Abnormality of Aldosterone and Cortisol Late Pathways in Glucocorticoid-Remediable Aldosteronism

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ABSTRACT

Patients with glucocorticoid-remediable aldosteronism (GRA) possess a chimeric gene resulting from fusion of the genes encoding steroid aldosterone synthase and 11β-hydroxylase. In the adrenal zona fasciculata, this may lead to ectopic expression under ACTH control of aldosterone synthase activity and increased formation of cortisol C_{18} oxidation products. We assessed mineralocorticoid and glucocorticoid pathways in three patients with GRA. Baseline plasma progesterone, 17α-hydroxyprogesterone, corticosterone, and cortisol were normal in all patients, whereas 11-deoxycorticosterone, aldosterone, and 11-deoxycortisol were above normal. The ratios of both corticosterone/11-deoxycorticosterone and cortisol/11-deoxycortisol were abnormally low, and decreased further 60 min after administration of ACTH-(1–24) (250 μg) as an iv bolus. A low corticosterone/11-deoxycorticosterone ratio is consistent with an increased aldosterone synthase activity forming aldosterone by corticosterone. Similarly, a decreased cortisol/11-deoxycortisol ratio could reflect enhanced cortisol C_{18} oxidation. Our findings are in agreement with a hyperfunction of the 11β-hydroxylase/aldosterone synthase complex in the adrenal zona fasciculata of GRA induced by the new chimeric gene. (*J Clin Endocrinol Metab* **79**: 772–774, 1994)

G LUCOCORTICOID -remediable aldosteronism (GRA) is an ACTH-dependent autosomal dominant form of mineralocorticoid hypertension in which the excessive aldosterone production and clinical syndrome are corrected by the administration of glucocorticoids (1, 2). The genetic abnormality has recently been described (3, 4); the mutation results from fusion of the genes encoding steroid 11β-hydroxylase and aldosterone synthase. In the adrenal zona fasciculata, this may lead to ectopic expression under ACTH control of aldosterone synthase activity, which normally catalyzes both corticosterone and 18-hydroxycorticosterone methyl oxidations in the zona glomerulosa. A specific biochemical abnormality of this disease is, in fact, the overproduction of cortisol C_{18} oxidation metabolites (5–7). Scattered data are available on precursor steroids of aldosterone and cortisol in this disease. In particular, whereas aldosterone precursors are reported variably high (8–10) or normal (11, 12), cortisol precursors have been found in the normal range (7, 13). We studied three patients with GRA, assessing mineralocorticoid and glucocorticoid pathways both under baseline conditions and after ACTH stimulation.

Subjects and Methods

Three siblings (patient 1, female, aged 19 yr; and patients 2 and 3, males, aged 23 and 35 yr, respectively) in a family of nine siblings were shown to have GRA. The family pedigree and a detailed biochemical and hormonal assessment of all family members have been previously reported (14). The chimeric bands analyzed by Southern blot in leuko-

cyte DNA indicating the genetic abnormality in patients 1 and 2 have been reported previously (15), whereas in patient 3 this genetic study was not performed. Hormonal evaluation was conducted under baseline conditions before glucocorticoid treatment while patients received a normal sodium (150 mmol/day) and potassium (60 mmol/day) diet. All three patients were hypertensive and hypokalemic at the time of the study. Urinary sodium excretion was 136, 142, and 140 mmol/day in patients 1, 2, and 3, and urinary potassium excretion was 74, 66, and 70 mmol/day in patients 1, 2, and 3, respectively. As previously reported (16), urinary products of cortisol C_{18} oxidation 18-oxocortisol (as the tetrahydro derivative) and 18-hydroxycortisol, measured by gas chromatography-mass spectrometry, were very high (18-oxotetrahydrocortisol: 154, 356, and 608 nmol/day; normal mean ± SD, 7 ± 5 nmol/day; 18-hydroxycortisol, 1048, 2768, and 2943 nmol/day; normal, 110 ± 60 nmol/day in patients 1, 2, and 3, respectively). Plasma levels of progesterone, 11-deoxycorticosterone, corticosterone, aldosterone, 17α-hydroxyprogesterone, 11-deoxycortisol, and cortisol were measured at 0900 h after a 30-min rest in an armchair, before and 60 min after ACTH-(1–24) administration (Synacthen, Ciba, Basel, Switzerland; 250 μg as an iv bolus). Four unaffected siblings of the family underwent the same hormonal evaluation. Twenty healthy subjects (10 males and 10 females, aged 17–44 yr) were used as normal controls. All plasma steroids were measured by the method of Sippell *et al.* (17), using mechanized Sephadex LH-20 multiple column chromatography and specific RIAs. For normal values, see Table 1.

