Bartter like syndromes

Fakhrossadat Mortazavi

Professor of Pediatric Nephrology

Tabriz University of Medical sciences

Introduction

- In 1962, Frederic Bartter Reported two African American patients presenting a new entity characterized by hypokalemic metabolic alkalosis and salt wasting.
- In1966, Gitelman Reported another entity with hypokalemic metabolic alkalosis susceptible to carpopedal spasm due to hypomagnesemia.
- Over decades many similar cases and several phenotypic variants were recognized and included in a group of hypokalemic salt loosing tubulopathies referred to as Bartter like syndromes.

Introduction

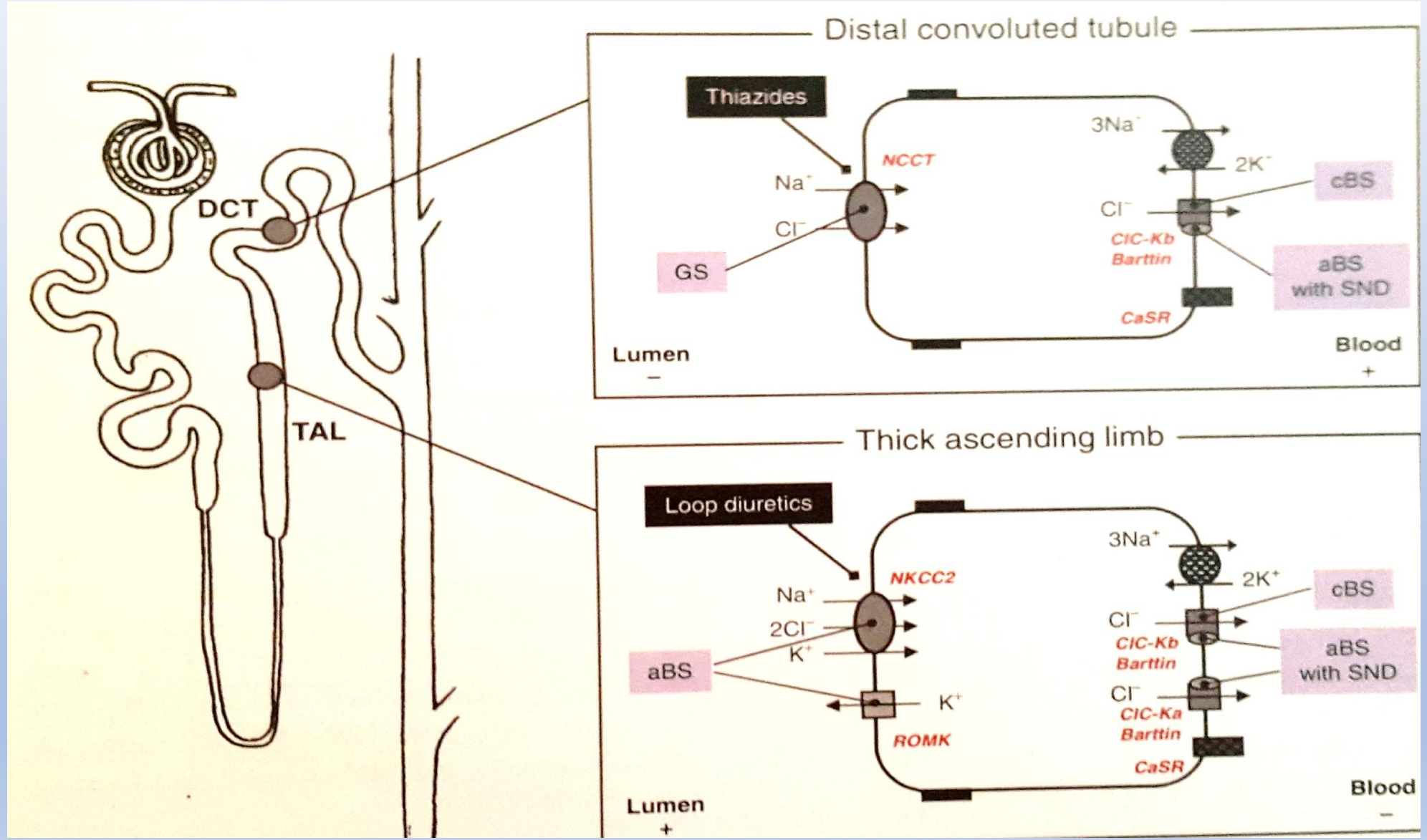
Bartter like syndromes differ in terms of:

- age of onset and severity
- magnitude of urine Ca excretion and presence of nephrocalcinosis
- presence of hypomagnesemia
- urine concentrating defect

All of these disorders are autosomal recessive inherited diseases involved in

cl^- reabsorption at the level of TAL of Henle and distal convoluted tubule.

