Chapter 3

Metabolic Alkalosis

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http://dx.doi.org/10.5772/intechopen.78724

Abstract

Metabolic alkalosis is a disorder where the primary defect, an increase in plasma bicarbonate concentration, leads to an increase in systemic pH. Here we review the causes of metabolic alkalosis with an emphasis on the inherited causes, namely Gitelman syndrome and Bartter syndrome and syndromes which mimic them. We detail the importance of understanding the kidney pathophysiology and molecular genetics in order to distinguish these syndromes from acquired causes. In particular we discuss the tubular transport of salt in the thick ascending limb of the loop of Henle, the distal convoluted tubule and the collecting duct. The effects of salt wasting, namely an increase in the renin-angiotensin-aldosterone axis are discussed in order to explain the biochemical phenotypes and targeted treatment approaches to these conditions.

Keywords: salt-wasting, inherited tubulopathy, renin-angiotensin-aldosterone axis

1. Introduction

Metabolic alkalosis is a disorder where the primary defect, an increase in plasma bicarbonate concentration, leads to an increase in systemic pH. Various mechanisms underpin the pathophysiology of metabolic alkalosis, which is defined by an arterial bicarbonate concentration of over 28 mmol/L or a venous total carbon dioxide concentration of greater than 30 mmol/L. The body compensates for alkali retention and subsequent elevated arterial pH by inducing respiratory hypoventilation resulting in an accompanying rise in $PaCO_2$. Normally the kidney, which has a protective mechanism against the development of significant increases in bicarbonate, will excrete excess alkali to restore the body to its homeostatic pH, but certain factors can impair this ability resulting in a sustained alkalotic state. Here we will review the pathophysiological mechanisms and clinical settings in which metabolic alkalosis

may occur [1–4] and give an overview of the causes of the inherited forms of metabolic alkalosis. The importance of defining a molecular genetic cause of metabolic alkalosis is reviewed alongside the common mimics of some of the inherited metabolic alkalosis syndromes.

2. Pathophysiology of metabolic alkalosis

The following mechanisms result in the elevation of serum bicarbonate; excessive loss of hydrogen ions by the kidney or via the GI tract, intracellular shift of hydrogen ions, retention of exogenous bicarbonate ions or volume contraction around a constant supply of extracellular bicarbonate (contraction alkalosis) [5].

As water dissociates in the body to hydrogen and hydroxyl ions, the hydroxyl ions combine with carbon dioxide, resulting in bicarbonate, as hydrogen ions are removed from extracellular fluid. Hydrogen ion removal in the kidney and GI tract is accompanied by loss of potassium and chloride so hypokalaemia and hypochloraemia often coexist with metabolic alkalosis.

Ability to excrete excess bicarbonate depends on the normal function of nephrons within the kidneys. The kidney therefore is implicated in the pathophysiology of most forms of metabolic alkalosis. The following scenarios result in a degree of impairment of this important mechanism: hypovolaemia, reduced glomerular filtration rate (GFR), reduced effective arterial volume, hypokalaemia, hypochloraemia or hyperaldosteronism.

2.1. Volume depletion

Both reduced extracellular volume and arterial pressure will reduce GFR and thus activate the renin-angiotensin-aldosterone and sympathetic nervous system. Decreased GFR reduces bicarbonate filtration by the kidney and angiotensin and sympathetic activation increases bicarbonate reabsorption and generation in addition to sodium reabsorption in the tubule. This is done in the following ways:

- Angiotensin-2 stimulates apical sodium-hydrogen exchange and basolateral sodium bicarbonate co-transport in the proximal tubule. This increases bicarbonate and sodium reabsorption.
- In the apical membrane of alpha-intercalated cells of the collecting duct angiotensin-2 and aldosterone increase H^+-ATPase pump activity resulting in increased urinary excretion of hydrogen ions. This results in increased intracellular bicarbonate generation which exits the cell in exchange for chloride via the basolateral membrane.
- Increases in aldosterone stimulate the apically located ENaC channel in the principal cells, which generates an electronegative potential in the tubular lumen. This enhances hydrogen and potassium ion excretion.

2.2. Sodium intake

A low sodium chloride diet will increase the bicarbonate reabsorption in the kidney enough to elevate serum pH although the reverse is not true with a high salt diet even though this will encourage the kidney to excrete sodium bicarbonate.

2.3. Chloride depletion

Chloride depletion secondary to vomiting or nasogastric suction leads to a metabolic alkalosis. Chloride depletion metabolic alkalosis causes concomitant potassium depletion through renal loss of potassium. A less severe chloride depletion metabolic alkalosis is seen with the use of thiazide and loop diuretics.

2.4. Hypokalaemia

Hypokalaemia causes alkalosis by moving hydrogen ions into the intracellular space in exchange for extracellular movement of potassium and hypokalaemia maintains an alkalosis by increasing renal bicarbonate reabsorption. Hypokalaemia (and aldosterone) stimulates the distal Na^+-K^+-ATPase and H^+-ATPase pumps in the apical membrane of alpha-intercalated cells to reabsorb potassium and secrete hydrogen and subsequently maintain alkalosis. Hypokalaemia also causes extracellular movement of potassium in exchange for intracellular movement of sodium and hydrogen which generates extracellular bicarbonate although co-existent intracellular acidosis. This intracellular acidosis stimulates renal bicarbonate reabsorption, hydrogen secretion and ammonium synthesis and excretion.

