



Potassium hemostasis

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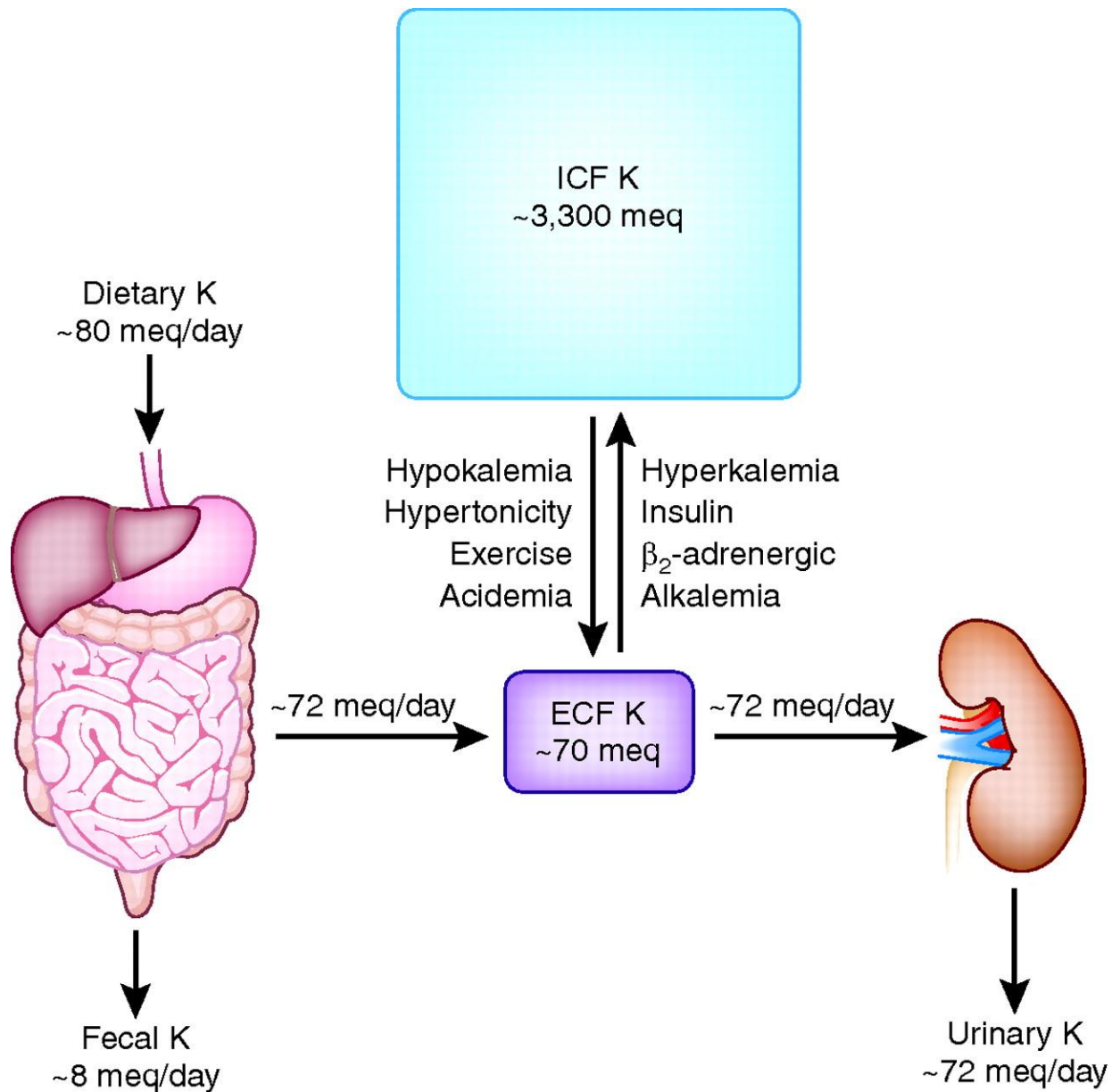
- Nearly 98% of the body's potassium is intracellular.
- The ratio of intracellular to extracellular potassium is important in determining the cellular membrane potential.
- Small changes in the extracellular potassium level can have profound effects on the function of the cardiovascular and neuromuscular systems.

- Total body store of potassium is 3000-4000 Meq while its ECF concentration is 3.5 to 5meq per liter.
- The **kidney** determines potassium homeostasis, and excess potassium is excreted in the urine.

- potassium homeostasis is tightly regulated by specific ion-exchange pumps (primarily by a cellular, membrane-bound, sodium-potassium ATP-ase).
- Derangements of potassium regulation often lead to neuromuscular, gastrointestinal, and cardiac conduction abnormalities