Pathophysiology of Cl^- reabsorption in TAL and DCT



Renal tubular disorders of electrolyte regulation in children, Devuyst O et al, Pediatric nephrology , 2016

Disorder	Protein	Affected tubular segment	Associated gene mutation Gene locus
Antenatal Bartter syndrome Type 1 Hyperprostaglandin E	Na-K-2Cl cotransporter NKCC2	TAL	SLC12A1 15q15q21.1
Antenatal Bartter syndrome Type 2 Hyperprostaglandin E	K channel ROMK	TAL Cortical Collecting Duct	KCNJI 11q24
Classic Bartter's syndrome type 3	Cl channel ClC-Kb	TAL Distal convoluted tubule	CLCNKB 1p36
Bartter's syndrome with sensorineural deafness Type 4	Bartin,beta subunit of ClC-Ka/b	TAL Distal convoluted tubule	BSND 1q31
Gitelman syndrome	Na-Cl cotransporter NCCT	Distal convoluted tubule	SLC12A3 16q13

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Age at manifestation and primary symptoms of genetically defined salt-wasting kidney disorders

Disorder	Affected protein	Polyhydramnios	Age at first manifestation	Primary symptoms
Bartter syndrome type I	NKCC2	+++	Perinatal	Polyuria, hypochloremia, alkalosis, hypokalemia, nephrocalcinosis
Bartter syndrome type II	ROMK	+++	Perinatal	Polyuria, hypochloremia, alkalosis, hyperkalemia initially, hypokalemia later, nephrocalcinosis
Bartter syndrome type III	ClCKB	+	0–5 years	Hypokalemia, hypochloremia, alkalosis, failure to thrive
Bartter syndrome type IV (BSND)	Barttin	+++	Perinatal	Polyuria, hypochloremia, alkalosis, hypokalemia, deafness
Gitelman syndrome	NCCT	–	>5 years	Hypokalemia, hypomagnesemia, alkalosis, hypocalciuria, growth retardation