2.5. Increased aldosterone

Hyperaldosteronism in addition to increased distal tubule sodium delivery results in sodium reabsorption and hydrogen and potassium ion secretion. Any hyper-reninaemic state which will result in an increase in aldosterone production will have the same effects.

2.6. Volume contraction and beta-intercalated cells

Distal tubule chloride delivery is essential for the beta-intercalated cell to secrete bicarbonate as this occurs by an apical anion exchange protein called Pendrin (**Figure 3**). As volume contraction reduces distal chloride delivery, bicarbonate secretion will reduce as will chloride reabsorption. Urine pH becomes acidic with little chloride, sodium and potassium, so beta-intercalated cells are blunted from excreting bicarbonate and correcting the metabolic alkalosis [1–4].

3. Causes of metabolic alkalosis

3.1. Diuretics

Loop diuretics (Furosemide, Bumetanide, Torsemide) inhibit the apical Na^+–K^+–$2Cl^-$ co-transporter in the thick ascending limb of the loop of Henle where 20–25% of sodium is typically reabsorbed. Metabolic alkalosis occurs in several ways [6, 7]:

- Increased distal sodium delivery results in stimulation of the aldosterone sensitive sodium channel (ENaC) which increases hydrogen/potassium ion excretion.
- Hypochloraemia will also contribute to the metabolic alkalosis.

The same principle also applies to other diuretics such as thiazides.

3.2. Post-hypercapnia

Patients who are chronic CO_2 retainers typically develop a compensatory metabolic alkalosis due to renal bicarbonate retention. Once the hypercapnia is reversed with ventilatory support, the renal bicarbonate retention takes longer to correct and these patients usually have a chronically elevated bicarbonate [8].

3.3. Non-reabsorbable anion delivery

Antibiotics particularly Beta-lactams act as non-reabsorbable anions in the renal tubule which therefore promotes potassium and hydrogen excretion which results in metabolic alkalosis [9].

3.4. Inherited salt wasting alkaloses

Bartter and Gitelman syndromes are both autosomal recessive inherited disorders which result in characteristic features due to a hereditary dysfunction in a tubular salt handling [10]. Both result in hypokalaemia, metabolic alkalosis, hyper-reninaemia and hyperaldosteronism with low blood pressure. The prevalence of Gitelman syndrome is about 1 in 40,000 compared with Bartter syndrome, which has a prevalence of 1 in 1,000,000. Bartter syndrome is more severe and may cause perinatal death due to salt wasting crises. The clinical phenotype that is seen with Gitelman syndrome mimics the chronic ingestion of a thiazide diuretic and that of Bartter syndrome mimics a chronic loop diuretic effect (**Table 1**). Bartter and Gitelman syndrome carriers (heterozygous for a mutation in causative gene) typically have lower blood pressure than that of the general population and may have mild biochemical phenotypes and some clinical symptoms.

Bartter syndrome results from a primary defect in sodium chloride reabsorption in the thick ascending limb of the loop of Henle (**Figure 1**). Salt (sodium) wasting results in volume depletion which activates juxtaglomerular secretion of renin and subsequent juxtaglomerular hyperplasia and hyperaldosteronism. Volume depletion and increased distal tubular sodium delivery result in tubular potassium and hydrogen secretion in the urine [11, 12]. Paracellular reabsorption of calcium and magnesium in the thick ascending limb of the loop of Henle is driven by sodium chloride reabsorption in this nephron segment. Reduced sodium absorption here results in hypercalciuria and hypomagnesaemia [13].

To date, there are five types of Bartter syndrome based on different genetic defects (**Figure 1**) with slightly variable phenotypic presentations [14].

Type 1: mutations *SLC12A1* which encodes the apically located Na-K-2Cl (NKCC2) result in a severe phenotype which can cause maternal polyhydramnios and prematurity. Subsequently, few survive infancy due to extreme salt wasting resulting in significant hypokalaemia, metabolic alkalosis, polyuria and hypercalciuria.

Type 2: mutations in *KCNJ1*, which encodes the apical potassium channel ROMK essential for potassium recirculation in the thick ascending limb of the loop of Henle results in salt-wasting alkalosis. Nephrocalcinosis is common which often results in later renal dysfunction and, in some cases, end stage renal failure [15].

	Bartter syndrome	**Gitelman syndrome**
Site of defect	NKCC2, ROMK, CLC-KB, CLC-KA and CaSR in the thick ascending limb of the loop of Henle	Apical sodium chloride co-transporter (NCCT) at the distal convoluted tubule
Metabolic alkalosis	Present	Present
Hypokalaemia	Present	Present
Hypocalcaemia	Rare (seen in Type 5 Bartter syndrome)	Absent
Hypomagnesaemia	Occasionally present	Present
Urine chloride and sodium excretion	High	Normal/high
Urine potassium excretion	Normal/high	High
Urine calcium excretion	Normal/high	Low
Urinary concentrating ability	Impaired	Normal
Urine prostaglandin excretion	High	Normal
Hyper-reninaemic Hyperaldosteronism	Present	Present
Age at presentation	Antenatal/neonatal periods	Childhood/adolescence/adult
Polyhydramnios	Common	Absent
Failure to thrive	Typically present	Absent
Growth retardation	Typically present	Rarely present
Polyuria and polydipsia	Present	Absent
Sensorineural deafness	Present in Type 4 Bartter syndrome	Absent
Chondrocalcinosis	Absent	Occasionally present
Nephrocalcinosis	Present in Type 1 and Type 2 Bartter syndrome	Absent
Muscle weakness/tetany	Occasionally present	Present

Table 1. Differences between Bartter and Gitelman syndrome.

