Editorial

The syndrome of apparent mineralocorticoid excess

The elucidation of the basis of a rare inherited disorder is satisfying in itself, but particularly so if it leads to a greater understanding of normal physiology and other disease processes. Such insight has been provided by the study of a heritable form of hypertension, the syndrome of apparent mineralocorticoid excess (AME).

Approximately 50 individuals with AME have been identified in the last two decades with a form of early onset, low renin, low aldosterone hypertension associated with hypokalaemia. They commonly have growth retardation, nephrogenic diabetes insipidus secondary to the hypokalaemia, bone disease and are prone to sudden death due to intracranial haemorrhage or cardiac arrhythmias. The avid renal salt and water retention and excessive potassium loss, but with suppression of both plasma renin and aldosterone levels initially suggested that an unidentified mineralocorticoid explained the condition, leading to the term syndrome of apparent mineralocorticoid excess. However assays for all known mineralocorticoids and an extensive search for other novel mineralocorticoids were negative.

Detailed investigation of these individuals showed that the plasma half-life for cortisol was considerably prolonged and that they excreted an excess of urinary cortisol compared to cortisol metabolites. In vivo, hormonally-active cortisol is normally converted to inactive cortisone by the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD), but the activity of this enzyme was severely attenuated in patients with AME. Despite the ensuing prolonged cortisol half-life, AME patients are not cushingoid; normal serum cortisol concentrations are maintained because endogenous ACTH secretion and adrenal corticosteroid production are concomitantly reduced. Nevertheless, despite these normal circulating levels, studies revealed that cortisol was the offending mineralocorticoid in patients with AME. A natriuresis and reduction in blood pressure could be achieved by the administration of dexamethasone (which suppressed endogenous cortisol secretion), and the condition could be reproduced by cortisol administration. This condition resembled liquorice ingestion in the development of hypertension, the biochemical abnormalities and the disturbances in cortisol metabolism. How then could cortisol, conventionally regarded as a glucocorticoid, act as a potent mineralocorticoid? This was clarified when the specificity of the mineralocorticoid receptor (MR) was determined. The MR was shown to have a similar affinity for cortisol and aldosterone, yet in vivo this receptor remains specific for aldosterone despite much higher serum cortisol concentrations. This led to the hypothesis that 11β-HSD itself dictated specificity upon the MR; cortisol is inactivated to cortisone, thereby enabling aldosterone to bind to the MR in vivo.

In keeping with this hypothesis, mineralocorticoid target tissues such as kidney and colon did indeed possess 11β-HSD activity and the reaction catalysed was strongly in favour of the formation of inactive cortisone from cortisol. A search for the protein, its cDNA and the gene sequence of this enzyme initially led to the identification of a 34-kDa NADP-dependent enzyme from rat liver homogenates which had both reductase and dehydrogenase activities. The kinetics of this enzyme (11β-HSD1), however, were different than those found in vivo, and no mutations in the 11β-HSD1 gene could be identified in patients with AME. Subsequently a second enzyme, 11β-HSD2 was characterized and cloned from human kidney. This was an NAD-dependent enzyme which almost exclusively catalysed the dehydrogenase reaction. Its affinity and rate constant in vitro matched that of human kidney in vivo, and it was inhibited by glycyrrhetinic acid, the active component of liquorice.

The gene for 11β-HSD2 lies on chromosome 16q22, has five exons and codes for a protein with a molecular mass of 41 kDa. It is expressed most strongly in classical mineralocorticoid target tissues where it co-localizes with the MR (renal collecting tubules, colonic mucosal epithelial cells and the tubular elements of salivary glands). To date, 15 mutations of the 11β-HSD2 gene have been described in 23 patients with AME when these mutant sequences are expressed in mammalian cells devoid of 11β-HSD activity, they all have abol-
ished or severely reduced enzyme activity when compared to the wild-type sequence. The condition is inherited as an autosomal recessive trait with affected siblings reported in many kindreds. Most patients with AME so far studied have had homozygous mutations whilst only two have compound heterozygous mutations. In the majority of cases, the heterozygote state is normal with no evidence of low renin hypertension, suggesting that one normal allele is sufficient to allow adequate 11β-HSD2 activity. However there are notable exceptions to this and as AME usually manifests in childhood, further follow-up of the relatively young heterozygous parents into late adulthood will be required to evaluate the implications of the heterozygote state more thoroughly.

On the basis of the degree of derangement of the urinary steroid profile, AME has been divided into types I and II, with the type II subjects having less severely abnormal urinary profiles and a milder phenotype. Until recently, only type I AME patients had been sequenced with respect to the 11β-HSD2 gene. Evaluating an extensive Sardinian kindred with the type II AME variant, we have identified a further novel homozygous mutation in the 11β-HSD2 gene (R279C) in four affected individuals. In vitro expression studies indicate only partial reduction in the activity of the enzyme, in keeping with their milder clinical phenotype and near-normal urinary steroid profiles. This suggests a greater heterogeneity of AME than previously recognized, with a spectrum of abnormality of the steroid profile and clinical features depending upon the underlying mutation. Classification of AME into distinct variants is unnecessary.

AME represents the most florid example of loss of 11β-HSD2 activity; the physiological ‘protective gate’ around the MR is lost, enabling cortisol to act as a potent mineralocorticoid. The clinical relevance of 11β-HSD2 activity, however, does not stop at AME. Liquorice and its derivative carbenoxolone both inhibit this enzyme and this accounts for their mineralocorticoid and hypertensinogenic activity. The mineralocorticoid excess state which characterizes the ectopic ACTH syndrome is due to saturation of endogenous 11β-HSD2 activity by the overwhelming cortisol concentrations seen in this condition. 11β-HSD2 expression is reduced in patients with renal disease and such a mechanism may mediate enhanced sodium retention observed in some such patients, for example those with nephrosis. Furthermore, a detailed analysis of the function and expression of both 11β-HSD isoforms has brought to the forefront the concept of tissue metabolism of corticosteroid hormones and its possible relevance to processes such as foetal growth and development, insulin resistance and obesity. For the present though, the holy grail may be ‘essential’ hypertension. Whilst some studies have demonstrated abnormal urinary steroid profiles and prolonged plasma cortisol half-life in untreated hypertensives, suggesting reduced 11β-HSD2 activity, the functional significance of this is at present unclear. The reason for this inconsistency could be due to the limitations in detecting partial reductions in enzyme activity, and a more promising approach, using the power of molecular genetics, is the genotypic analysis of microsatellite polymorphic markers adjacent to the 11β-HSD2 gene in large hypertensive populations.

Clinically AME should be considered as the underlying cause of hypertension in any child or young adult, and in any adult with severe hypertension or with a family history of hypertension. In all cases an assessment of the renin-aldosterone axis should be made, and the diagnosis confirmed by analysing urinary cortisol and cortisone metabolites. Serum corticosteroid concentrations are normal and are of no help; similarly hypokalaemia suggests a mineralocorticoid excess state, and should prompt further investigation, but its absence does not exclude it. Once the diagnosis is made, small doses of dexamethasone to suppress endogenous cortisol secretion, or high doses of amiloride, are the treatments of choice.

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References