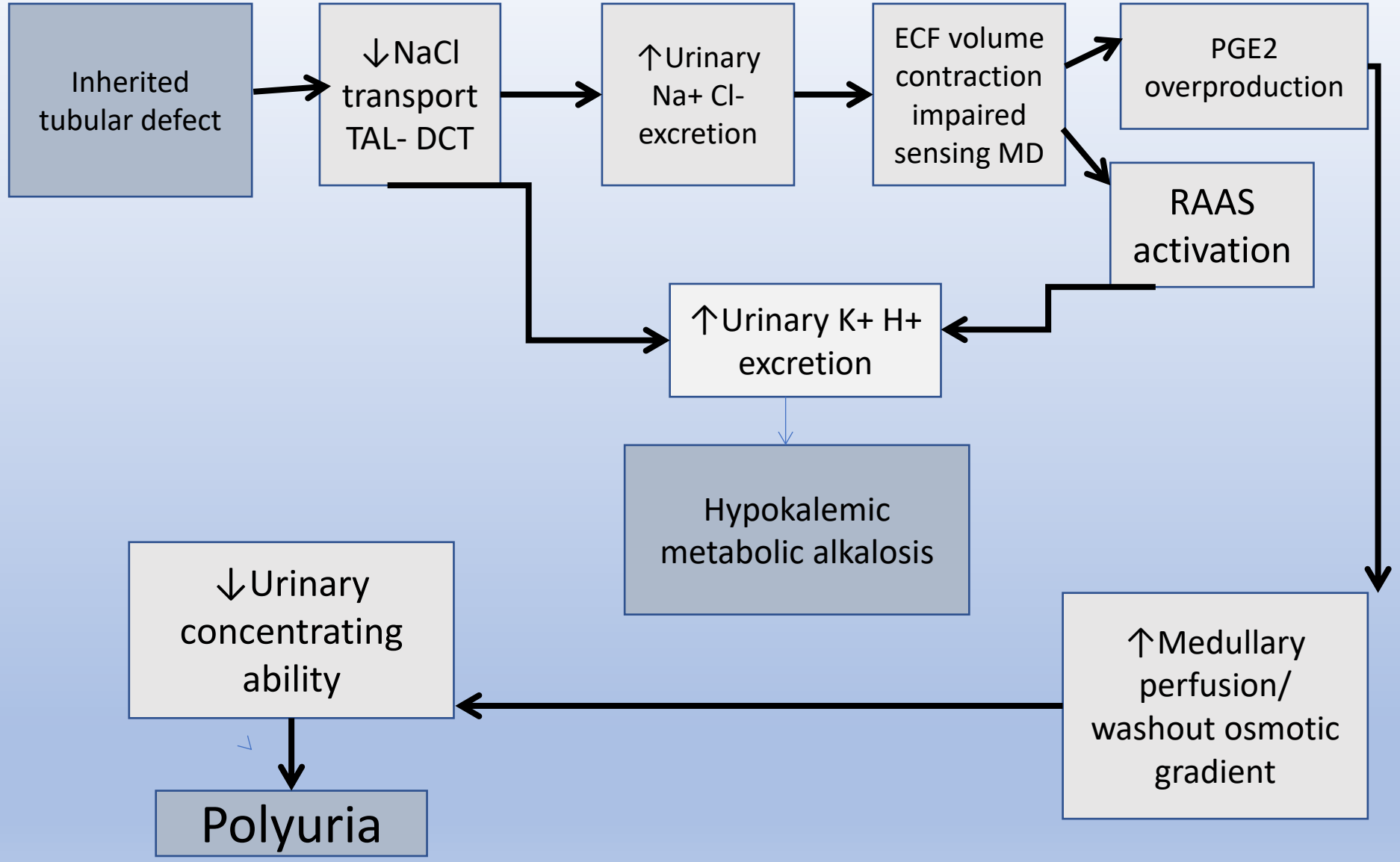
Abbreviations: –, absent; +, present; +++, highly present; BSND, Bartter syndrome with sensorineural deafness.

Mechanism of disease the kidney-specific chloride channesl_Kramer_NatureClinicPractNeph_2007

Clinical and laboratory findings of Barter syndrome

- Triangular facies
- Protruding ears
- Large eyes with strabismus
- Drooping mouth
- Growth retardation
- Muscle weakness and cramps
- Polydipsia and polyuria
- Salt craving and constipation

- Severe hypokalemia <2.5
- metabolic alkalosis
- Elevated urine cl, Na, K
- High aldosterone and renin levels
- Normal BP, Normal GFR
- High Prostaglandine E_2 level
- Nephrocalcinosis in type 1, 2



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Findings in kidney biopsy

- Kidney biopsy is rarely performed for diagnosis and usually is not necessary.
- Renal biopsy demonstrates hyperplasia and hypertrophy of the juxtaglomerular cells as well as of the medullary interstitial cells, the site of prostaglandin E_2 synthesis.

Antenatal Bartter syndrome :Type 1,2

- The most severe form with severe electrolyte derangements
- Polyhydramnios, premature delivery
- Growth retardation, salt wasting
- marked hypercalciuria leading to nephrocalcinosis
- Type 1 is caused by a mutation in the gene encoding the Na^+-K^+-$2Cl^-$ cotransporter (NKCC2)
- Type 2 is caused by outwardly rectifying potassium channel (ROMK= Renal Outer Medullary Potassium channel), a regulator of NKCC2.

Classical Bartter syndrome (Type 3)

- Symptoms typically start Insidiously before the age of 6 yr and typically present in infancy or early childhood
- polyuria that may manifest as bedwetting, polydipsia
- vomiting, constipation
- salt craving, failure to thrive, fatigue, and volume depletion
- Nephrocalcinosis is typically absent (hypercalciuria is lesser extent than type1,2)
- Muscle weakness and cramping are invariable.
- Is caused by mutation in the gene encoding the chloride channel (CLCNKB), also a regulator of NKCC2