Type 3: mutations in *CLCNKB* result in loss of function of the basolateral chloride channel ClC-Kb which is historically described as the 'classical' form of Bartter syndrome. This form is less severe and may present later in childhood. Co-expression of ClC-Ka results in a less severe phenotype. Some patients with *CLCNKB* mutations have a Gitelman syndrome phenotype with hypocalciuria and thiazide non-responsiveness because ClC-Kb is also involved with chloride reabsorption along the distal convoluted tubule in addition to the thick ascending limb of the loop of Henle. Late renal impairment can feature in this form of Bartter syndrome mainly due to nephrocalcinosis and the adverse effects of NSAIDS (used as treatment for the condition) [16].

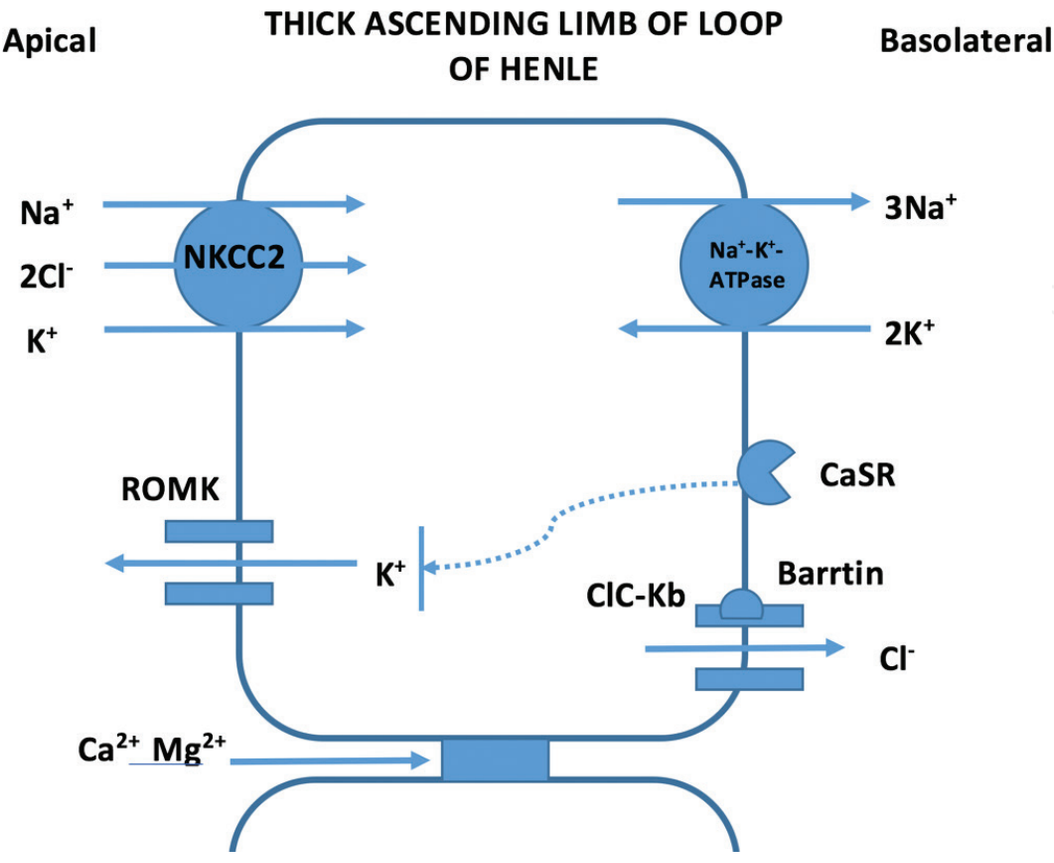

Figure 1. The thick ascending loop of Henle and the transporters and channels associated with tubulopathies.

Type 4: two mechanisms underlie type 4 Bartter syndrome. Both defects cause severe disease in the antenatal period and present with co-existent congenital deafness. Progressive renal failure is more common but nephrocalcinosis is less commonly seen. Type 4A is a consequence of a defect in the Barttin subunit that is essential to the function of both the chloride channels ClC-Ka and ClC-Kb which are present in both the renal tubule and the stria vascularis of the cochlear (inner ear). Bartter type 4b involves a second mechanism whereby digenic mutations affect both chloride channels (*CLCNKA* and *CLCNKB*) [17].

