The role of 11-deoxycorticosterone in human hypertension

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Summary

1. Using a newly developed and validated radio-assay method, we have measured plasma 11-deoxycorticosterone concentrations in a wide spectrum of human hypertensive states.

2. Patients with essential and renovascular hypertension have normal plasma concentrations of 11-deoxycorticosterone.

3. Elevated concentrations are seen in some patients with primary aldosteronism, Cushing's syndrome, low-renin hypertension, and in adult hypertensive subjects with elevated urinary 17-ketosteroid excretion.

4. An aetiological role for deoxycorticosterone in certain forms of human hypertension appears likely.

Key words: 11-deoxycorticosterone, hypertension.

Introduction

Mineralocorticoid hypersecretion is known to occur in certain forms of human hypertension, the best example being the hyperaldosteronism of Conn's syndrome. Excess of production of another potent mineralocorticoid, 11-deoxycorticosterone, is seen in hypertensive infants with congenital adrenal hyperplasia (Eberlein & Bongiovanni, 1955), and this steroid has also been implicated in various forms of experimental animal hypertension. Other mineralocorticoids such as 18-hydroxydeoxycorticosterone (Melby, Dale & Wilson, 1971) and 16β-hydroxydehydroepiandrosterone (Sennett, Brown, Island, Yarbro, Watson, Slaton, Hollifield & Liddle, 1975) have also been reported to be elevated in hypertensive patients, although these findings await confirmation. With the recent development by Tan & Mulrow (1975a) of a reliable radioassay method for measuring plasma concentrations of deoxycorticosterone, we have been able to study its physiological regulation, showing it to be dependent on adrenocorticotropic hormone, and primarily a product of the zona fasciculata (Tan & Mulrow, 1975b). The current study was carried out to define the role of this mineralocorticoid in a wide spectrum of human hypertensive states.

Methods

Eighty-two adult hypertensive subjects and forty healthy normotensive volunteer subjects were studied. Of the eighty-two patients, thirty-six had essential hypertension. Renovascular hypertension was diagnosed in twenty-one patients by intravenous pyelography, angiography and split renal vein renin studies. Six patients had primary aldosteronism and five had Cushing's syndrome. Nine adult hypertensive patients with elevated urinary excretion of 17-ketosteroids, but who did not have Cushing's syndrome, were studied. Six patients with suppressed plasma renin activity after 3 days of a 10 mmol/day sodium diet, coupled with 4 h of ambulation, but with normal aldosterone excretion, were diagnosed as having low-renin hypertension.

Plasma DOC(1) was measured by the recently described competitive protein-binding radioassay method of Tan & Mulrow (1975a). Plasma samples with elevated DOC values were also re-assayed by radioimmunoassay, with an antibody directed against DOC-3-oxime-bovine serum albumin conjugate kindly provided by Dr C. D. West of Salt Lake City,

(1) Abbreviation: DOC, deoxycorticosterone; ACTH, adrenocorticotropic hormone.
Utah. In general, values obtained by both methods were in close agreement.

Samples were usually obtained between 08.00 and 10.00 hours. Plasma cortisol was measured in all samples which yielded high DOC values in order to rule out a possible stress-related ACTH effect. Most of the subjects were not on anti-hypertensive medication at the time steroid measurements were made, and none was receiving spironolactone, a drug known spuriously to elevate plasma DOC concentration (Tan & Mulrow, 1975c).

Methods for the measurement of plasma renin activity, aldosterone and cortisol were as described previously (Tan & Mulrow, 1975b).

Results

Fig. 1 shows the range of plasma DOC values in healthy normotensive subjects as well as in the hypertensive patients studied. Values in normal subjects range from 30 to 805 pmol/l (1-26.9 ng/100 ml) with a mean value of 269 pmol/l (SEM 24, n = 40).

Essential hypertension

All except two of the thirty-six hypertensive subjects had normal plasma DOC values. In the two patients with elevated values, plasma cortisol and serum potassium were normal. Base-line plasma renin activity values were in the normal range, although studies during sodium depletion were not carried out.

Renovascular hypertension

Normal DOC values were found in all twenty-one patients.

Primary aldosteronism

All six patients with this diagnosis had suppressed renin, elevated plasma and urinary aldosterone, and hypokalaemia. Two patients studied on a single occasion had normal DOC values, whereas the other four had elevated concentrations confirmed on multiple determinations. An occasional value, however, fell within the normal range. Of the two patients with normal plasma DOC values, one had an adenoma removed surgically. Elevated DOC values in patients with primary aldosteronism were not suppressed by a high sodium diet or by dexamethasone.

Cushing's syndrome

Of the five patients with Cushing's syndrome, three had elevated DOC concentrations. One of these had an adrenal carcinoma and the other two showed the ectopic ACTH syndrome secondary to a lung malignancy. All three patients had diastolic pressures in excess of 120 mmHg and marked hypokalaemic alkalosis. Plasma renin activity and aldosterone were suppressed in these patients. In contrast, the two patients with normal DOC values (one with an adenoma and the other with bilateral adrenal hyperplasia) had only mild hypertension and were normokalaemic. Plasma cortisol values were also much higher in patients with elevated DOC concentrations. Both cortisol and DOC were not suppressed by dexamethasone.

