Cortisol, hypertension and obesity: the role of 11β-hydroxysteroid dehydrogenase

The adrenal glands produce two classes of steroid hormones, glucocorticoids and mineralocorticoids. Hench, Kendall and Reichstein were awarded the Nobel prize in 1950 for their discovery of the 'glucocorticoid' cortisol ('Kendall's compound E') from adrenal extracts and demonstrating its therapeutic efficacy, at least in the short term, in patients with rheumatoid arthritis. Although unaware at the time, they had in fact discovered an inactive steroid which requires activation in the liver to the active hormone cortisol (compound F) by an enzyme complex 11β-hydroxysteroid dehydrogenase (11β-HSD). In some tissues, notably the placenta, early activity studies indicated that this enzyme could also perform the reverse reaction (ie inactivate cortisol to cortisone). Aldosterone, the adrenal mineralocorticoid hormone, was isolated from adrenal venous blood in 1952 by Simpson, Tait and Bush. In contrast to the many diverse actions of glucocorticoids (anti-inflammatory, stress response, homoeostasis, growth and differentiation, salt and water control), mineralocorticoids have a single defined action: to stimulate epithelial sodium transport in target tissues such as kidney, colon and salivary gland. Clinical studies on patients with an unusual form of hypertension have highlighted the pitfalls of this functional classification and have brought the concept of steroid metabolism to the forefront of clinical medicine.

Apparent mineralocorticoid excess, liquorice, and mineralocorticoid receptor specificity

In Edinburgh in the mid-1980s we described a rare case of mineralocorticoid hypertension, the so-called syndrome of apparent mineralocorticoid excess (AME). AME is a cause of low-renin, low-aldosterone hypertension and hypokalaemia found predominantly in children. About 50 cases have been reported worldwide. Children present with failure to thrive, short stature, thirst and polyuria, with severe and often fatal hypertension and hypokalaemia. Several cases with affected siblings have been reported, and the condition is inherited as an autosomal recessive condition. Defective peripheral conversion of cortisol (F) to cortisone (E), reflecting impaired activity of 11β-HSD, was first suggested by Ullick and co-workers in patients with AME in the late 1970s and has been further investigated by other groups. Urinary steroid metabolite profiles on such patients indicate that the majority of cortisol metabolites are excreted as A-ring reduced metabolites of cortisol (the so-called tetrahydrocortisols (THF) and allo-THF) with very low levels of tetrahydrocortisone (THE) in the urine. Despite this defect in the conversion of F to E, patients with AME are not Cushingoïd. Cortisol secretion rate falls often to very low levels due to an intact negative feedback mechanism; normal circulating concentrations are therefore maintained in the presence of impaired metabolism of cortisol. However, despite these normal concentrations, cortisol has profound mineralocorticoid effects in the kidney and rectal colon. Dexamethasone suppresses endogenous cortisol secretion, resulting in natriuresis, potassium retention and lowered blood pressure, and has been used therapeutically to treat AME patients.

A similar mechanism also explains the mineralocorticoid excess state following the ingestion of liquorice and related compounds (glycyrrhetinic acid, carbenoxolone). Glycyrrhetinic acid, which had been thought to act directly as a mineralocorticoid, is a potent inhibitor of 11β-HSD, and cortisol is the 'offending' mineralocorticoid following liquorice and carbenoxolone ingestion.

The critical observation from these clinical studies was that cortisol, conventionally regarded as a glucocorticoid, can act as a potent mineralocorticoid in the setting of reduced 11β-HSD activity. In vitro mineralocorticoid receptor (MR) binding studies and studies on the expressed human MR cDNA indicated that cortisol, corticosterone and aldosterone all have an equal affinity for this receptor - an observation clearly at variance with normal physiology where aldosterone occupies the MR in preference to glucocorticoids. Simultaneously, two groups provided evidence that this in vivo specificity for the MR is conferred by 11β-HSD itself. Thus, the inactivation of cortisol and corticosterone within the mineralocorticoid target tissues (kidney, rectal colon and salivary gland) enables aldosterone to act on the MR. When this protective mechanism is disrupted, as in AME and following liquorice ingestion, cortisol is able to bind to the MR to act as a potent mineralocorticoid.

