Molecular basis of Bartter’s syndrome: new insights into the correlation between genotype and phenotype

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The kidney plays a key role in determining the long-term set points of fluid and electrolyte balance, maintaining homeostasis despite wide variation in environmental exposure. Maintenance of the correct ionic composition and volume of the intravascular space is critical for normal neuromuscular function, delivery of oxygen and nutrients to tissues, as well as for blood pressure. Derangements in kidney function, due to mutations in the mediators of renal Na⁺ reabsorption, may cause a number of mendelian forms of hyper- and hypotension that arise from changes in intravascular volume and abnormalities of electrolyte homeostasis.

Inherited renal tubular disorders associated with hypokalaemic metabolic alkalosis (Bartter-like syndromes) can be divided into at least three clinical phenotypes: (1) Gitelman’s syndrome; (2) ‘true Bartter’s syndrome’; and (3) the antenatal hypercalciuric variant. Gitelman’s syndrome (1) refers to the predominant subset of patients with hypokalaemic alkalosis in conjunction with hypocalciuria and hypomagnesaemia. These patients typically present at older ages without overt hypovolaemia.

‘True Bartter’s syndrome’ (2) is an autosomal recessive form of hypokalaemic metabolic alkalosis associated with salt wasting, normal or hypercalciuria, typically normal magnesium levels and normal or reduced blood pressure. Affected patients are discovered clinically at early ages (less than 5 years) and have been shown to have a hyperreninaemic hyperaldosteronism, altered prostaglandin metabolism, elevated levels of atrial natriuretic peptide, insensitivity to the vasoconstrictive effects of angiotensin II and noradrenaline, and an abnormal platelet function. This latter finding may be related to an increase in plasma cAMP levels resulting from excessive prostaglandins or to the presence of a circulating inhibitor of platelet aggregation, probably a prostaglandin. These different physiological findings are responsible for several symptoms and signs, including intravascular volume depletion, seizures, tetany, muscular weakness, paresthesias and joint pain with chondrocalcinosis. Moreover, persistent abnormalities in electrolyte composition have resulted in stunted growth and mental retardation in some affected subjects.

The antenatal variant of Bartter’s syndrome (3) is a life-threatening disorder in which both renal tubular hypokalaemic alkalosis, hypercalciuria and severe systemic symptoms are manifest. The abnormalities begin in utero with marked fetal polyuria which leads to polydramnios between 24 and 30 weeks of gestation and, typically, premature delivery. Affected neonates have severe salt wasting and hyposthenuria, moderate hypokalaemic metabolic alkalosis, hyperprostaglandinuria and failure to thrive. The essential manifestation of this variant is the hypercalciuria that leads to nephrocalcinosis and osteopenia. Fever, vomiting and occasional diarrhoea associated with the disorder have been attributed to the stimulation of renal and systemic prostaglandin E₃ activity in affected infants. These symptoms are effectively treated with inhibitors of prostaglandin synthesis. On the basis of these clinical features, the antenatal form of Bartter’s syndrome has been referred to as hyperprostaglandin E₃ syndrome.

The overlapping features of these disorders resulted in considerable confusion and controversy about their classification, with many patients with features of Gitelman’s syndrome being diagnosed as having Bartter’s syndrome in the literature. Also, the pathogenesis of these disorders remained uncertain, with wide speculation as to which observed abnormalities are primary and which are secondary consequences of underlying primary abnormalities (4).

Analysis of renal electrolyte homeostasis has resulted in selection of a number of potential candidate genes for Bartter’s syndrome, such as atrial natriuretic peptide (5) and angiotensin II receptor (AT1) (6). However, no link between atrial natriuretic factor gene and Bartter’s syndrome has been found, and, as far as the AT1 gene is concerned, a point mutation (A931G) has been identified in only one of five affected individuals, indicating that this abnormality may represent a subset of Bartter’s syndrome, which consists of multiple entities originating from different pathogenetic events. Several genetic studies have recently been performed that have provided new insights into the pathophysiology of these diseases, thus permitting their genetic classification and a better correlation between genotype and phenotype.

