Editorial Comments

Blood pressure and salt and water-relevant genes

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When I was assigned the task of ‘getting interested’ in hypertension and genetics 20 years ago, I was crestfallen. Hypertensive patients didn’t even have an abnormal urinary sediment. Genetics conjured up thoughts of rare, eminently forgettable paediatric syndromes and fruit flies. In any event, Sir George Pickering had already figured almost everything out. We did have a family in the outpatient clinic with glucocorticoid-remediable aldosteronism (GRA), and folks down in Tennessee had some patients who also had an inherited form of hypertension described earlier by Grant Liddle. Fat chance that those things would ever be figured out! Appetite comes with tasting the meal and currently, we are being served a banquet of which any five star restaurant would be proud.

Glucocorticoid remediable aldosteronism (GRA)

Patients with GRA have an autosomal dominant monogenic hypertension and are usually suspected of having primary aldosteronism. They have a volume expansion, salt-sensitive, form of hypertension, tend to metabolic alkalosis with hypokalaemia (not invariably), and respond to both thiazide diuretics and spironolactone. The latter fact is a clinical clue that mineralocorticoid products may be involved. Their renin values are low while the aldosterone values are both elevated. The patients also have 18-hydroxy and 18-oxocortisol, steroids not normally found in appreciable amounts, in their urine. Recognizing these abnormal products (an intermediate phenotype) led to solving the mystery. Replacement amounts of prednisone ameliorate the hypertension, cause the abnormal steroids to disappear, and give the syndrome its name. The mystery of GRA was solved by Ulick, Rich, Lifton and colleagues [1]. The abnormal cortisol derivatives and the favorable effects of glucocorticoid treatment suggested that inner cortical zones, which express the gene for 17 a-hydroxylase (CYP17) and are ACTH-responsive, were the source of the excess mineralocorticoids. Two distinct gene products (11 β-hydroxylase and aldosterone synthase) perform the terminal steps in glucocorticoid and mineralocorticoid biosynthesis, respectively. A linkage analysis in a large pedigree localized the responsible gene to chromosome 8, exactly at the site where the genes for 11 β-hydroxylase and aldosterone synthase also reside. This fact suggested that a chimeric gene might be responsible, which indeed proved to be the case (Fig. 1). Aldosterone synthase (CYP11B2) and 11 β-hydroxylase (CYP11B1) reside on chromosome 8 as shown in the upper panel. In affected individuals, a chimeric gene consisting of the promoter-regulatory region of CYP11B1 and the structural portion of CYP11B2 is located between CYP11B2 and CYP11B1. The protein product resulting from this gene performs all reactions required for aldosterone production, thus causing ACTH-dependent hyperaldosteronism. Ectopic expression of the chimeric protein in the inner cortical zones, which also express CYP17, permits the formation of 18-hydroxy and 18-oxocortisol, the biochemical hallmarks of GRA (Fig. 2). Finally, suppressing steroidogenesis in the zona fasciculata and reticularis with exogenous glucocorticoids, alleviates the hypertension. The chimeric gene results from a miotic mismatch and unequal crossing over. In all instances, the crossover is located 5' to intron 4 of the CYP11B genes. Lifton kindly verified the diagnosis of GRA in our family.

Fig. 1. The genes CYP11B2 (aldosterone synthase) and CYP11B1 reside next to one another on chromosome 8 (upper). An error in meiosis (lower) results in the formation of an extra (chimeric) gene CYP11B1/CYP11B2, which has the CYP11B1 promoter and makes the product of CYP11B2.
Apparent mineralocorticoid excess (AME)

Licorice gluttony and treatment with carbenoxolone both cause a volume expansion, low renin, low aldosterone, salt-sensitive form of hypertension, which may also feature metabolic alkalosis and hypokalaemia. Interestingly, the hypertension responds to both thiazide and spironolactone, but no abnormal steroid products are present in the urine. Both licorice and carbenoxolone contain glycyrrhetinic acid, which was found to inhibit the enzyme 11 \( \beta \)-hydroxysteroid dehydrogenase. 11 \( \beta \)-hydroxysteroid dehydrogenase is responsible for converting cortisol to cortisone. In the distal renal tubule, this step is crucial for protecting the mineralocorticoid receptor, which has the same affinity for cortisol as it does for aldosterone (Fig. 3).

This step protects us all from developing AME. Inhibition of 11 \( \beta \)-hydroxysteroid dehydrogenase results in AME. Interestingly, AME may also occur as a rare, autosomal recessive form of monogenic hypertension. Needless to say, the 11 \( \beta \)-hydroxysteroid dehydrogenase gene, which has a renal-specific renal isoform, was a hot candidate gene for this condition. The clinical clues helpful in resolving this condition were: volume dependent salt sensitive hypertension, tendency to hypokalaemia and metabolic alkalosis, low renin and low aldosterone values, responsiveness to both thiazides and spironolactone despite absence of aldosterone or any abnormal mineralocorticoid products, and resemblance to licorice gluttony. Mune et al. [2] solved the mystery. In eight of nine families, mutations in the renal-specific isoform gene for 11 \( \beta \)-hydroxysteroid dehydrogenase were found which indeed rendered the product incapable of converting cortisol to cortisone. Thus, the mineralocorticoid receptor is unprotected from cortisol in these patients and cortisol functions to occupy the mineralocorticoid receptor.