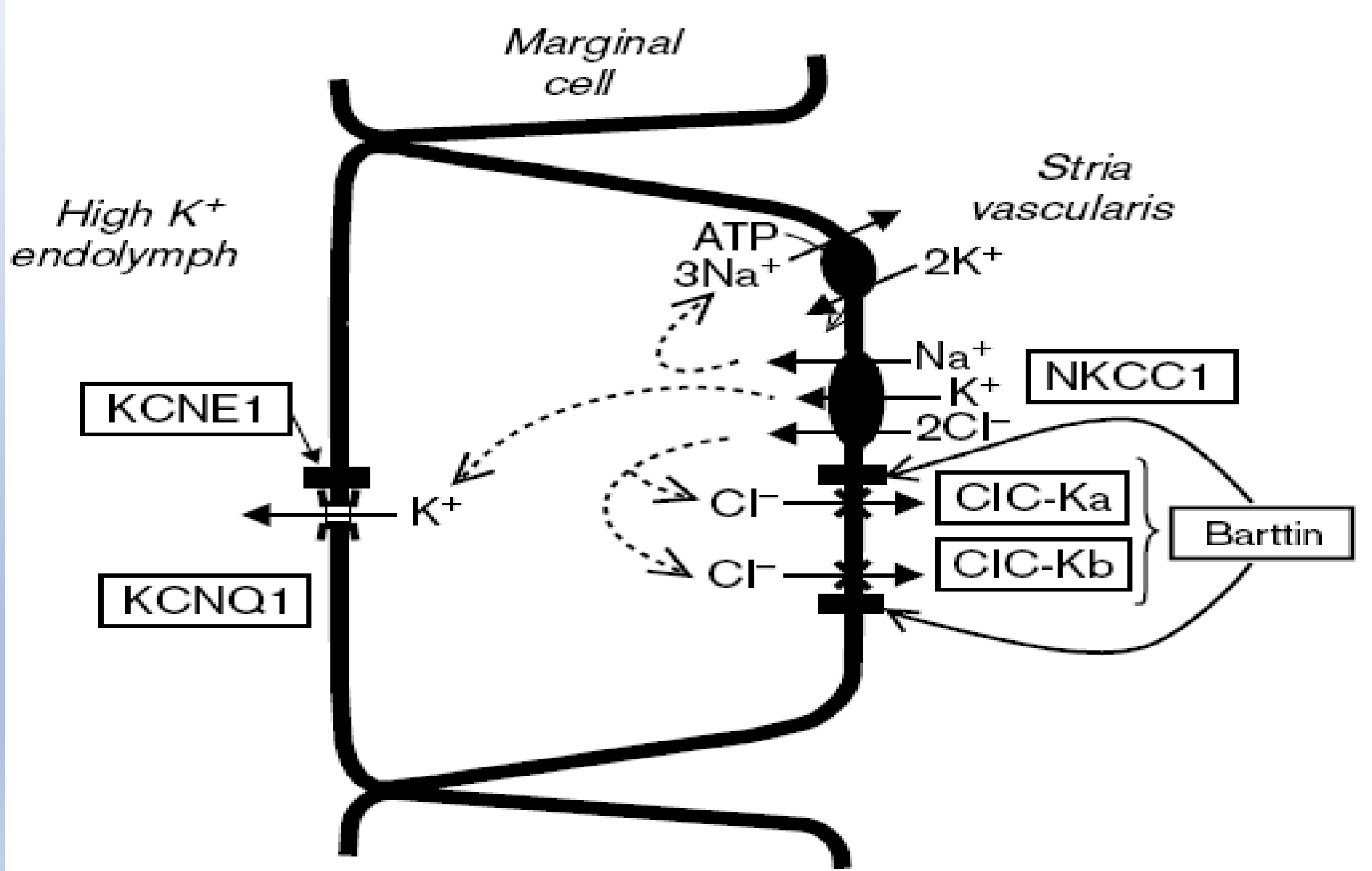
Bartter syndrome with sensory-neural deafness (BSND) , Type 4

- Neonatal/infancy ,More sever than type III
- Polyhydramnios, premature delivery
- Growth retardation, salt wasting, dehydration
- Vomiting, failure to thrive
- Polyuria, polydypsia
- Nephrocalcinosis is absent
- sensory neural deafness