Results

Plasma steroid results are reported in Table 1. Baseline progesterone, corticosterone, 17α-hydroxyprogesterone, and cortisol levels were normal in all three patients and responded normally to ACTH standard stimulation test. Baseline and ACTH-stimulated 11-deoxycorticosterone, aldosterone, and 11-deoxycortisol levels were above normal. Both baseline corticosterone/11-deoxycorticosterone and cortisol/11-deoxycortisol ratios, expressed on an equimolar basis, were abnormally low [24, 19, and 12 (normal range, 46–78) and 17, 13, and 12 (normal range, 158–210), respectively]

TABLE 1. Plasma steroid levels in the three patients with GRA and normal controls before and after ACTH treatment

	P (nmol/L)	DOC (nmol/L)	B (nmol/L)	ALDO (pmol/L)	17-OHP (nmol/L)	S (nmol/L)	F (nmol/L)
Patient 1							
Baseline	0.58	0.37	9.02	416.8	2.3	13.2	221.2
ACTH	2.49	4.55	87.1	1156	7.0	43.1	594.0
Patient 2							
Baseline	0.66	0.46	8.82	341.2	3.7	14.1	181.8
ACTH	2.27	5.72	47.9	890.2	11.0	78.3	380.7
Patient 3							
Baseline	0.28	0.37	4.46	205.4	2.6	14.5	178.8
ACTH	1.80	5.22	52.4	818.3	8.7	77.7	525.0
Normal subjects (n = 20)							
Baseline	0.45 ± 0.3	0.13 ± 0.04	8.42 ± 5.1	124.2 ± 27	2.4 ± 0.8	1.65 ± 0.7	281.4 ± 99
ACTH	1.51 ± 0.5	1.54 ± 0.27	97.4 ± 36.2	196.8 ± 66	6.4 ± 2.1	6.7 ± 1.5	642.8 ± 151

P, Progesterone; DOC, 11-deoxycorticosterone; B, corticosterone; ALDO, aldosterone; 17-OHP, 17α-hydroxyprogesterone; S, 11-deoxycortisol; F, cortisol.

and decreased further after ACTH-(1–24) administration [19, 8, and 10 (normal range, 52–84) and 14, 5, and 7 (normal range, 104–153), respectively]. Four unaffected siblings of the family showed no steroid abnormalities either under baseline conditions or after ACTH stimulation (data not shown).

Discussion

Recently, fusion genes generated by unequal cross-over were identified as the underlying cause of GRA in 16 kindreds, including ours (15). The gene is a hybrid with a 5'-regulatory ACTH-responsive region of the gene encoding for isoenzyme CYP11B1 (P450c11), which mediates the last step of cortisol synthesis, 11β-hydroxylation, and the 3'-coding region of the gene encoding for isozyme CYP11B2 (P450aldo synthase), which mediates the final three steps of aldosterone synthesis, 11β- and 18-hydroxylation, and 18-oxidation (3, 4, 18). These two P450 enzymes are normally encoded by twin genes on chromosome 8 and share greater than 90% homology (19). The biochemical consequence of the genetic rearrangement in GRA is the formation of aldosterone under ACTH drive by the zona fasciculata, together with 18-hydroxy- and 18-oxocortisol formation from the methyl oxidation of cortisol. Interestingly, both baseline and ACTH-stimulated 11-deoxycorticosterone and 11-deoxycortisol were above normal in our cases, suggesting hyperresponsivity of the zona fasciculata to ACTH, involving multiple steroidogenic steps. Overproduction of sodium-retaining steroids other than aldosterone has been advocated to explain the dramatic effect of increasing blood pressure in these patients after prolonged ACTH administration (20). However, due to abnormal adrenal zonation, it is not possible to separate mineralocorticoid and glucocorticoid pathways in the absence of glucocorticoid treatment.

The ratios of plasma concentrations of corticosterone to 11-deoxycorticosterone and cortisol to 11-deoxycortisol are considered an indirect assessment of 11β-hydroxylase activity (21), i.e. increased function of this enzyme corresponds to decreased ratios due to enhanced formation of end products. Accordingly, both of these ratios were below normal in our patients, in whom an accelerated metabolism of corticos-

terone and cortisol, due to abnormal sensitivity of 11β-hydroxylase/aldosterone synthase to endogenous ACTH, occurred. Moreover, exogenous ACTH administration further lowered both corticosterone/11-deoxycorticosterone and cortisol/11-deoxycortisol ratios, confirming the marked ACTH dependence of cortisol metabolites (22) and aldosterone (14, 23) as a typical feature of GRA. In conclusion, our data are in agreement with a hyperfunction of the 11β-hydroxylase/aldosterone synthase complex in the adrenal zona fasciculata induced by the new chimaeric gene in this disorder.

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