11β-hydroxysteroid dehydrogenase enzymology and molecular biology

Two isozymes of 11β-HSD have been cloned and characterised in many mammalian species including man. The
first isozyme to be purified and cloned, 11\(\beta\)-HSD1, is a low affinity, NADP(H)-dependent dehydrogenase/11-oxoeductase; this enzyme will thus inactivate cortisol to cortisone and vice versa. In vitro, the expressed enzyme has a higher affinity for E (\(K_m = 0.3\) \(\mu\)mol) than for F (\(K_m = 2.1\) \(\mu\)mol), suggesting that it acts predominantly as an oxoeductase, generating active F from E in vivo\(^{12,18}\). In contrast, the 11\(\beta\)-HSD2 isozyme is a unidirectional, high affinity (\(K_m = 50\) nmol), NAD-dependent dehydrogenase\(^{18-20}\). Using in-house antibodies against both human 11\(\beta\)-HSD isozymes\(^{21,22}\), we have demonstrated tissue-specific expression in human tissues. 11\(\beta\)-HSD1 is localised principally in glucocorticoid target tissues, liver, lung, gonad, decidua, adipose tissue, pituitary and cerebellum; in contrast, 11\(\beta\)-HSD2 is expressed in placenta and the mineralocorticoid target tissues, kidney, colon and salivary gland. Little or no 11\(\beta\)-HSD1 is expressed in the human kidney or colon. Within the human kidney and colon, 11\(\beta\)-HSD2 is localised to the MR-expressing epithelial cells of the cortical and medullary collecting ducts and distal/rectal colon, indicating that it is this 11\(\beta\)-HSD isofrom which protects the MR in an autocrine fashion\(^{21,23}\). 11\(\beta\)-HSD1, on the other hand, modulates glucocorticoid exposure to the glucocorticoid receptor\(^{24,25}\).

In keeping with their differing function and tissue expression, the isozymes are separate gene products:

- 11\(\beta\)-HSD1 gene is localised to chromosome 1: its cDNA is 1,265 bp in length, encoding a protein of 292 amino acids which requires glycosylation for full activity.

- The human 11\(\beta\)-HSD2 gene is found on chromosome 16q22: its cDNA is 1,873 bp in length, encoding a protein of 405 amino acids.

Although both isozymes are members of the short-chain alcohol dehydrogenase superfamily, they share only 14\% homology.

### Molecular basis for apparent mineralocorticoid excess

From the tissue distribution and function of the 11\(\beta\)-HSD2 isozyme, it is not surprising that mutations in the 11\(\beta\)-HSD2 gene have been reported in patients with AME\(^{26-28}\). To date, 14 mutations have been described in 23 cases of AME\(^{16,26-32}\) (Fig 1). Most of these have been point mutations resulting in premature stop sites or amino substitutions, revealing critical insights into the structure-function relationships of the enzyme. In each case, expression studies on the mutant cDNAs have revealed a high correlation between phenotype and genotype: a severe, often fatal phenotype can be explained on the basis of a mutant enzyme with no activity\(^{31}\). There are, in fact, two variants of AME\(^{33,34}\):

- the milder type 2 variant, often presents in adulthood with hypertension and only slightly deranged THF+allo-THF/THE ratio.

In four cases of AME type 2 belonging to an extensive Sardinian kindred, we have recently demonstrated a novel mutation in the 11\(\beta\)-HSD2 gene (R279C) which explains the underlying molecular basis of the condition\(^{35}\). The expressed R279C mutant cDNA has the same affinity for F as the wild-type enzyme, but a 50\% lower \(V_{max}\).

In summary, 20 years after its original description, the molecular basis for AME has been explained. It is always due to a mutation in the 11\(\beta\)-HSD2 gene, with the phenotype closely dependent upon genotype.