Barttin, beta subunti of ClC-Ka and ClC-kb

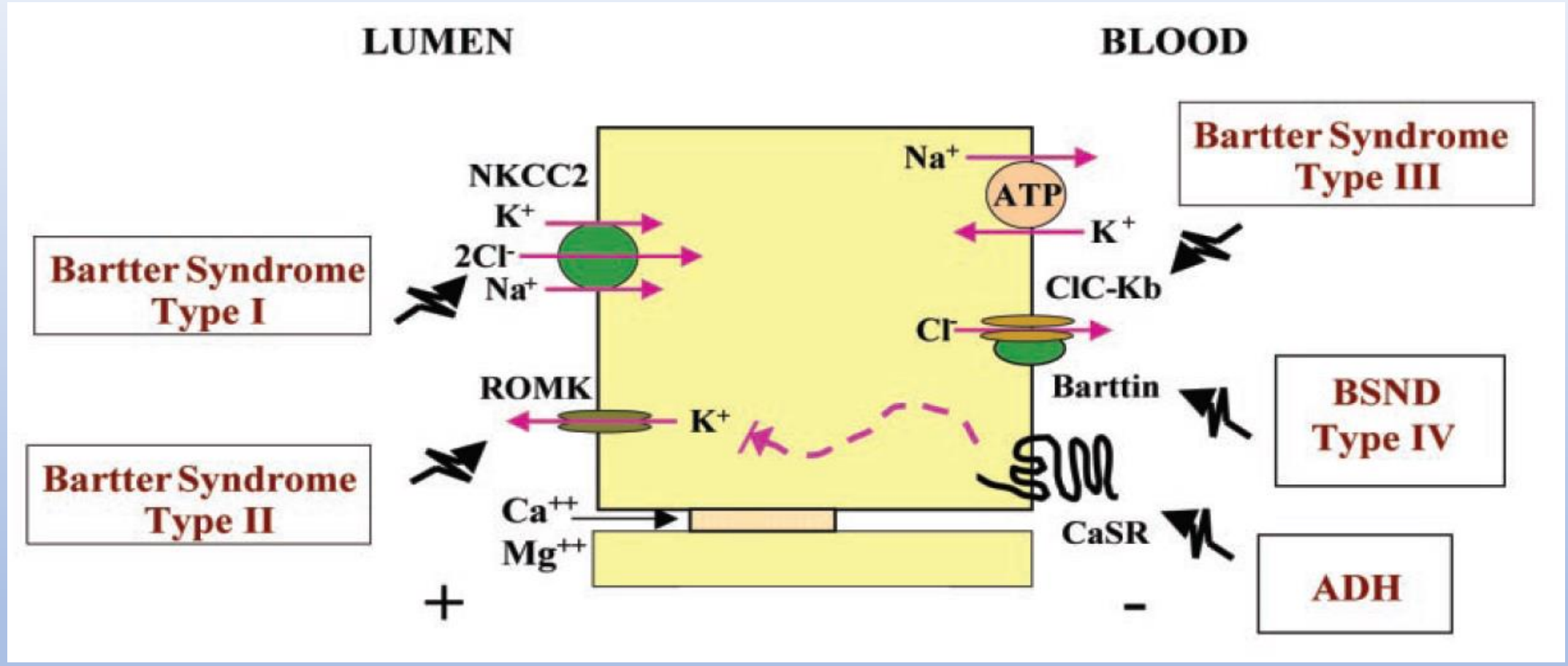
- The gene BSND encodes an essential beta subunit, Barttin, for chloride channels: Responsible for the basolateral exit of Cl^- to the plasma.
- these heteromeric channels localize to basolateral membranes of renal tubules and of potassium-secreting epithelial cells of the inner ear.

BSND – a model of K+ secretion in the inner ear



Bartter syndrome_Herbert_CurrOpinHTNNeph_2003

Hypercalciuria in Bartter syndrome



Hypokalemic salt-losing tubulopathies_Zelikovic_Nephrology Dialysis Transplant_2003

Treatment of Bartter syndrome

- Appropriate compensation of fluid and salt wasting by continuous saline infusion
- K supplement as KCl
- Prostaglandin synthetase inhibitors 4-6 wk after birth (indomethacin): 0.5-2.5 mg/kg
- Selective Cyclooxygenase 2 inhibitors: Refocoxib
- K-sparing diuretic specially spironolactone (1-1.5 mg/kg)
- Preemptive nephrectomy, early Peritoneal dialysis and Transplantation

Continuation of treatment

- Side effects of indomethacine in premature neonates: severe GI complication, ulcer, perforation, NEC, oliguric ARF with hyperkalemia (specially in ROMK deficient neonates)
- ACE inhibitors (may block the distal compensatory Na reabsorption)
- Thiazides should not be used for hypercalciuria, since they interfere with DCT compensatory Na reabsorption.