Regulation of K Homeostasis

- Oral intake
- Cellular shift
- Renal
- GI



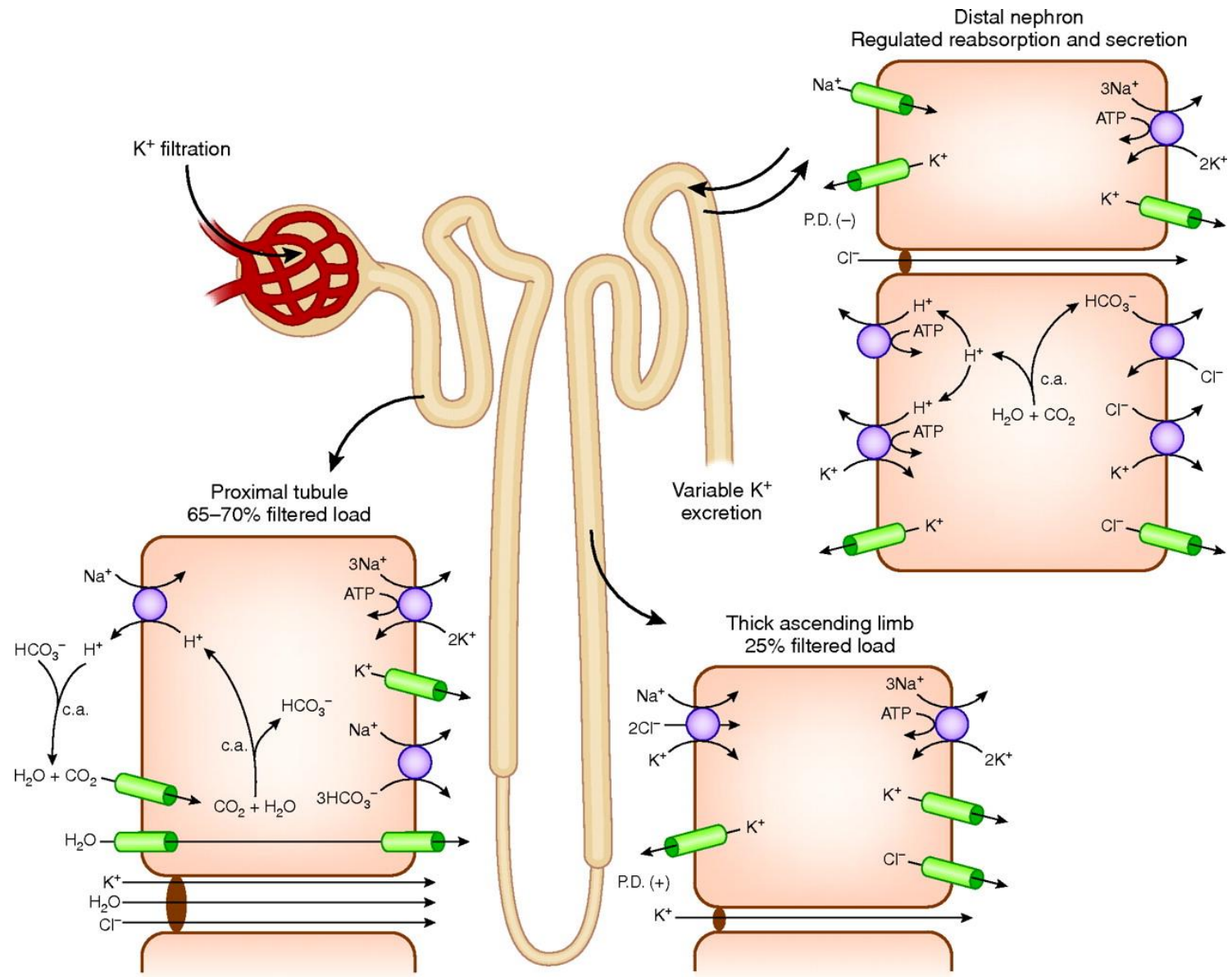
Hypokalemia

Hypokalemia

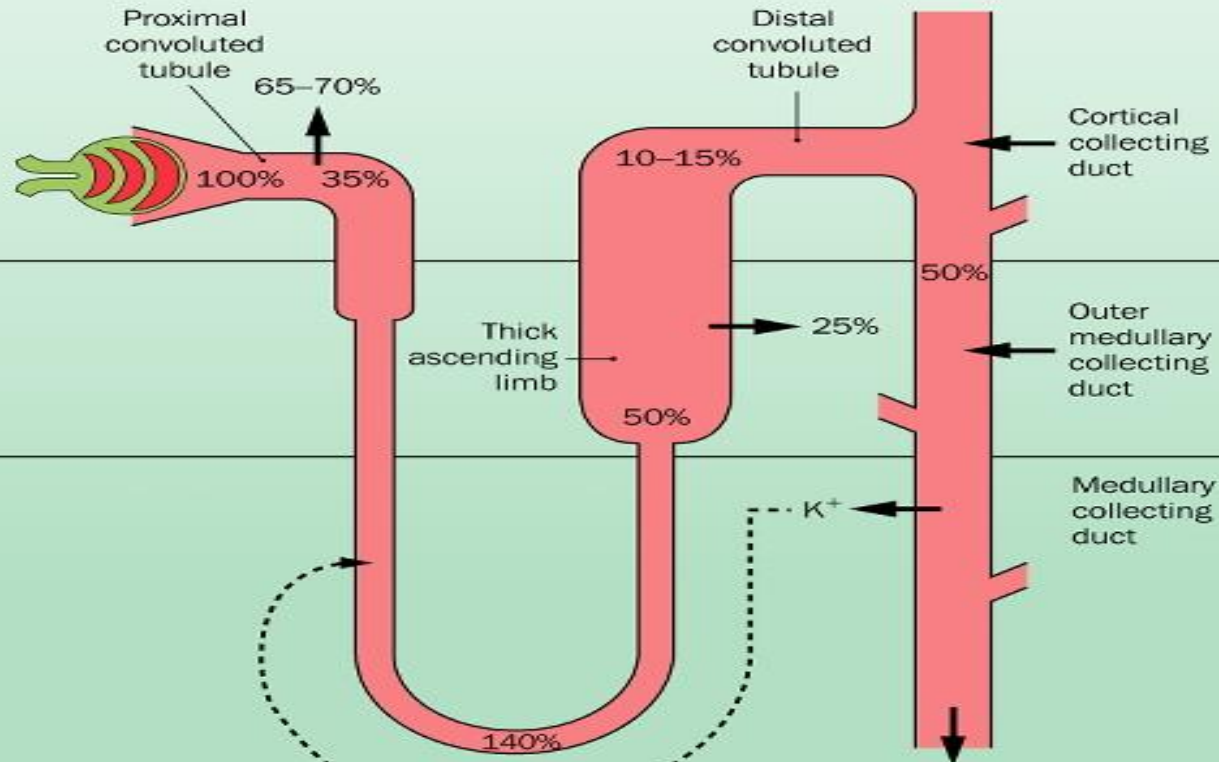
- *Hypokalemia* is defined as a potassium level less than 3.5 mEq/L.
- *Moderate hypokalemia* is a serum level of 2.5-3 mEq/L.
- *Severe hypokalemia* is defined as a level *less than 2.5 mEq/L.*
- In up to 20% of hospitalized patients