Liddle syndrome

Liddle described patients with autosomal-dominant monogenic hypertension who also tended to metabolic alkalosis with hypokalaemia [3]. These patients had low renin and low aldosterone values; however, they did not respond to spironolactone, while thiazides and triamterene reduced the blood pressure. This observation convinced Liddle that they probably didn’t have a form of mineralocorticoid excess. Liddle speculated that they would show a distal tubular defect of enhanced sodium and chloride reabsorption. A renal transplant performed on a patient with Liddle syndrome who developed renal failure cured the disease, providing strong evidence that the problem resided within the kidneys rather than in a regulatory system [4]. Shimkets et al. [5] subsequently localized the responsible gene of a family with Liddle syndrome to chromosome 16 and were able to show that the gene encodes for the \( \beta \) subunit of the epithelial sodium channel (ENaC). The channel is amiloride and trim
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terene sensitive, explaining the efficacy of these drugs in the syndrome. The channel remains inappropriately permeable even in the face of high salt intake (Fig. 4), thereby explaining the salt sensitive hypertension. Subsequently a mutation in the γ subunit of ENaC has been found, which can also result in Liddle syndrome [6].

Analogous to the presumed existence of 'black holes' and 'antimatter', one might speculate that the reverse of such a syndrome could also exist. Indeed, mutations in the subunits of ENaC were found to cause relative hypotension and salt wasting with hyperkalaemic acidosis (pseudohypoaldosteronism type 1). Mutations in either the α or the β subunit result in loss of channel activity, thereby explaining the pathophysiology of the disease [7]. Other channel gene mutations can also result in blood pressure and salt and water regulatory diseases. For instance, Gitelman syndrome is a variant of Bartter syndrome and features inherited hypokalaemic alkalosis, hypomagnesemia, and hypocalciuria. The syndrome is caused by mutations in the thiazide-sensitive Na–Cl cotransporter [8]. Clinically, the patients look like individuals who surreptitiously are ingesting thiazide diuretics.

Non-salt and water syndromes

Not all blood pressure-relevant genetic diseases are based on problems with salt and water regulation. Several hypotensive disorders based on problems with catecholamine synthesis exist. For instance, dopamine β-hydroxylase deficiency is a rare, autosomal recessive disease that features severe orthostatic hypotension, retrograde ejaculation, ptosis, nocturia, and nasal stuffiness [9]. Plasma noradrenaline and adrenaline are entirely absent or barely detectable in this disease. Interestingly, the blood pressure responds to the administration of dihydroxyphenylserine, a compound which can be converted by the enzyme dopa decarboxylase to noradrenaline, thereby bypassing the dopamine β-hydroxylase step [10].

These genetic diseases have contributed fantastically to our understanding of the pathophysiology of blood pressure and salt and water regulation. However, their relevance to essential hypertension is not yet clear. Elucidation of autosomal-dominant monogenic hypertension with brachydactyly may help further. Affected persons are somewhat shorter and have brachydactyly, but are not obese, are not mentally retarded, and have no overt disturbance in parathyroid hormone function. This form of genetic hypertension is not characterized by salt-sensitivity, hypokalaemia, or metabolic alkalosis. The renin-angiotensin-aldosterone axis appears normal as do the catecholamine responses [11]. By the fifth decade, the blood pressure difference of affected persons remains high. A single gene locus in this family is responsible for a massive increase in blood pressure.
and nonaffected persons is 50 mmHg, indicating a profound blood pressure effect by a single gene locus (Fig. 5). The responsible gene has been mapped to chromosome 12p [12]. We have no idea how this form of hypertension works. Candidate genes in the neighborhood, encoding the 1-type voltage dependent calcium channel and the parathyroid hormone related peptide have been excluded. Elucidation of this mystery may provide insight into as yet unappreciated mechanisms of blood pressure regulation. In any event, hypertension and genetics have never ever been more exciting. Sir George Pickering would surely agree.

References


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**Toward understanding the molecular pathogenesis of monoclonal immunoglobulin light-chain deposition**

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**Introduction**

Monoclonal immunoglobulins can cause severe systemic manifestations essentially through their physicochemical properties and their antibody activity [1]. The tissue deposition of monoclonal immunoglobulins (intact, heavy and light chains or fragments thereof) is involved in several ominous conditions like light-chain amyloidosis and light-heavy-chain deposition disease. The kidney is the major target organ for monoclonal immunoglobulin deposits, which can be organized in various forms: fibrillar (amyloid and non-amyloid fibrillar and microtubular deposits), amorphous (light-heavy-chain deposition disease), crystalline (Fanconi's syndrome and other conditions), and cast (tubular cast nephropathy). Clinical and experimental evidence suggests a close correlation between the chemical characteristics of some monoclonal proteins and their specific renal toxicity. Here we will discuss some pathogenic aspects of the two most common and most investigated conditions: light-chain amyloidosis and light-chain deposition disease.

**Light-chain amyloidosis (AL amyloidosis)**

**Structural data**

That the ability to form amyloid depends on structural features of the light chains is suggested by the predominance of lambda-type monoclonal protein (in contrast...