Type 5: this form of Bartter syndrome is due to a gain of function mutation in *CASR* encoding the calcium sensing receptor (CaSR). This is also termed autosomal dominant hypocalcaemia. This condition results in a low serum calcium as a result of downward 'resetting' of the parathyroid gland and hypocalcaemia subsequently inhibits parathyroid hormone release. The gain of function mutation in CaSR additionally regulates paracellular calcium transport in the thick ascending limb of the loop of Henle. CaSR over-activation reduces ROMK expression in addition to blunting Na^+–K^+–$2Cl^-$ co-transporter expression resulting in renal sodium chloride wasting. Calcium and magnesium reabsorption via paracellular channels is inhibited due to lack of electrochemical gradient to drive paracellular reabsorption. This Bartter syndrome subtype is unique due to the presence of hypocalcaemia and an autosomal dominant inheritance pattern and has a milder phenotype (with much less alkalosis) and with later onset [18].

A transient form of Bartter syndrome exists as an X-linked pattern of inheritance which manifests in the antenatal period. This form presents with severe polyhydramnios and prematurity

if the foetus survives to this stage. Severe salt wasting results in foetal polyuria and those that survive to birth have spontaneous resolution in symptoms over the first few months/years of life. Mutations in *MAGED2*, which encodes melanoma-associated antigen D2, underlie this condition. The gene is thought to affect the antenatal expression and function of NKCC2 and NCC via adenylate cyclase, a cytoplasmic heat-shock protein and cyclic AMP [19].

The apically expressed furosemide sensitive co-transporter/sodium potassium chloride co-transporter (NKCC2) is shown. Mutations in Type 1 Bartter syndrome are associated with dysfunction in this channel, leading to salt wasting. Mutations in the apical potassium channel *ROMK* cause Type 2 Bartter syndrome. ROMK is essential for potassium recycling back to the lumen of the tubule in this nephron segment. Mutations in *CLCNKB* encoding the basolateral chloride channel ClC-Kb cause type 3 Bartter syndrome (as well as causing phenotypes similar to Gitelman syndrome). Type 4 Bartter syndrome is due to mutations in *BSND* which acts as a subunit for both ClC-Kb and ClC-Ka (not shown). *BSND* mutations also cause sensorineural deafness. The basolateral calcium-sensing receptor (CaSR) regulates ROMK and its overstimulation/gain of function causes an inhibition of ROMK, producing a Bartter-like phenotype. Calcium and magnesium are resorbed via paracellular channels, and any loss of the electrochemical driving force will lead to hypercalciuria and magnesium wasting. Dysfunction at this nephron segment leads to severe renal salt wasting, which activates the renin-angiotensin-aldosterone system. The increased delivery of salt to the cortical collecting duct promotes aldosterone dependant Na^+ reabsorption via ENaC, which is coupled to K^+ and H^+ secretion, thus accounting for the hypokalaemic alkalosis seen.

Gitelman syndrome differs from Bartter syndrome due to the presence of hypocalciuria and does not typically manifest until adolescence or adulthood. Differentiating Gitelman syndrome from Type 3 Bartter syndrome can be difficult [20] due to expression of CLCKNB in distal nephron segments as well as the thick ascending limb of the loop of Henle.

Gitelman syndrome results from inactivating mutations in *SLC12A3* which encodes the sodium chloride co-symporter (NCCT) (**Figure 2**) in the distal convoluted tubule [21]. The clinical phenotype can be variable and no phenotype-genotype correlation is yet understood. It is theorised that lack of correlation could be due to differences in function and/or expression of other basolateral chloride channels such as the voltage-gated chloride channel, KCl co-transporter or the cystic fibrosis transmembrane conductance regulator [22].

EAST syndrome (alias SeSAME, OMIM #612780) is causes by mutations in *KCNJ10*, a basolateral potassium channel (**Figure 2**) expressed in the distal convoluted tubule [23, 24]. Biochemically, the phenotype exactly mimics Gitelman syndrome. Extra-renal manifestations of epilepsy, ataxia and speech dyspraxia make the syndrome recognisable.

The apically expressed thiazide sensitive co-transporter/sodium chloride co-transporter (NCCT) is shown. Mutations in Gitelman syndrome are associated with dysfunction in this channel, leading to salt wasting. Mutations in the basolateral potassium channel *KCNJ10* cause EAST syndrome and the serum biochemistry phenotypically mimics Gitelman syndrome. This channel is required for potassium recycling from the Na^+–K^+–ATPAse. Mutations in *CLCNKB* encoding the basolateral chloride channel ClC-Kb can also mimic Gitelman syndrome (as well as causing Bartter syndrome). Dysfunction of the apical magnesium channel in the distal convoluted tubule encoded by *TRPM6* is seen in Gitelman syndrome, explaining