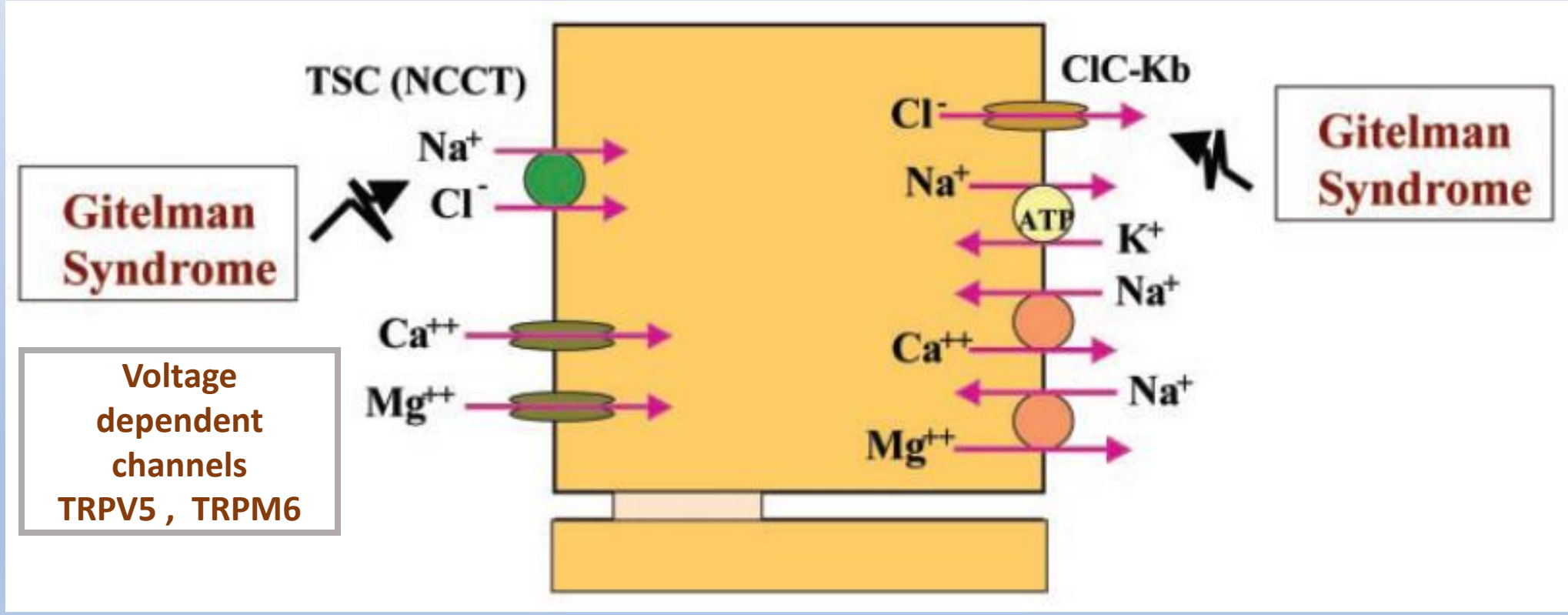
Long term prognosis of Bartter syndrome

- Optimal treatment may result in catch of growth, normal pubertal and intellectual development.
- Most patients show a persistent deficiency in height and weight specially in Type 4 (Growth hormone may have positive effect in some)
- Nephrocalcinosis
- Hypokalemic nephropathy
- Indomethacin induced tubulointerstitial nephritis
- Proteinuria, Reduced GFR and ESRD

Gitelman syndrome

Mutant alleles occur in approximately 1% of the population

Its prevalence is 1/40000, the most frequent inherited tubulopathy detected in adults



Hypokalemic salt-losing tubulopathies_Zelikovic_Nephrology Dialysis Transplant_2003

Gitelman syndrome In contrast to bartter syndrome:

- Diagnosed in adolescence or early adulthood
- May be asymptomatic
- Muscle cramps are Predominant
- Hypomagnesemia
- Hypocalciuria

