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FAMILIAL AND IATROGENIC CORTISOL RECEPTOR RESISTANCE

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Summary—Primary cortisol receptor resistance has been reported in 6 patients and 14 asymptomatic family members We observed an additional 6 patients (2 males and 4 females) The male patients presented with hypertension The female patients presented with acne, hirsutism and irregular menstruations Dexamethasone therapy (1–1 5 mg/day) was of considerable clinical benefit All 6 patients showed insufficient suppression of cortisol after 1 mg dexamethasone The diurnal rhythm of ACTH and cortisol was intact, albeit at an elevated level There was a normal increase of ACTH, cortisol, and GH to insulin-induced hypoglycemia, while cortisol production was (slightly) elevated Adrenal androgen levels were increased in all patients Glucocorticoid receptors measured in a whole cell dexamethasone binding assay in mononuclear leukocytes showed a lowered affinity in 1, and lowered numbers of receptors in 4 patients In 1 patient no abnormalities were found As a "bioassay" for glucocorticoid action dexamethasone suppressibility of mitogen-stimulated incorporation of [^{3}H]thymidine in mononuclear leukocytes was measured In this last patient dexamethasone suppressibility of [^{3}H]thymidine incorporation was significantly lowered Twelve months' treatment with 200 mg RU 486 per day in meningioma patients induced a similar biochemical picture as observed in primary cortisol receptor resistance Partial cortisol receptor resistance might be less rare than previously thought In the 6 patients presented at least 3 different forms can be recognized Therapy with dexamethasone was successful in female patients with acne and hirsutism, as the secondary overproduction of adrenal androgens was effectively controlled Chronic therapy with RU 486 causes a biochemical picture similar to primary cortisol receptor resistance

INTRODUCTION

End organ resistance to steroid hormones in man has been described for androgens, vitamin D, aldosterone, progesterone and cortisol [see 1]. Generalized primary resistance to glucocorticoids was originally described by Vingerhoeds *et al* [2] in a patient who presented with hypertension and hypokalemia Subsequently it was shown to be a familial disease involving an abnormality of cortisol receptors [3] The disease has been considered to be extremely rare and up till recently, a total of only 6 symptomatic and 14 asymptomatic family members have been described [4–9] However, careful analysis of a group of patients in our own clinic who were found to have abnormalities of the hypothalamo–pituitary–adrenal (HPA)-axis (i e. decreased sensitivity to dexamethasone) without the signs and symptoms of Cushing's syndrome, revealed an additional group of 6 patients [10] Interestingly, the biochemical changes in the HPA-axis observed in these patients were similar to those found in a number of normal individuals which had been treated chronically with the progesterone and glucocorticoid receptor blocking drug RU 486 In the present review we analyze how to optimalize the diagnosis of patients with glucocorticoid receptor resistance

FAMILIAL CORTISOL RECEPTOR RESISTANCE

Primary (partial) cortisol receptor resistance is characterized biochemically by an increased activity of the HPA-axis resulting in elevated circulating ACTH and cortisol levels in order to overcome the peripheral decreased "efficacy" of cortisol at the target cell level Depending on the severity of end-organ resistance equilibrity is eventually reached by an activation of the HPA-axis reset at a higher level, resulting in elevated circulating cortisol levels This by itself does not result in clinical symptomatology The elevated circulating ACTH levels necessary to stimulate

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adrenal cortisol production in these patients, however, activate as a "side-effect" both adrenal androgen, as well as to a lesser extent mineralocorticoid production Elevated adrenal androgens cause only in female patients hirsutism, acne and irregular menstruations, but are asymptomatic in most males, because testicular androgen production is so much higher that a change in adrenal androgen production is not recognized clinically In one boy, isosexual precocity was observed to be the first symptom of cortisol receptor resistance [5] Elevated adrenal mineralocorticoid production causes both in male and female patients hypertension, as well as hypokalemia Interestingly, in the patients described so far it seems that a low degree of cortisol receptor resistance will induce clinically recognizable adrenal androgen overproduction only, while signs and/or symptoms of mineralocorticoid hypersecretion were only observed in a few patients with a more severe glucocorticoid receptor abnormality [11]

Biochemically the syndrome of cortisol receptor resistance is characterized by increased serum cortisol concentrations (and/or cortisol production) Both ACTH (at the upper limit of normal or slightly elevated) and cortisol levels show a normal circadian pattern, while there is a normal increase of ACTH, cortisol as well as of GH and prolactin (PRL) secretion in response to an insulin-induced hypoglycemia The sensitivity of the HPA-axis to the negative feed-back of dexamethasone is diminished Most patients recognized so far, showed an abnormal suppression of early morning cortisol levels in the overnight 1 mg dexamethasone test Depending on the degree of cortisol receptor resistance, circulating androgens (e g androstenedione) and/or mineralocorticoids (desoxycorticosterone) are elevated [10]

The hallmark of the clinical and biochemical diagnosis of cortisol receptor resistance is the recognition of signs and symptoms related to androgen and/or mineralocorticoid excess in a patient with high cortisol levels and a disturbed dexamethasone suppression test, who does not have the classical clinical stigmata of Cushing's syndrome [10]