Causes of hypokalemia

- Decreased potassium intake
- Increased entry into cells
- Increased losses



Renal handling of potassium

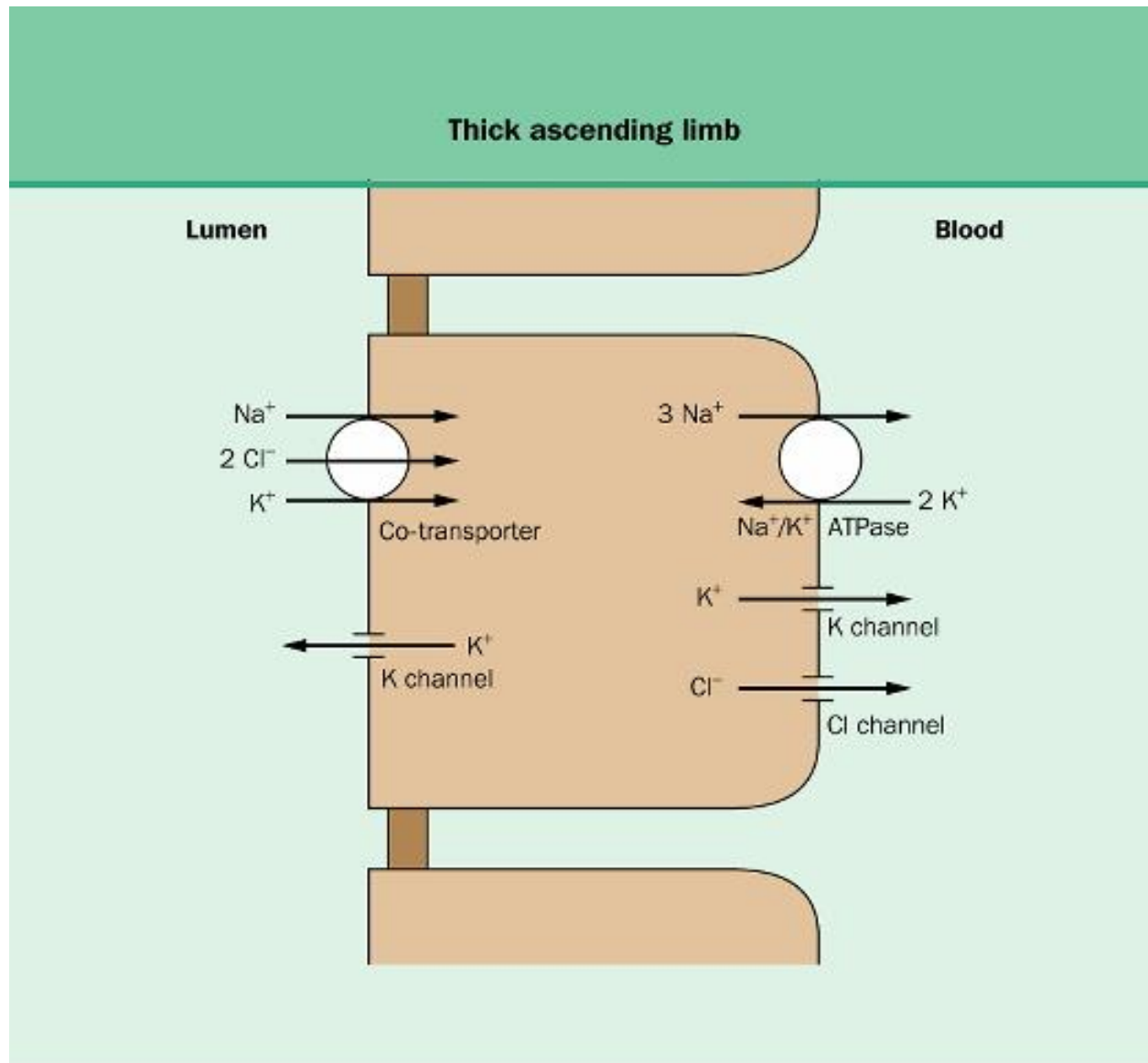


Fractional excretion of K^+ :

$$FE_{K^+} = \frac{(K^+)_u (Cr)_s}{(K^+)_s (Cr)_u} \times 100$$

$$= 10-20\% \text{ or } \sim 90 \text{ mmol/day}$$

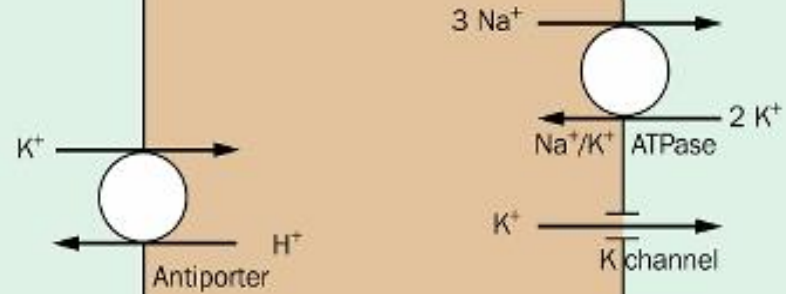
where Cr is creatinine,
s is serum, and u is urine