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Fig 1. Reported mutations in the human 11\(\beta\)-hydroxysteroid dehydrogenase (HSD) type 2 gene in patients with apparent mineralocorticoid excess. The human 11\(\beta\)-HSD 2 gene is 5 exons in length, localised to chromosome 16q22.
11β-hydroxysteroid dehydrogenase in clinical medicine

Hypertension

The recent description of the basis of AME has focused immediate attention on the role of 11β-HSD2 in patients with hypertension. Liquorice and related compounds are competitive inhibitors of 11β-HSD2, which explains the mineralocorticoid activity of these compounds. Substrate saturation of the enzyme in part explains the mineralocorticoid excess state that occurs in the ectopic adrenocorticotropic hormone (ACTH) syndrome. In contrast to patients with pituitary-dependent Cushing's syndrome and adrenal adenomas, the ectopic ACTH syndrome is invariably associated with hypertension and hypokalaemia, the cause of which has remained obscure. In 22 patients with Cushing's syndrome, the urinary ratio of THF+allo-THF/THE was significantly higher in the ectopic ACTH group than in other causes of Cushing's syndrome, indicative of impaired 11β-HSD activity, and was inversely correlated with serum potassium. The THF+allo-THF/THE urinary ratio reflects 'global' 11β-HSD2 activity, but the urinary free cortisol/urinary free cortisone (UFF/UFE) ratio is a more sensitive marker of renal 11β-HSD2 activity. The UFF/UFE ratio is grossly elevated in ectopic ACTH syndrome. UFE levels are not reduced – on the contrary, they are 10–20 times normal – but the huge levels of cortisol characteristic of ectopic ACTH syndrome overwhelm renal 11β-HSD2 activity, the Vmax is exceeded and cortisol spills over to act upon the MR.

Hypertension occurs in 10–20% of the population, but in over 95% of cases no underlying cause can be elucidated, and the patients are labelled as having 'essential' hypertension. AME has become only the third example of monogenic hypertension (ie hypertension arising from a single gene defect). Glucocorticoid-suppressible hyperaldosteronism (GSH) was the first such example and arises from the formation of a chimaeric gene containing both CYP11B1 11β-hydroxylase 1 and CYP11B2 11β-hydroxylase 2 sequences. This gene product can synthesise aldosterone, but is regulated by ACTH and not by the normal secretagogue angiotensin II. The second example is Liddle's syndrome, recently explained on the basis of mutations in the β- and γ-subunits of the apical epithelial sodium channel. The reported C-terminal deletions in these subunits result in constitutive activation of the sodium channel and unopposed sodium retention. All three examples in some way relate to mineralocorticoid hormone action, and it is exciting to speculate that such defects may be more prevalent in patients with essential hypertension, specifically low-renin hypertension (Fig 2).
In terms of 11β-HSD2 activity, it is now clear from some kindreds with AME that the heterozygous state can be affected. We have reported a 38-year old man, the father of a known case of AME due to a A328V mutation in the 11β-HSD2 gene. He had hypertension despite triple anti-hypertensive therapy, but on investigation was found to have cortisol-induced, mineralocorticoid-based hypertension (suppressed plasma renin activity, aldosterone), a borderline/high tension measurement, and a renalase defect. We have investigated in the A328V 11β-HSD2 mutation. He was nevertheless persistently normokalaemic, confirming the finding emerging from other cases of mineralocorticoid hypertension that serum potassium is not a sensitive screening test for mineralocorticoid excess states. Up to 50% of cases of GSH, Liddle’s syndrome and primary aldosteronism have normal serum potassium levels. Furthermore, we and others have reported abnormalities in 11β-HSD activity in patients labelled as having ‘essential’ hypertension. Genetic linkage studies using polymorphic markers close to the 11β-HSD2 gene are now required in larger cohorts of hypertensive patients. As with other causes of monogenic hypertension, there is a pressing need to define the prevalence of mutations in the 11β-HSD2 gene in an unselected population of patients with ‘essential’ hypertension.

