can identify the non-classical form [10].

In the hypertensive disorders where DOC levels are extremely high, driven by ACTH, there is growing evidence of a second regulator of the 17-deoxy pathway. This has been shown in a number of situations where dissociations between ACTH stimulated cortisol and DOC have been seen: in the DOC recovery from the contralateral adrenal after removal of a DOC-producing tumor, severely burned patients and patients with AIDS. Thus, the high levels of DOC may be caused by dual mechanisms [15]. There is a second unique observation in DOC regulation. In ACTH deficient patients (dexamethasone suppressed or hypopituitarism) administered ACTH produces prompt and sustained normal increases in DOC. There is a considerable delay in cortisol response. This independent secretion of DOC in ACTH deficiency could be operative during the treatment periods to maintain higher levels but without significant mineralocorticoid activity [16].

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