Collecting tubule intercalated cell: K^+ reabsorption

Lumen

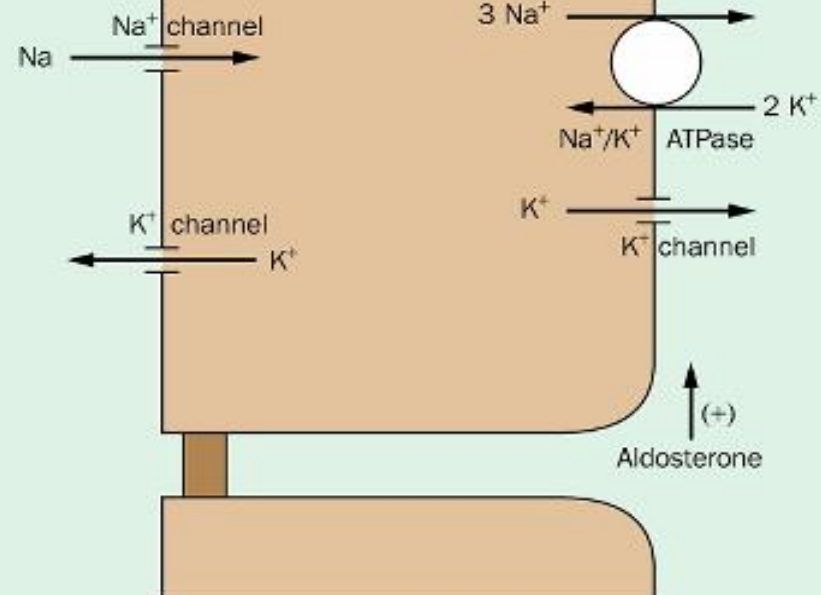
Blood

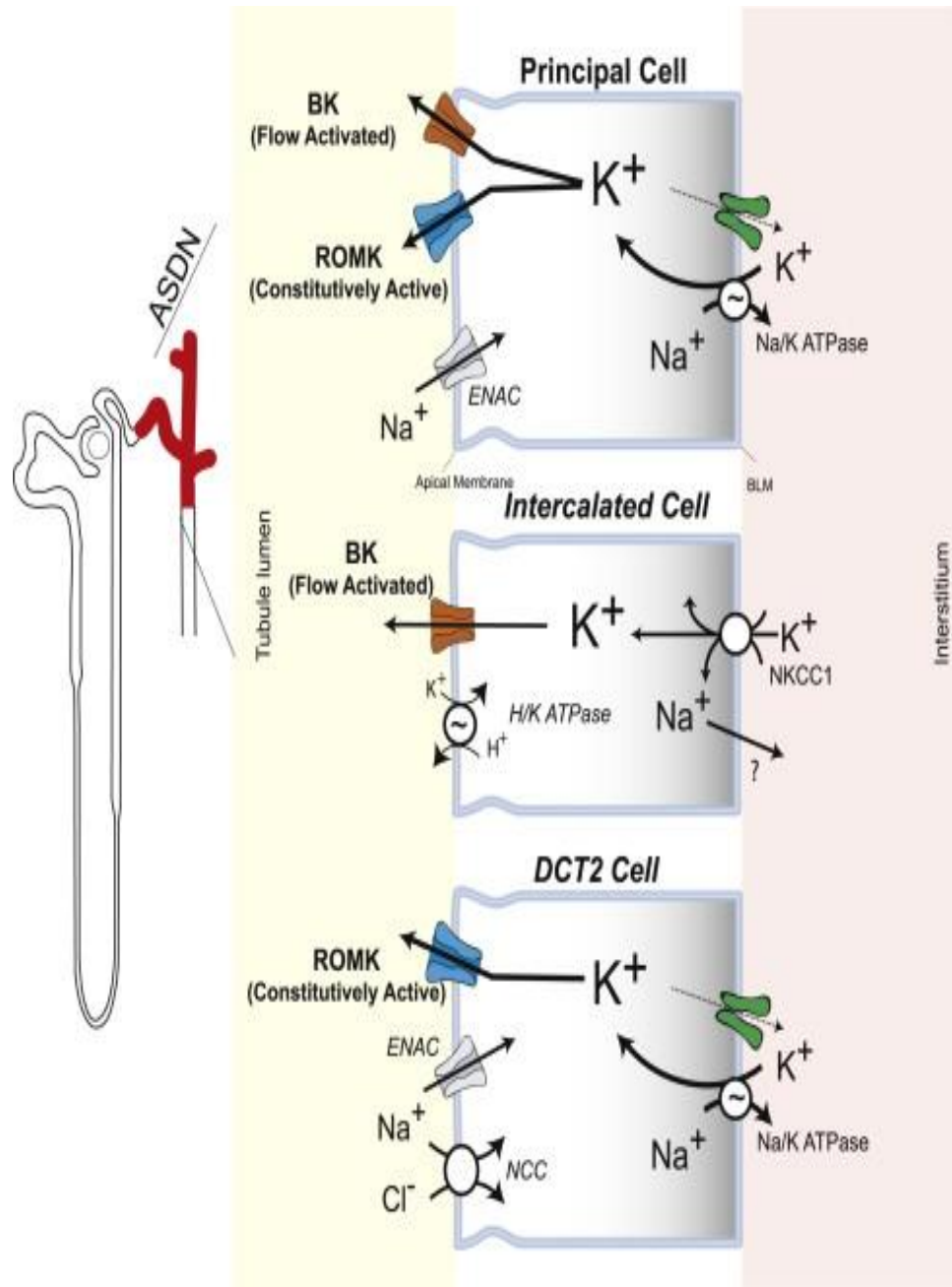


Collecting tubule principal cell: K^+ secretion

Lumen

Blood





Multiple factors modulate K^+ secretion in these distal nephron segments:

- **plasma K^+ concentration** is an important determinant of the rate of K^+ secretion
- **aldosterone**, stimulated by elevated plasma K^+ , is a major regulator of K^+ secretion in distal nephron segments
- **fluid delivery** to distal K^+ secretory sites..

Causes of hypokalemia

Decreased potassium intake :

Decreased K intake  Decreased urinary K excretion
(5 to 25 meq/day)

Active K reabsorption in the intercalated cells
(mediated by H-K-ATPase pumps)

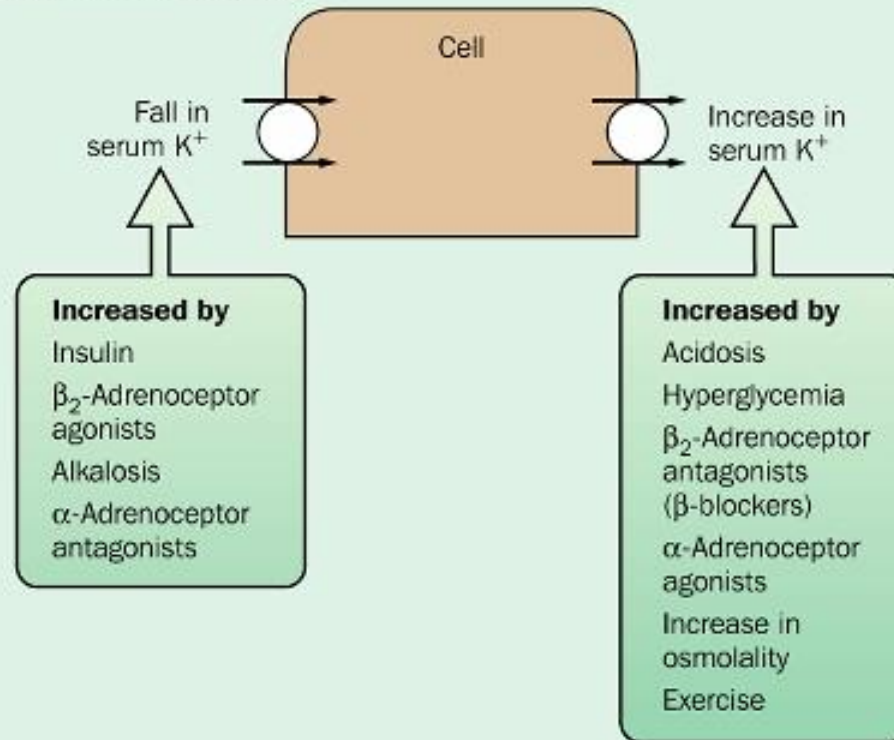
Causes of hypokalemia

Increased entry into cells :