Low-renin hypertension

Multiple plasma DOC measurements were performed in six patients with low-renin hypertension. None had unprovoked hypokalaemia. Plasma DOC concentrations were normal in four patients, but were episodically elevated in two low-renin hyper-
tensive patients, both of whom had undetectable renin values even after sodium depletion and assumption of the upright posture (less than 0.1 ng h⁻¹ ml⁻¹).

Patients with elevated urinary 17-ketosteroids

Three of the nine patients with hypertension and elevated urinary 17-ketosteroids, but without Cushing's syndrome, showed elevated plasma DOC concentrations. DOC concentrations as well as 17-ketosteroid excretion were suppressible by dexamethasone in these patients, and two of the three patients with DOC excess experienced an improvement in blood pressure after the institution of dexamethasone therapy (0.5–1.5 mg daily). Seven normotensive patients with anovulatory cycles and comparable elevations in urinary 17-ketosteroids had plasma DOC concentrations in the normal range.

Discussion

In contrast to the impressive evidence implicating DOC as an aetiological factor in various forms of experimental animal hypertension (Skelton, Brownie, Nickerson, Molteni, Gallant & Colby, 1969; Hyde & Daigneault, 1968), there is only scattered documentation of DOC excess in human hypertensive states. Our findings of normal DOC concentrations in essential and renovascular hypertension would suggest that DOC excess is not present in most hypertensive patients. Normal urinary DOC excretion in essential hypertension has recently been reported by Cope & Loizou (1975). Plasma DOC concentrations are, however, elevated in the majority of patients with primary aldosteronism and in hypercortisolism secondary to a malignancy, confirming the findings of Biglieri, Slaton, Schambelan & Kronfield (1968), Powell-Jackson, Calin, Fraser, Grahame, Mason, Missen, Powell-Jackson & Wilson (1974), Crane & Harris (1966), Brown & Strott (1971) and Oddie, Coghan & Scoggins (1972). In the former instance, concentrations may reach more than twenty times normal, representing a significant contribution to the hypermineralocorticoidism of primary aldosteronism. The hypertension associated with Cushing's syndrome is generally assumed to be the result of the mineralocorticoid action of cortisol. It is likely, however, that DOC excess may in some cases be the more important factor, since plasma concentrations are as high as or exceed those seen in adrenal 17β-hydroxylase deficiency, a condition characterized by hypertension and low plasma cortisol (Biglieri et al., 1968). Schambelan, Slaton & Biglieri (1971) have indicated that, in the ectopic ACTH syndrome, hypokalaemia is seen only when DOC excess is present, despite the presence of high plasma cortisol.

In the 11β- and 17α-hydroxylase deficiency variants of congenital adrenal hyperplasia, DOC secretion is increased, and this is thought to cause the hypertension seen in such patients (Eberlein & Bongiovanni, 1955; Biglieri et al., 1968). We have interpreted our findings of elevated plasma DOC concentrations in non-Cushingoid hypertensive patients with increased urinary 17-ketosteroid excretion as a manifestation of a partial adrenal 11β-hydroxylase deficiency. These adult hypertensive patients share many of the features of the two case reports published by Gabrilove, Sharma & Dorfman (1965). In their patients, increased excretion of urinary tetrahydro-compound S led to the diagnosis of adrenal 11β-hydroxylase deficiency, and hypertension was attributed to excess DOC production, although direct measurements were not made. The elevated plasma DOC values, their suppression by dexamethasone, and the improvement in blood pressure after treatment with physiological doses of glucocorticoid all support the presence of an adrenal 11β-hydroxylase deficiency in our patients.

Brown and co-workers (1972) reported elevated plasma DOC concentrations in six of twenty-one patients with low-renin hypertension, although similar results were not obtained by Woods, Liddle, Stant, Michelakis & Brill (1969) or by Brown & Strott (1971). There is compelling evidence to suggest a mineralocorticoid aetiology in this syndrome; indeed, it may represent an early form of primary aldosteronism, as suggested by Grim (1975). Whether a twofold episodic elevation in plasma DOC concentrations as seen in some of our patients can result in renin suppression and hypertension is, however, uncertain.

In assessing a possible role for DOC in human hypertension, one might ask whether the elevated plasma concentrations are sufficient to raise the blood pressure. The mineralocorticoid activity of DOC has been variously estimated at between 1/10 and 1/50 that of aldosterone, so that at least a severalfold increase in DOC production is probably needed to cause hypertension. On the other hand,
DOC, unlike aldosterone, is not suppressed by a high sodium intake (Tan & Mulrow, 1975b). The combination of DOC excess and a high salt diet could therefore have a particularly deleterious effect on the cardiovascular system. Finally, one might expect corticoidism, e.g. normokalaemic aldosteronism hypokalaemia and suppression of plasma renin (Conn, Cohen, Rovner et al., 1965) well known to occur in states of hypermineralocorticidism, e.g. normokalaemic aldosteronism (Conn, Cohen, Rovner & Nesbit, 1965) and adrenal 11β-hydroxylase deficiency (Shepard et al., 1951; Green, Migeon & Wilkins, 1960; Gabrilove et al., 1965).

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References