Clinical manifestation associated with Gitelman syndrome

Most common >50% of patients	Prominent 20-50% of patints	Occasional Less than 20%	Rare Case reports
Salt craving	Fainting	Onset before 6 yr.	Seizure
Muscle weakness and pain	Polyuria	Failure to thrive	Ventricular Tachycardia
Muscle Cramps	Arthralgia	Growyh retardation	Rhabdomyolysis
Nocturia, polydipsia	Chondrocalcinosis	Vertigo, Ataxia	Blurred vision
Paresthesia, numbness	Prolonged QT interval	Carpopedal spasm, Tetany	Pseudotumor cerebri
Palpitation	Febrile episodes	Vomiting	Sclerochoroidal calcification
Low blood pressure		Constipation, Enuresis	
Fatigue, Dizziness		Paralysis	

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Treatment of Gitelman syndrome

- Lifelong Mg and K supplementation
- Magnesium chloride is the best recommended salt which is adjusted individually in 3-4 daily doses (diarrhea is limiting factor)
- Potassium Chloride
- Amiloride or spironolactone
- Eplerenone a selective aldosterone antagonist with significantly lower affinity to androgen, progesterone and glucocorticoid receptors with no antiandrogenic side effects


Thank you for your attention

Table 3 Clinical and biochemical features of Gitelman's syndrome and the various types of Bartter's syndrome.

Feature	Gitelman's syndrome	Type I Bartter's syndrome	Type II Bartter's syndrome	Type III Bartter's syndrome	Type IV Bartter's syndrome
Age at presentation	Late childhood/ adult	Neonatal/infancy	Neonatal/infancy	Childhood onward	Neonatal/infancy
Pregnancy	Normal	Polyhydramnios Prematurity	Polyhydramnios Prematurity	Usually normal	Polyhydramnios Prematurity
Symptoms	Often nonspecific Weakness Tetany Chondrocalcinosis Polydipsia Salt craving	Vomiting Dehydration Polyuria Polydipsia Failure to thrive	Vomiting Dehydration Polyuria Polydipsia Failure to thrive	Variable Intermediate between symptoms for Gitelman's syndrome and Type 1 and Type 2 Bartter's syndrome	Sensorineural hearing loss Vomiting Dehydration Polyuria Polydipsia Failure to thrive
Biochemistry	Hypochloremic hypokalemic alkalosis	Hypochloremic hypokalemic alkalosis Very high urine prostaglandin E_2	Hypochloremic hypokalemic alkalosis after salt replacement (initially high serum potassium levels) Very high urine prostaglandin E_2	Hypochloremic hypokalemic alkalosis	Hypochloremic hypokalemic alkalosis
Serum magnesium level	Low	Normal	Normal	Normal or low	Normal
Urine calcium level	Low	High	High	Normal	Often normal
Nephrocalcinosis	No	Yes	Yes	No	No
Associated gene	*SLC12A3* (*NCCT*)	*SLC12A1* (*NKCC2*)	*KCNJ1* (*ROMK2*)	*CLCNKB*	*BSND*

Type 1 , 2 Barter

- Type I, Na-K-2Cl cotransporter at the luminal side of the tubular epithelial cells, acts like furosemide, lead to hypercalciuria

- This co-transporter is driven by the low intracellular Na and Cl– concentrations generated by the basolateral Na–K-ATPase and ClC-Kb, respectively.
- In addition, ROMK enables functioning of NKCC2 by recycling K back to the lumen.

Type 2 Barter

- Type II, mutated protein is the potassium recycling channel, ROMK, also at the luminal side
    - **ROMK** is an acronym for the Renal Outer Medullary Potassium channel. This is an ATP-dependent potassium channel ($K_{ir}1.1$) that transports potassium out of cells.
    - The ATP-sensitive ROMK is involved in the regulation of renal NKCC2 cotransporter activity and net salt reabsorption by recycling K entering cells of the TAL back to the lumen.
    - If the ROMK channel is inactive, K levels in the lumen are then too low to permit continued Na-K-2Cl cotransport activity.

Type 3 Barter

- The reabsorption of NaCl in the thick ascending limb requires exit of these ions across the basolateral membrane into the blood through the chloride channel and the Na-K-ATPase pump.
- Dysfunction of the chloride channel thus impairs NKCC2 activity.
- This subset of Bartter's syndrome is often called type III, or classic Bartter syndrome. In this distinct subset nephrocalcinosis is typically absent.