- Increased availability of insulin
- Elevated beta-adrenergic activity
- Elevated extracellular pH
- Hypokalemic periodic paralysis
- Paradoxical hypokalemia after repletion
- Increased blood cell production
- Hypothermia
- Barium intoxication
- Cesium intoxication
- Chloroquine intoxication
- Antipsychotic drugs

Cellular potassium shifts

Plasma/extracellular space



Hypokalemic periodic paralysis

- Intermittent attacks of muscle weakness associated with hypokalemia
- Triggered by large carbohydrate meals and strenuous exercise
- Autosomal dominant:
 - manifest at age of 10-20
 - mutation in voltage activated Ca channel
- Thyrotoxicosis
 - Asian
 - manifest later in life

Causes of hypokalemia

Increased losses :

- Increased gastrointestinal losses
- Increased urinary losses
- Increased sweat losses
- Dialysis

Causes of hypokalemia

Increased gastrointestinal losses :

- ☐ Upper gastrointestinal losses
- ☐ Lower gastrointestinal losses

Causes of hypokalemia

Increased urinary losses :

- ❑ Diuretics
- ❑ Increased mineralocorticoid activity
- ❑ Increased distal delivery of sodium and water
- ❑ Nonreabsorbable anions
- ❑ Loss of gastric secretions

Causes of hypokalemia

Less common causes of urinary potassium wasting :

- ☐ Polyuria
- ☐ Renal tubular acidosis
- ☐ Hypomagnesemia
- ☐ Amphotericin B
- ☐ Salt-wasting nephropathies
- ☐ Liddle's syndrome
- ☐ Bartter and Gitelman syndromes
- ☐ Low-calorie diets

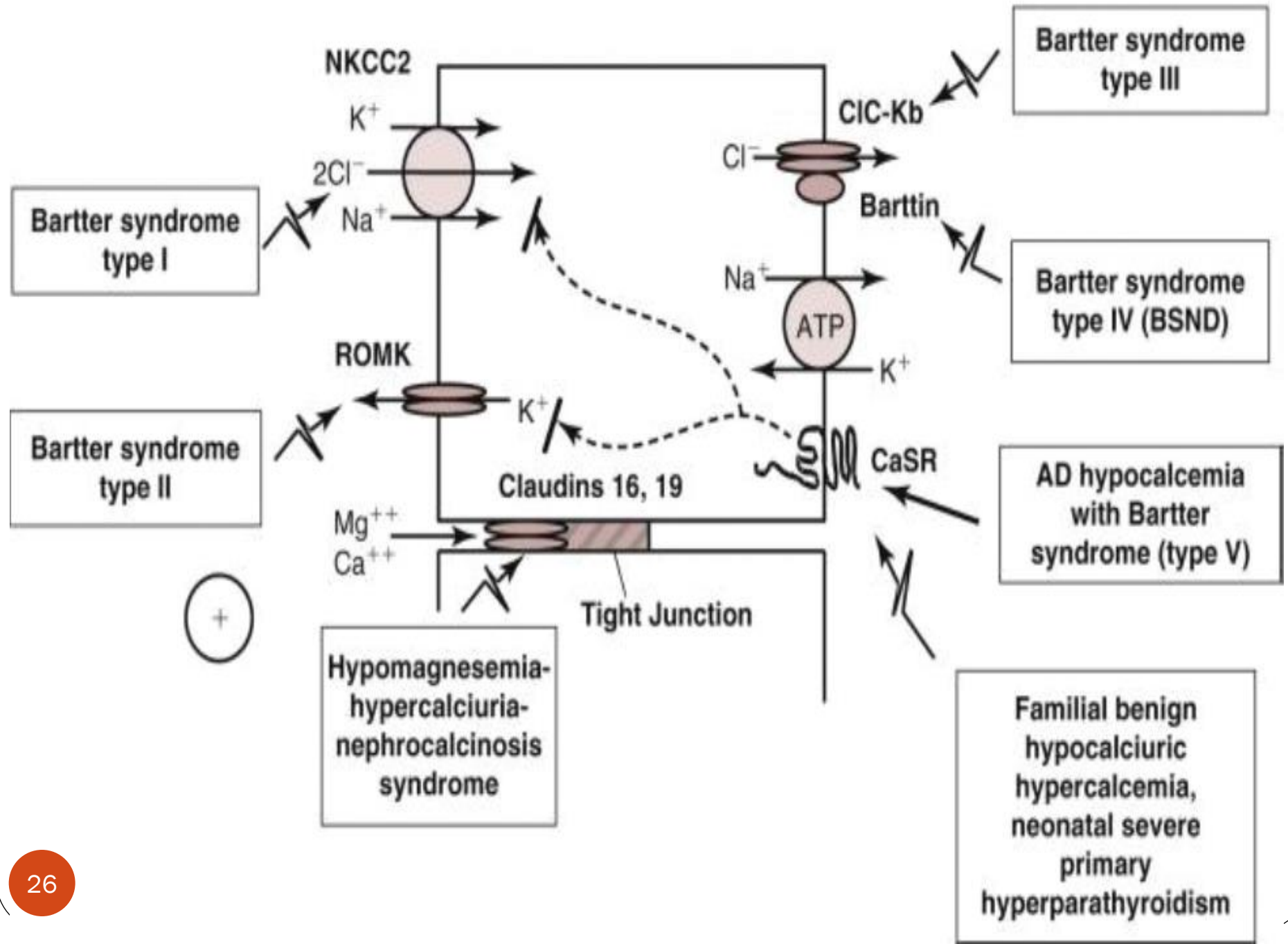
Bartter's syndrome

- It generally presents **early in life** and is often associated with growth and mental retardation
- **hypokalemia and metabolic alkalosis ,polyuria** and decreased concentrating ability.
- **Urinary ca excretion is increased** and plasma Mg is normal or mildly reduced.
- The primary defect is in **Na Cl reabsorption in TAL** of Henle which has a central role in countercurrent gradient required for urine concentration & in Ca and Mg reabsorbtion