A primary defect in renal NaCl reabsorption has been suggested by a thorough analysis of the phenotype of Bartter-like syndromes. Starting from this observation, Simon and co-workers have identified attractive candidate genes encoding different mediators of Na⁺ and Cl⁻ reabsorption at various levels of the nephron (Fig. 1) (7–9). In particular, a loss of function of the thiazide-sensitive Na–Cl co-transporter (TSC) of the distal convoluted tubule was found in Gitelman’s syndrome.
This co-transporter is believed to be the most important mediator of Na–Cl reabsorption in this nephron segment and represents the target of the antagonist effect of thiazide diuretics used in the treatment of hypertension. Similarities in some features of patients with Gitelman’s syndrome and patients receiving thiazide diuretics have raised the possibility that mutations in TSC causing loss of function could result in Gitelman’s syndrome. This hypothesis was supported by linkage analysis of Gitelman’s syndrome kindreds. In affected subjects, a complete linkage of Gitelman’s syndrome to the locus encoding TSC on chromosome 16q13 was found and a wide variety of non-conservative mutations of the gene encoding TSC (NCCT, locus symbol SLC12A3), resulting in loss of function alleles, were identified. This defect would be expected to result in NaCl wasting, hypovolaemia and metabolic alkalosis. The reduced vascular volume activates the renin–angiotensin system, increasing aldosterone levels. This event leads to increased electrogenic Na⁺ reabsorption via an epithelial Na⁺ channel of the distal nephron in order to maintain intravascular volume. Na⁺ reabsorption via this channel is indirectly coupled to K⁺ and H⁺ excretion, producing the characteristic hypokalaemic alkalosis. How this primary defect in TSC function results in loss of magnesium and hypocalciuria observed in these patients remains to be clarified.

As far as Bartter’s syndrome is concerned, two different genes were shown to be involved in both ‘true Bartter’s’ and the ‘antenatal’ variant, indicating a genetic heterogeneity of these disorders. The bumetanide-sensitive Na-K-2Cl co-transporter (NKCC2, also known as SLC12A1) represents the primary mediator of Na⁺ and...
Cl⁻ reabsorption in the ascending thick limb of Henlé’s loop (TAL), and loss of function of this co-transporter could produce many of the features seen in patients affected with Bartter’s syndrome. Indeed, loop diuretics, specific antagonists of this co-transporter, can produce electrolyte disturbances very similar to those seen in patients with Bartter’s syndrome. Simon and colleagues (8) demonstrated linkage of Bartter’s syndrome to the NKCC2 locus on chromosome 15q15-q21 and identified frameshift or non-conservative missense mutations for this gene that co-segregate with the disease. These mutations are responsible for Na-K-2Cl co-transporter inactivation, resulting in salt wasting, activation of the renin–angiotensin system, increased aldosterone secretion, and increased Na⁺ reabsorption at distal nephrons in exchange for K⁺ and Cl⁻, accounting for hypokalemic alkalosis. Moreover, the reabsorption of approximately 25% of filtered calcium also occurs in the TAL and is coupled to Na⁺ reabsorption. Loss of Na⁺ reabsorption here consequently results in the hypercalciuria seen in these patients.

As in some Bartter’s kindreds NKCC2 mutations were not found, Simon and collaborators (9) examined the regulators of co-transporter activity. An apical ATP-sensitive K⁺ channel is believed to be one such regulator of the Na-K-2Cl co-transporter in TAL. Since K⁺ levels in TAL are much lower than levels of Na⁺ and Cl⁻, the availability of tubular K⁺ is rate-limiting for co-transporter activity. This K⁺ channel is able to ‘recycle’ reabsorbed K⁺ to the lumen, permitting sustained co-transporter activity. This key role in regulation of co-transporter activity is demonstrated by the ability of K⁺ channel antagonists to virtually abolish Na-K-2Cl co-transporter activity. Ho et al. (10) have cloned an inwardly rectifying channel, named ROMK (locus symbol KCNJ1). This channel, expressed in the kidney on the apical membrane of TAL cells, is characterized by two transmembrane-spanning domains and contains protein kinase A phosphorylation sites required for normal channel activity. ROMK has been proposed to be involved in K⁺ recycling in the TAL. As a consequence, mutations in the ROMK gene that cause the loss of ROMK function result in an inability to recycle K⁺ to the renal lumen. As a consequence, K⁺ levels in the renal lumen are too low to permit continued Na-K-2Cl co-transporter activity. This situation is similar to that observed when the primary defect is at the Na-K-2Cl co-transporter level and leads to the same pathophysiological features of Bartter’s syndrome as described above. Simon et al. (9) demonstrated that the ROMK gene mutations co-segregate with Bartter’s syndrome in four kindreds, confirming the genetic heterogeneity of the disease.

Taken together, the above findings establish a molecular basis for inherited renal tubular disorders associated with hypokalemic alkalosis and permit genetic distinction of these diseases. The entire spectrum of clinical and physiological features resulting from mutations in NCCT, NKCC2 and ROMK genes remains to be defined. Further examination of genotype–phenotype relationships should permit rigorous classification based on analysis of mutations and clinical features.

References