    - Some reports of many individuals with type III BS exhibit a mixed Bartter-Gitelman pnenotype c/w the role of this Cl ion channel in both TAL and DCT

BSND, Type 4

- The association of deafness with Barter type 4 can be explained by the role of the ClCK/barritin channels in the inner ear. The secretion of the potassium ion-rich endolymph by marginal cells in the stria vascularis of the inner ear is required for the normal function of the inner hair cells mediating hearing. ClCkb mutation will not effect, because ClC-ka exist, but barttin will effect both ClC-Ka and ClC-Kb.

Deafness Type 4

- A model of K+ secretion in the stria vascularis of the inner ear.

- K+ is taken up by basolateral NKCC1 and Na,K-ATPase and extruded through an apical K+ channel comprised of KCNQ1 and KCNE1 subunits.

- Na+ taken up through NKCC1 is extruded by Na,K-ATPase, whereas Cl– recycling is mediated by basolateral ClC-Ka–Barttin and ClC-Kb–Barttin channels.

Gitelman Syndrome

- Cl– transport occurs via the luminal, thiazide-sensitive NaCl co-transporter (TSC).
  - Cl– exit to blood is mediated by basolateral Cl– channels.
  - Ca2 and Mg2 enter the cell via luminal voltage activated Ca2 and Mg2 channels and exit the cell via basolateral Na/Ca2 and Na/Mg2 exchangers.
  - The depicted apical Mg2 channel and basolateral Na/Mg2 exchanger are putative.
  - Variants of Bartter syndrome caused by defects in these transport mechanisms are depicted. BSND, Bartter syndrome with deafness; ADH, autosomal dominant hypocalcaemia.

Gitelman Syndrome

- Chondrocalcinosis has been reported in hypomagnesemic patients with Gitelman syndrome, and similar lesions have been induced by magnesium deficiency in animals. Hypomagnesemia reduces the activity of pyrophosphatase, thus promoting pyrophosphate crystallization. Magnesium supplementation in asymptomatic patients with Gitelman syndrome has been advocated to avoid this complication.

Hypercalciuria

- The lumen-positive electrical potential, which is generated by Cl^- entry into the cell and K exit from the cell, drives paracellular Ca^{2+} and Mg^{2+} transport from lumen to blood.
- Activation of the basolateral calcium-sensing receptor (CaSR) inhibits the luminal ROMK channel which, in turn, results in decreased NaCl reabsorption and (secondary to the reduction in the intraluminal positive potential) increased urinary Ca and Mg excretion.

Gitelman syndrome

Is characterized by hypokalemic metabolic alkalosis and hypomagnesemia.

In contrast to bartter syndrome:

- Gitelman syndrome often diagnosed in adolescence or early adulthood.
- It may be asymptomatic and may be found on routine lab tests.
- Muscle weakness and Intermittent muscular symptoms like Carpopedal spasm, tetanus and cramps are Predominant.
- Pronounced hypocalciuria
- Findings mimic administration of a thiazide diuretic.

Gitelman syndrome

- Inherited as an autosomal recessive disease
- Inactivating mutations in the SLC12A3 gene on chrosome 16q13
- Mutant alleles occur in approximately 1% of the population
- Its prevalence is 1/40000, the most frequent inherited tubulopathy detected in adults
- Loss of function of a thiazide sensitive Na^{+}-Cl^{-} cotransporter NCCT in DCT

Hypocalciuria in Gitelman Syndrome

- Volume contraction causes a compensatory increase in proximal Na^{+} reabsorption, driving passive Ca^{++} transport in the Proximal Tubule.
- Hyperpolarization of DCT cells due to lower intracellular activity of Cl^{-} opens the apical voltage dependent Ca^{++} channels (TRPV5) resulting in increased Ca reabsorption.
- Hyperpolarizatioin of DCT cells could stimulate the basolateral Na^{+}/Ca^{++} exchanger, further increases Ca^{++} reabsorption.

Hypomagnesemia in Gitelman Syndrome

Several mechanisms have been proposed:

- K^+ depletion
- Increased passive Mg^{++} secretion
- Defective active Mg^{++} transport in the DCT
- Down regulation of TRPM6, a Mg^{++} permeable channel in the DCT which occurs in chronic thiazide treatment and defective NCCT.