Lumen

Cell

Blood



Gitelman's syndrome

- It is an **autosomal recessive** syndrome that is often not diagnosed until late childhood or even adulthood.
- mutations in the gene coding for the **thiazide-sensitive Na-Cl cotransporter in the distal tubule**
- **magnesium wasting** and the often marked decrease in calcium excretion, opposite of the hypercalciuria seen in classic Bartter's syndrome

Liddle's syndrome

- Rare **autosomal dominant** condition (mutation in the SCNN1B or SCNN1G gene)
- primary increase in collecting tubule sodium reabsorption and, in most cases, potassium secretion
- The genetic abnormality involves the **beta or gamma subunit of Enac**
- Loss of inhibition of channel activity

Liddle's syndrome

- Severe hypertension
- Hypokalemia and metabolic alkalosis
- Polyuria, polydipsia and muscle weakness
- Low aldosterone and renin levels
- Blood pressure does not improve with aldactone but does improve with triamterene and amiloride



Hypoaldosteronism

- Pseudohypoaldosteronism type 1 (PHA1) was first described in 1958 by Cheek and Perry
- PHA1 results in **mineralocorticoid resistance** of the kidney and/or other mineralocorticoid target tissues
- **very high levels of plasma aldosterone and renin**

Pseudohypoaldosteronism type1

- Dehydration and failure to thrive at neonates
- Hypotension , hyperkalemia and metabolic acidosis
- Aldosterone resistance in kidney , sweat and salivary glands, colonic mucosa
- Autosomal recessive
- Treatment with NaCl
- High dose fludrocortisone (1 to 2 mg/day)
- carbenoxolone (antagonism of cortisol metabolism)

Approach to hypokalemia

- ❑ Assessment of urinary potassium excretion
- ❑ Assessment of acid-base status

Assessment of urinary potassium excretion:

- 24-hour urine potassium
- Spot urine potassium concentration
- Urine potassium-to-creatinine ratio ($< 13\text{meq/g}$)

Metabolic acidosis:

- With a low rate of urinary potassium :

Lower GI (laxative abuse or a villous adenoma)

- With urinary potassium wasting :

Diabetic ketoacidosis

Type 1 (distal) renal tubular acidosis

Type 2 (proximal) renal tubular acidosis

Metabolic alkalosis:

➤ With a low rate of urinary potassium excretion :

Surreptitious vomiting (bulimic patients)

Diuretics (recent usage)

Metabolic alkalosis:

With urinary potassium wasting:

❖ **In the setting of normal blood pressure**

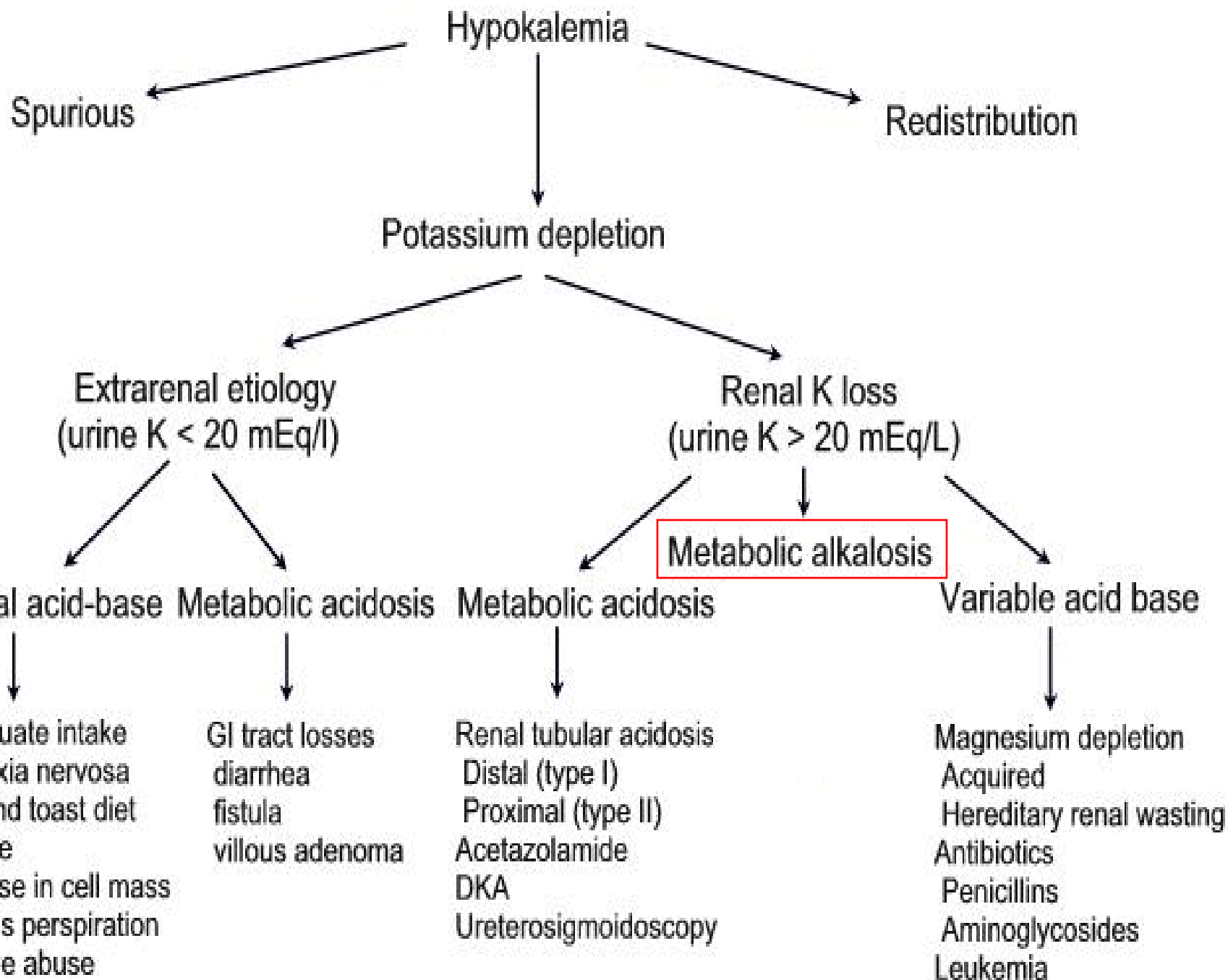
- Diuretic use
- Vomiting
- Gitelman or Bartter syndrome

Metabolic alkalosis:

With urinary potassium wasting

❖ In the setting of hypertension:

- Diuretic therapy in a hypertensive patient
- Renovascular disease
- One of the causes of primary mineralocorticoid excess.