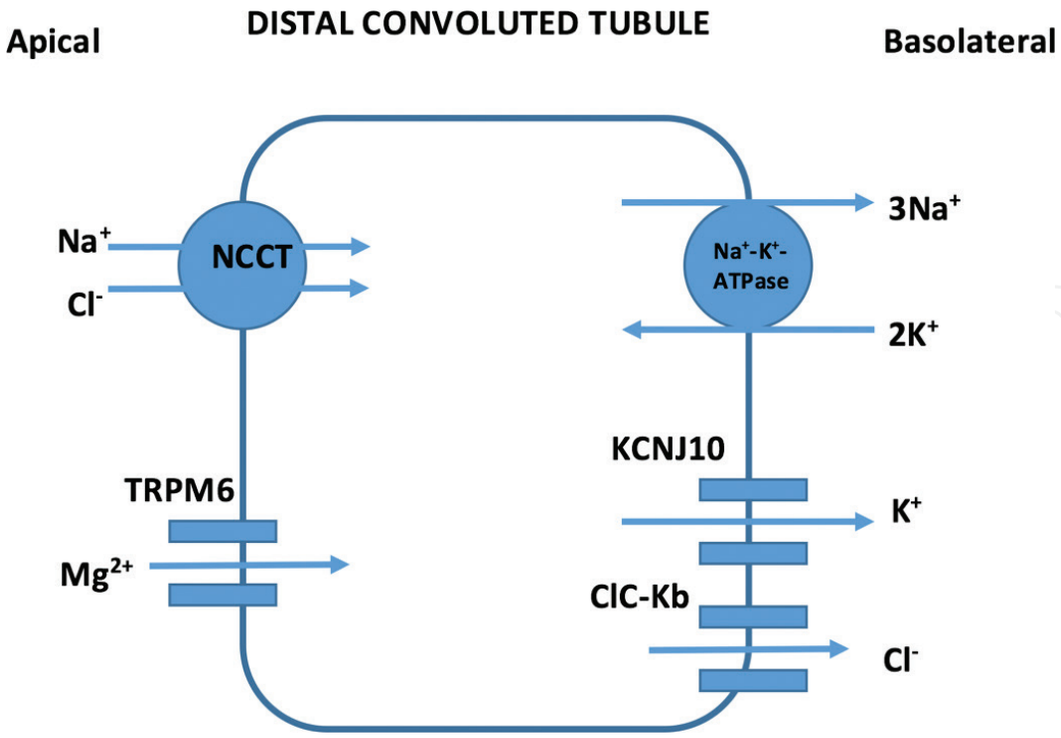

Figure 2. The distal convoluted tubule and the transporters and channels associated with tubulopathies.

the hypomagnesaemia. Renal salt loss activates the renin-angiotensin-aldosterone system and increased delivery of salt to the cortical collecting duct promotes aldosterone dependant Na^+ reabsorption via ENaC, which is coupled to K^+ and H^+ secretion, thus accounting for the hypokalaemic alkalosis seen.

Treatment for these in inherited salt wasting alkaloses conditions, in addition to electrolyte replacement, can comprise of NSAIDs, typically indomethacin. Renal production of PGE2 is typically elevated in response to reduced entry of chloride into the macula densa in the end of the thick ascending limb in these conditions [25]. Cyclooxygenase 2 expression is subsequently increased. PGE2 stimulates renin release by the juxtaglomerular apparatus contributing to the phenotype. PGE2 synthesis inhibition by NSAIDS will therefore reverse many of the clinical and biochemical abnormalities found in Bartter syndrome or phenotypically severe Gitelman syndrome (and EAST syndrome) [26].

4. Pendred Syndrome

Pendred syndrome is an autosomal recessive disorder resulting from biallelic mutations in *SLC26A4* which encodes Pendrin, a multi-functional anion transporter. Pendrin acts a chloride/bicarbonate exchanger in the cochlear, mediates iodide transport in the apical membrane of thyrocytes and as a chloride/bicarbonate exchanger in the apical membrane of beta-intercalated cells in the collecting duct (**Figure 3**). The resulting clinical picture is of sensorineural deafness, hypothyroidism, goitre and impaired bicarbonate secretion in states of metabolic alkalosis.

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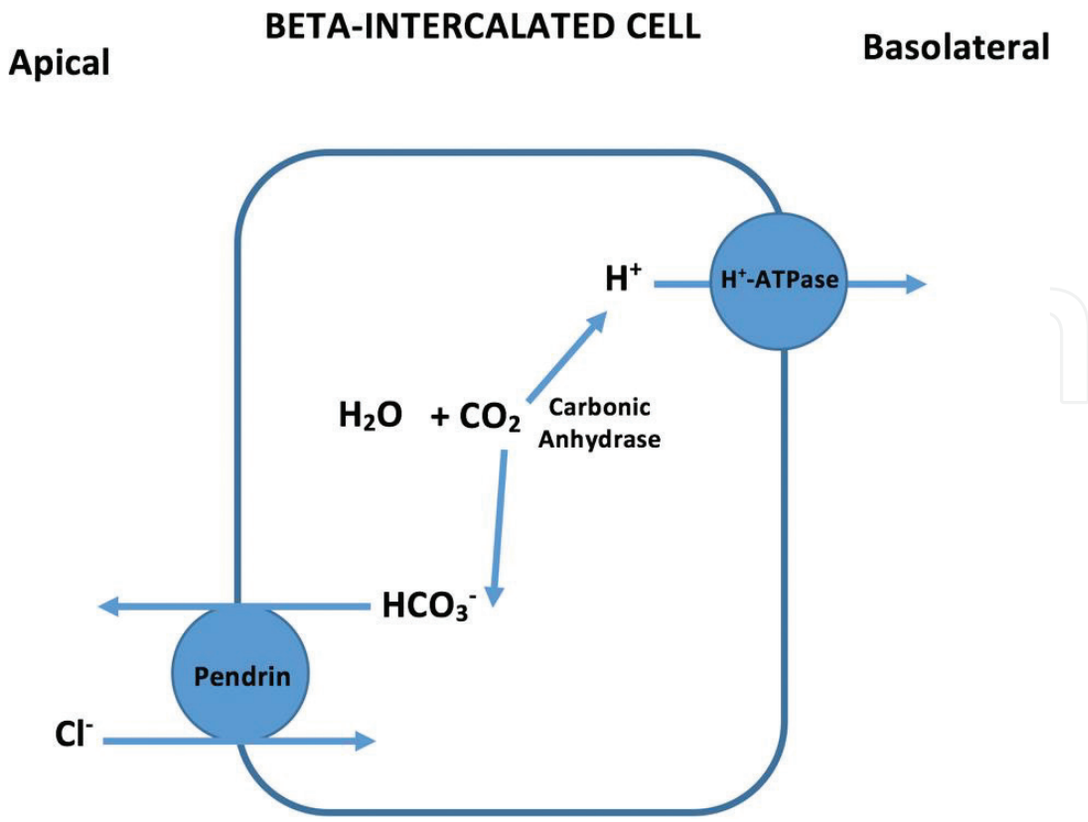