Placenta and fetus

The distribution of 11β-HSD2 in adult tissues is largely restricted to kidney, colon, salivary gland and other mineralocorticoid-reactive tissues such as the eye and skin, but 11β-HSD2 appears to be more widely distributed in fetal tissues including the placenta. Using a combination of enzyme activity and in situ hybridisation studies on human fetal tissues and umbilical venous and arterial F/E measurements in at-term deliveries, we have demonstrated extensive expression of this enzyme in the human fetus. Its role is uncertain, but it seems likely that in fetal life it modulates glucocorticoid rather than mineralocorticoid hormone action. In the placenta, it may inactivate the much higher circulating maternal cortisol concentrations and thereby prevent fetal growth restriction. With the renewed interest in the role of fetal growth as a predictor of adult diseases such as hypertension and diabetes, this is an area of active research.

Obesity

In the body, the 11β-HSD1 isoform acts predominantly as a reductase. Since any tissue expressing the 11β-HSD1 isoform can generate cortisol from cortisone, this may be an important mechanism in the pathogenesis of central obesity. Obesity is associated with premature mortality, predominantly from cardiovascular disease; for a given body mass index, mortality is higher if fat is distributed centrally. The marked but reversible changes in fat distribution in patients with Cushing’s syndrome demonstrate that glucocorticoids play a crucial role in modulating adipose tissue function. In patients undergoing elective abdominal surgery, we have demonstrated appreciable levels of 11β-HSD1 reductase activity in primary cultures of adipose stromal cells obtained from omental, but not from subcutaneous, fat. No 11β-HSD2 activity or mRNA was found, and the 11β-HSD1 activity was further increased by cortisol. Thus omental fat, through its expression of 11β-HSD1, has an ‘in-built’ mechanism to generate locally active glucocorticoid, and it is possible that central obesity merely reflects ‘Cushing’s disease of the omentum’. If our preliminary data are confirmed, the future development of specific 11β-HSD1 inhibitors may point to a novel approach to the treatment of central obesity (Fig 3). To date, most inhibitors of 11β-HSD1 (eg carbenoxolone, progesterone

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**Fig 3. Proposed role of the type 1 isoform of 11β-hydroxysteroid dehydrogenase (HSD) in the pathogenesis of obesity.** Glucocorticoids stimulate the differentiation of adipose stromal cells to adipocytes and, in turn, directly regulate the transcription of many adipocyte gene products. 11β-HSD1 activity is much higher in omental than in subcutaneous fat depots, and can mediate the local production of cortisol from inactive cortisone (IGF-1 = insulin-like growth factor-1; PGI2 = prostaglandin I2; TNFα = tumour necrosis factor α).
and its derivatives) also inhibit 11β-HSD2, precluding their therapeutic use. However, the enzymes are so dissimilar that specific inhibitors must be a reality.

Other areas

The most abundant site for 11β-HSD2 expression in the adult is the kidney, and it is possible that loss of enzyme activity in patients with renal disease may explain the sodium retention seen in some patients with nephrosis. Both isozymes are expressed in the gonads where they may be important in regulating sex hormone synthesis and fertility. Studies also indicate a role for the enzyme at other sites of expression, for example, in the vasculature, central nervous system tissues and endometrium.

Summary

AME has been a crucial experiment of biology from which much has been learnt about corticosteroid hormone action and mineralocorticoid hypertension. 11β-HSD is an important pre-receptor pathway determining corticosteroid hormone action. Any tissue expressing 11β-HSD1 or 11β-HSD2 can clearly modulate glucocorticoid and mineralocorticoid action independent of circulating concentrations. A series of related enzymes operates in a similar fashion to determine hormone action for other members of the thyroid/steroid hormone receptor superfamily (eg 17β-HSD, 25-hydroxyvitamin D 1α-hydroxylase, aromatase, 5α-reductase). Endocrinologists have been obsessed with measuring the concentrations of a hormone in the circulation and making their decisions on the basis of these results, whether or not that hormone is involved in the pathogenesis of a disease process. Such an approach needs to be revised, with greater emphasis on considering the action of a hormone within a given tissue and, in turn, on the role of these enzymes in the pathogenesis of human disease.

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