In several families of patients with cortisol receptor resistance, evidence has been presented for an autosomal dominant inheritance pattern with variable penetrance [1–4] However, a sporadic case has also been reported [9]

Functional studies of the glucocorticoid receptors on peripheral mononuclear leucocytes and/or on cultured fibroblasts of patients with cortisol receptor resistance showed either changes in the apparent dissociation constant (K_d) and/or in the number of receptors in most patients However, changes in thermolability of the glucocorticoid receptor were also recognized [8] We studied as a "bioassay" for glucocorticoid action dexamethasone suppressibility of mitogen-stimulated incorporation of [^{3}H]thymidine in mononuclear leukocytes of patients with cortisol receptor resistance [10] In all patients studied so far the concentration of dexamethasone needed to achieve 50% of the maximal inhibition of [^{3}H]thymidine incorporation was higher than in healthy controls Interestingly in 1 male patient with clinical and biochemical characteristics of cortisol receptor resistance we found normal numbers, and a normal affinity and thermolability of the dexamethasone receptors on his peripheral leucocytes, while only the dexamethasone suppressibility of mitogen-stimulated incorporation of [^{3}H]thymidine was significantly diminished [10]

Apart from these functional studies, molecular studies of the glucocorticoid receptors have also been carried out recently [11] In 2 patients, this has resulted in the characterization of the defect In both instances it only involved the substitution of a single amino acid within the glucocorticoid binding domain of the receptor [12, 13]

The recognition of patients with cortisol receptor resistance is of importance because part of the clinical and biochemical picture can be similar to that of Cushing's syndrome, especially the pituitary-dependent variety Also hirsutism, acne and irregular menstruations related to overproduction of adrenal androgens respond well in most patients to chronic therapy with low-dose dexamethasone [10]

THERAPY WITH THE GLUCOCORTICOID RECEPTOR ANTAGONIST RU 486

RU 486 or mifepristone is a compound with powerful progesterone and glucocorticoid receptor-blocking activities without agonist effects on these receptors [14, 15] In previous studies we showed that RU 486 exerts an inhibitory effect on growth and hormone secretion by transplantable PRL/ACTH-secreting 7315a rat pituitary tumors *in vivo* [16] and *in vitro* [17], while the compound also antagonized the inhibitory effect of dexamethasone on

corticotropin-releasing hormone (CRH)-stimulated ACTH release by cultured normal rat pituitary cells and human ACTH-secreting pituitary tumor cells Most human meningiomas contain high numbers of high-affinity progesterone receptors [18] We decided to investigate whether chronic therapy with RU 486 (200 mg/day) might induce via its antiprogestational effects control of meningioma tumor growth in patients with recurrent, inoperable tumors Indeed, a beneficial effect of therapy on tumor size and clinical symptomatology was recognized in part of the patients [19] However, the antiglucocorticoid effect of the compound also became evident within days in all patients [20] Both basal plasma cortisol levels and the urinary cortisol secretion increased in the first 5 patients from 330 ± 40 nmol/l at 8 a m and 210 ± 56 nmol/day before the start of therapy to 910 ± 138 nmol/l at 8 a m and 860 ± 156 nmol/day, respectively, after 8 days of therapy ($P < 0.01$ in both instances) In addition, the response of circulating cortisol levels to the i v administration of 1 μg/kg CRH was significantly increased with regard to both the maximal levels and the duration of the response The diurnal variation of cortisol remained intact at a much higher level, while the suppressive effect of dexamethasone had decreased considerably [see 20] These observations are in line with earlier reports on the short-term effects of RU 486 administration on the HPA-axis in normal individuals [21–23] During longer therapy with 200 mg RU 486 daily for 1 year, we observed in postmenopausal patients that apart from a continuing increase in circulating cortisol levels at 9 a m , an increase of plasma androstenedione levels also occurred from during therapy (Table 1) Interestingly, the normal postmenopausal low 17β-estradiol levels increased to levels well within the normal range observed during the early proliferative phase of the menstrual cycle No changes in the serum potassium concentrations or in the blood pressure were observed during this period

These observations show that chronic administration of the progesterone and glucocorticoid receptor blocking agent RU 486 induces in normal individuals an activation of the HPA-axis, resulting in a resetting of this system at a higher level at which the diurnal rhythm and the stimulability in response to CRH are maintained, while the sensitivity to dexamethasone is diminished [20, 24] Secondary to this phenomenon the production of androstenedione (presumably from adrenal origin) increases to pathological values, while this results (presumably via peripheral aromatization) in a considerable increase in circulating estrogen levels It is concluded that it is possible to induce in normal women the (partial) cortisol receptor resistance syndrome including high androgen levels as an iatrogenic side effect of RU 486 therapy It remains to be seen whether this will also result in the development of hirsutism

Table 1 The effect of RU 486 (200 mg/day) for 3 weeks in 4 postmenopausal women on circulating hormone concentrations

Cortisol (nmol/l)		Androstenedione (nmol/l)		17β-oestradiol (pmol/l)	
Before	During	Before	During	Before	During
348 ± 38	846 ± 82	3.2 ± 0.3	9.4 ± 0.5	30 ± 8	198 ± 36
$P < 0.01$		$P < 0.01$		$P < 0.01$	
Normal 220–420		3.0–4.5		20–50	

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