Figure 3. Pendrin expression in the intercalated cells of the kidney.

Failure of the compensatory mechanisms in alkalotic states such as those triggered by diuretics, including thiazides, can result in a life threatening metabolic alkalosis [27].

Pendrin is expressed on the apical membranes of type B intercalated cells (shown) as well as and non-A, non-B intercalated cells (not shown). Mutations in *SLC26A4*, which encodes Pendrin, lead to a failure of the kidney to secrete a bicarbonate load, which is generated from intracellular carbonic anhydrase type 2, leading towards a metabolic alkalosis.

4.1. Glucocorticoid remedial Aldosteronism

Glucocorticoid remediable aldosteronism (GRA) is an autosomal dominant inherited cause of hypertension and is one of three known forms of familial hyperaldosteronism. Normally, aldosterone synthesis occurs in the zona glomerulosa of the adrenal gland which intentionally lacks the 17-hydroxylase enzyme to synthesise cortisol. In GRA, aldosterone is synthesised in the ACTH-sensitive zona fasciculata. In the zona glomerulosa, the gene *CYP11B2* encodes aldosterone synthase which catalyses the conversion of deoxycorticosterone to corticosterone and 18-hydroxycorticosterone to aldosterone. In the zona fasciculata, *CYP11B1*, which encodes 11β-hydroxylase, catalyses the conversion of 11-deoxycortisol to cortisol. In GRA, there is a chimeric gene duplication that results from unequal crossing over of CYP11B1 and CYP11B2 resulting in ACTH-dependent activation of aldosterone synthase (rather than by the renin-angiotensin-aldosterone system) which causes a significant increase in 18-oxocortisol and

18-hydroxycortisol. As this reaction occurs in the zona fasciculate, the aldosterone secretion is not sensitive to potassium loading as it would be in a normal subject due to the consistent prolonged release of ACTH. Consequentially, you do not always get hypokalaemia with this condition in contrast to subjects with other forms of hyperaldosteronism. Hypertension typically develops before the age of 21 and significant hypokalaemia develops following thiazide diuretic administration due to its effect on increased distal tubular sodium delivery to aldosterone-sensitive potassium secretion site in the collecting duct. Although there is intra-family phenotypic variability with GRA, there is a strong prevalence of haemorrhagic stroke related to cerebral aneurysm which is even more prevalent than seen in autosomal dominant polycystic kidney disease [28, 29]. Subjects with GRA should subsequently have a cerebral MRA every 5 years from puberty. Genetic testing is now preferred to a dexamethasone suppression test and demonstration of elevated 18-oxocortisol and 18-hydroxycortisol [30]. Treatment comprises of ACTH suppression with glucocorticoids with careful attention to the growth retardation effects of over-treatment in paediatric subjects. This will restore normotension and normokalaemia. Alternatively, mineralocorticoid receptor antagonists such as spironolactone may be used [31].

4.2. Congenital adrenal hyperplasia

Over 95% of patients with congenital adrenal hyperplasia have defective conversion of 17-hydroxyprogesterone (17OHP) to 11-deoxycortisol. This is because of a mutation in the *CYP21A2* gene which encodes the enzyme 21-hydroxylase which is responsible for this conversion. CAH is an autosomal recessive disorder comprising two distinct types based on whether the condition is accompanied by salt wasting. Girls typically present with atypical genitalia (clitoral enlargement, urogenital sinus, labial fold fusion and genital orifice migration) but can present simply with severe salt wasting alone in the neonatal period. Boys typically present with severe salt wasting and do not manifest genital abnormalities until they reach an early onset puberty when they are toddlers. Phallic enlargement and hyperpigmentation can occur. CAH is diagnosed when the serum 17-hydroxyprogesterone concentration is elevated. Adrenal ultrasound has additional diagnostic value in the neonatal period revealing a lobulated surface, adrenal limb length greater than 4 mm and abnormal echogenicity. A prenatal diagnosis can be made by molecular analysis of *CYP21A2*. Treatment involves a glucocorticoid such as hydrocortisone to replace cortisol deficiency and hyperandrogenaemia and subsequent fertility difficulties. Mineralocorticoid replacement such as fludrocortisone is necessary to reverse salt wasting and volume depletion and testicular US surveillance from adolescence due to an increased risk of testicular adrenal rest tumours [32, 33].

4.3. Apparent mineralocorticoid excess

Mineralocorticoid receptors in the collecting duct bind aldosterone and cortisol with similar affinity. Cortisol is normally converted into its inactive form cortisone by the enzyme 11-beta-hydroxysteroid type 2 at sites of aldosterone activity to prevent competitive inhibition with aldosterone. In AME, a mutation in 11-beta-hydroxysteroid type 2 results in a reduction of cortisol conversion to cortisone and subsequently the mineralocorticoid receptor is activated

by excess cortisol. AME is autosomal recessive and causes severe hypertension in children in addition to hypercalciuria, nephrocalcinosis and renal failure due to an unknown mechanism. Nephrogenic diabetes insipidus can also occur due to chronic hypokalaemia. Defects in *HSD11B2* are responsible for this condition, some mutations result only in partial inhibition of 11-beta hydroxysteroid 2 resulting in a less severe phenotype. There is rough genotypic-phenotypic correlation which includes the ratio of cortisol to cortisol metabolites which can be measured. Treatment for this condition aims at reducing endogenous cortisol production by dexamethasone or by blocking the mineralocorticoid receptor with spironolactone/eplerenone. ENaC blockade has similar success with less side effects, so it is reasonable to instead use amiloride or triamterene especially in men. If hypercalciuria is present then it is reasonable to use a thiazide to prevent nephrocalcinosis and subsequent renal impairment [34–36].

4.4. Liquorice ingestion and carbenoxolone

Liquorice (root of *Glycyrrhiza glabra*) is found in tobacco, snuff, foods, soft drinks, herbal medicine and teas in addition to its popular consumption as a confectionary item. Not all sweets contain the compound glycyrrhiza but instead are flavoured with alternative compounds to mimic liquorice so chronic ingestion should not cause the clinical picture of apparent mineralocorticoid excess. Glycyrrhiza inhibits 11-beta hydroxysteroid dehydrogenase which converts cortisol to cortisone. Carbenoxolone, a liquorice-like compound has the same effect [37].

4.5. Liddle syndrome

Liddle syndrome is a rare autosomal dominant disorder associated with a gain of function mutation in the epithelial sodium channel (ENaC) situated on the luminal membrane of principal cells in the collecting duct. In Liddle syndrome, ENaC function is increased which results in hypokalaemia and metabolic alkalosis. Increased activity of ENaC results in increased sodium reabsorption and potassium secretion and subsequent hypertension, hypokalaemia and metabolic alkalosis. Most patients present at a young age and not all have hypokalaemia but their potassium does run at lower range of normal.

Net sodium reabsorption occurs down a concentration gradient in principle cells via both ENaC on the luminal membrane and the Na–K–ATPase on the basolateral membrane. The greater net sodium reabsorption enhances potassium secretion through basolateral Na–K–ATPase and subsequent open luminal potassium channels.

Mutations in *SCNN1B* and *SCNN1G* which encode the beta and gamma subunits of ENaC cause Liddle syndrome. When volume expansion occurs there is failure to remove ENaC channels from the luminal membrane under the influence of low renin and aldosterone and the phenotype mimics a hyperaldosteronism state yet plasma and urine aldosterone levels are in fact reduced. Treatment involves potassium paring diuretics which directly block ENaC such as Amiloride or Triamterene. Spironolactone, which competes with aldosterone to bind to the mineralocorticoid receptor, would not be effective as increased ENaC activity in not mediated by aldosterone [38, 39].

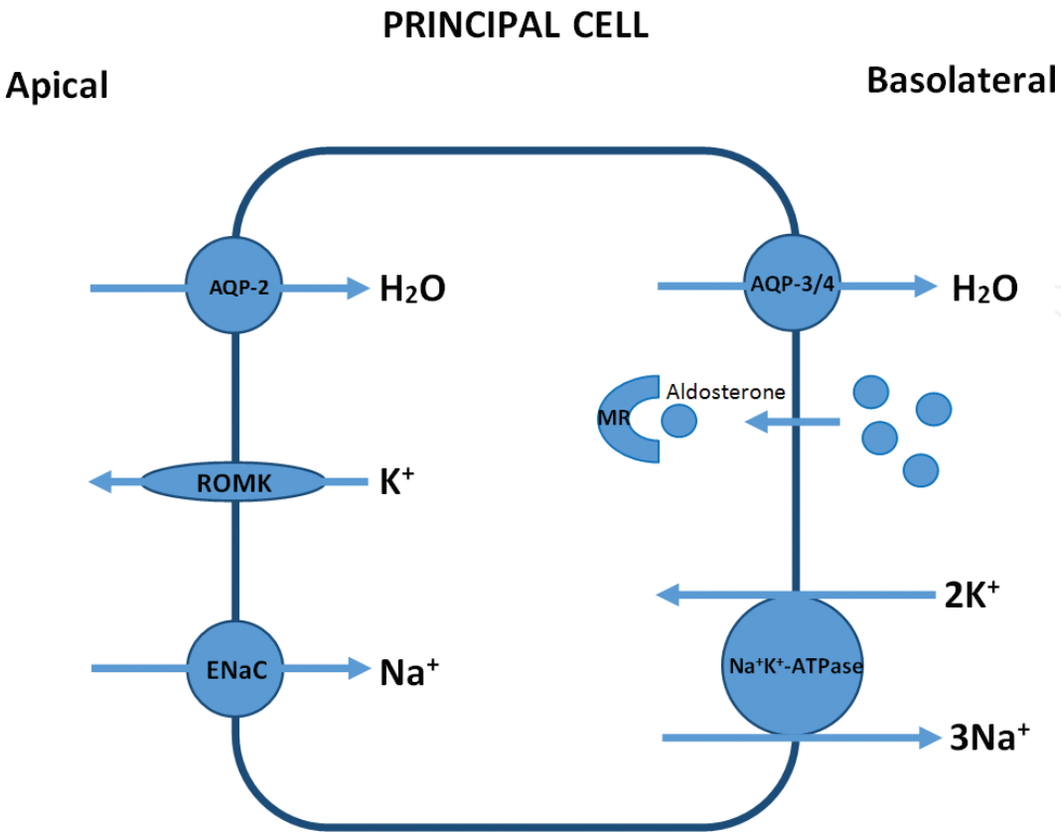

Figure 4. Salt transport in the principal cell.

4.6. Cortisol excess

Excess cortisol may allow stimulation of the mineralocorticoid receptor to leading to hypertension and a hypokalemic metabolic alkalosis. Causes include excess exogenous administration of glucocorticoids such as hydrocortisone or secondary to endogenous cortisol hypersecretion either by Cushing's syndrome or disease, ectopic ACTH production most commonly by small cell lung cancers or by a deoxycorticosterone-secreting tumour on the adrenal gland [2] (**Figure 4**).

Principal cells respond to a variety of stimuli to control Na^+ and K^+ transport. Aldosterone has the most pronounced effect. It acts through the mineralocorticoid receptor (MR) to increase surface expression of the epithelial sodium channel ENaC. Electrogenic Na^+ reabsorption via ENaC is balanced by K^+ secretion through ROMK and Cl^- reabsorption through multiple pathways (not shown). The driving force that sets the electrochemical gradient for principal cell Na^+ and K^+ transport is the basolateral Na^+–K^+–ATPase.

5. Reasons to suspect and inherited cause of alkalosis

Clinical features of a metabolic alkalosis include muscle cramps, weakness, arrhythmias and seizures. Some of these signs and symptoms may be related to alterations in ionised calcium

(increased pH causes plasma proteins to bind calcium more avidly, thus lowering ionised calcium concentration). The associated hypokalaemia may also give rise to many of these symptoms. Inherited forms of alkalosis are secondary to a heterogeneous group of renal tubulopathies. Typical manifestations range from asymptomatic biochemical disturbances to severe salt wasting leading in early life and may be complicated by renal failure. The important clues to diagnosing an inherited cause of metabolic alkalosis include consistent electrolyte abnormalities (versus acquired changes in serum biochemistry), nephrocalcinosis, renal stone formation and renal impairment. Historical blood values are invaluable in this regard. A detailed family history is required to look for autosomal dominant and recessive patterns of disease. In children, failure to thrive, short stature, learning difficulties and rickets may also be evident. A history of early onset hypertension and a family history of stroke at a young age provides clues to look for inherited forms of hypertension including Liddle syndrome and GRA.

Individual syndromes may be distinguished by distinct biochemical profiles but modern day molecular genetics allows a more robust means to come to a firm diagnosis. A very similar biochemical picture to Bartter and Gitelman syndromes can be induced by diuretic use or abuse, laxative abuse and chronic liquorice ingestion. However, urinary chloride will be raised in Bartter and Gitelman syndromes (>20 mmol/L) whereas vomiting, gastric drainage, diuretics and post-hypercapnia will all have a low urinary chloride concentration (<10 mmol/L). Therefore, obtaining a careful drug and food history is important together with urine electrolyte analysis and diuretic screening to make certain that the cause is not an acquired one. The optimal treatment of a metabolic alkalosis clearly depends on identifying the underlying cause. Treatment of life-threatening alkalosis may involve control of ventilation (sedation, intubation and controlled hypoventilation). Historically, administration of HCl or ammonium chloride/arginine chloride has been advocated. These are not advocated. Control of ventilation and correction of volume status and improvement of renal haemodynamics is effective in cases of chloride loss. Haemodialysis may be used in extreme cases. Hypokalaemia should be corrected alongside the alkalosis. Treatment of Bartter and Gitelman syndrome, as detailed above, relies upon electrolyte replacement, attempts at disrupting the renal production of renin with NSAIDs and blocking the effects of excess mineralocorticoids with spironolactone, eplerenone and amiloride. Treatment of Liddle syndrome relies on sodium restriction and potassium-sparing diuretics which block ENaC and allow the correction of blood pressure, hypokalaemia and metabolic alkalosis.

6. Conclusions

A systemic metabolic alkalosis is an important electrolyte disturbance which can have significant sequelae including neuromuscular irritability, tetany and cardiac rhythm disturbances. Hypokalaemia is a frequent accompanying electrolyte abnormality. Numerous inherited tubulopathies can cause this clinical and biochemical picture and acquired causes may mimic these. Molecular genetic testing allows a precise diagnosis and appropriate management to be given to patients with inherited salt wasting alkaloses.

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