Metabolic alkalosis

Low urine chloride
(urine cl < 10 mEq/L)

Normotensive

- vomiting
- gastric drainage
- diuretic use
- post-hypercapnea
- cl-losing diarrhea

High urine chloride
(urine cl > 10 mEq/L)

Normotensive

- diuretics
- Bartter's syndrome
- severe K depletion
- Gittelman's syndrome

Hypertensive

High aldosterone

Low renin

- primary hyperaldosteronism
- adenoma
- hyperplasia

High renin

- renovascular hypertension
- malignant hypertension
- renin secreting tumor

Low aldosterone
and low renin

- glycyrrhizic acid
- carbenoxolone
- exogenous mineralocorticoids
- Liddle's syndrome

Normal aldosterone
and normal renin

- Cushing's syndrome

Clinical Manifestations of Hypokalemia

- proportionate to the **degree** and **duration** of the reduction in serum potassium.
- Symptoms generally do not become manifest until the serum potassium **is below 3.0 meq/L**,

Pathogenesis of symptoms

The resting membrane potential is related to the ratio of the intracellular to the extracellular **potassium** concentration.

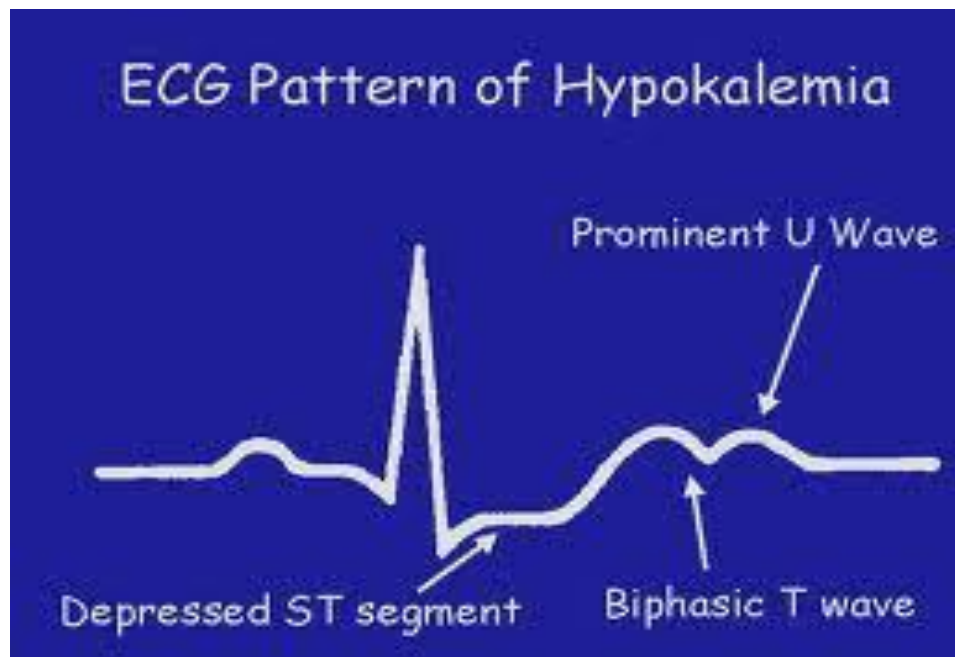
$$-61 \log \frac{r[K]_c + 0.01[Na]_c}{r[K]_e + 0.01[Na]_e}$$

Clinical Manifestations of Hypokalemia

- Cardiac arrhythmias and ECG abnormalities
- Severe muscle weakness or rhabdomyolysis
- Renal abnormalities

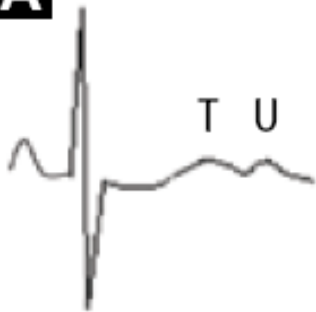
Clinical Manifestations of Hypokalemia

Cardiac arrhythmias and ECG abnormalities



Hypokalemia:

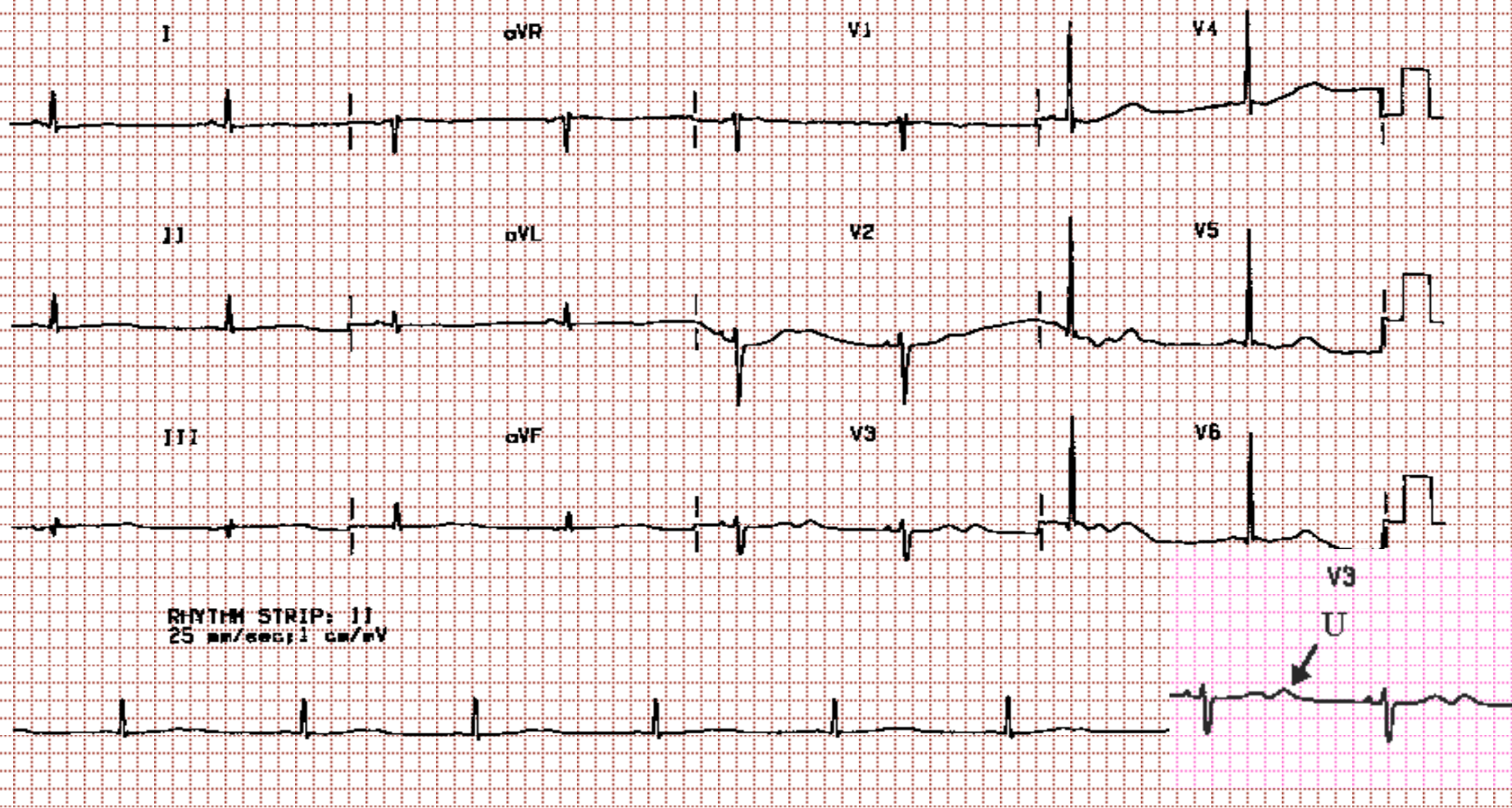
A



Flat T with $K \sim 3$



ST depression with
prominent T
(actually U) and
prolonged QT
when $K < 2.5-3$



The ECG findings in hypokalemia:

Ventricular dysrhythmia, Prolongation of QT interval, ST segment depression, T wave flattening & U waves.

Renal abnormalities

Prolonged hypokalemia can cause multiple structural and functional changes in the kidney

- ❑ Impaired concentrating ability
- ❑ Increased ammonia production
- ❑ Increased bicarbonate reabsorption
- ❑ Hypokalemic nephropathy
- ❑ Elevation in blood pressure

Treatment

Hypokalemia due to decreased K intake:

Estimation of the K deficit:

Loss of 400-800 mmol of total-body K results in a reduction in serum K by approximately 2 mmol

Route of administration

Oral: $K > 3 \text{ meq/L}$

Intravenous: $K < 3 \text{ meq/L}$ or in patients who are unable to take oral therapy

Intravenous Therapy

Adverse effects:

- Pain and phlebitis

What to do?

- Reasonable concentration of K infusion: 40-60meq/L from peripheral vein
- Reasonable speed of K infusion: 10-20meq/hour

Magnesium replacement therapy is often necessary in malnourished alcoholics with hypokalemia

Hyperkalemia

hyperkalemia

Defense against hyperkalemia:

- ❑ uptake of excess K by the cells
- ❑ urinary excretion of excess K within 6-8 hours

Movement of K out of the cells

pseudohyperkalemia
Met acidosis

Insulin
Deficiency
And
hyperglycemi
a

Tissue catabolism

β blockade
Dig toxicity
Succinylcholin
Arginin

Pseudohyperkalemia

- Mechanical trauma during venipuncture
- Repeated clenching and unclenching of fist
- Marked leukocytosis(>100000) or thrombocytosis (>400000)
- Familial xerocytosis
- Blood cooling after sampling

Hyperkalemia causes

Increased K release from cells:

- Pseudohyperkalemia
- Metabolic acidosis
- Insulin deficiency and hyperglycemia
- Increased tissue catabolism
- beta adrenergic blockers
- Exercise
- Arginin, succinylcholin
- Digitalis overdose
- Hyperkalemic periodic paralysis

Hyperkalemic periodic paralysis

- An **autosomal dominant**
- episodes of weakness or paralysis are usually precipitated by cold exposure, rest after exercise, fasting, or the ingestion of small amounts of potassium.
- point mutation in the gene for the alpha subunit of the skeletal muscle cell sodium channel.

Treatment

- β agonist
- High carbohydrate diet
- Thiazide
- Acetazolamide???

Hyperkalemia causes

Reduced urinary K excretion:

- ☐ Hypoaldosteronism
- ☐ Renal failure
- ☐ Effective circulatory volume depletion
- ☐ Ureterojejunostomy
- ☐ RTA type1 hyperkalemic

Causes of hypoaldosteronism

- Decreased activity of RAS
- Primary decrease in adrenal synthesis
- Ald resistance

Causes of hypoaldosteronism

Associated with decreased activity of the renin-angiotensin system

- A. Hyporeninemic hypoaldosteronism with mild to moderate renal insufficiency
- B. Nonsteroidal anti-inflammatory drugs, with the possible exception of sulindac
- C. Converting enzyme inhibitors
- D. Cyclosporine
- E. Acquired immune deficiency syndrome
- F. Hypervolemia in chronic dialysis patients

Primary decrease in adrenal synthesis

- A. Low cortisol levels
 - 1. Primary adrenal insufficiency
 - 2. Congenital adrenal hyperplasia—primarily 21-hydroxylase deficiency
- B. Normal cortisol levels
 - 1. Heparin
 - 2. Isolated hypoaldosteronism
 - 3. Post—removal of adrenal adenoma

Aldosterone resistance

- A. Potassium-sparing diuretics (including high-dose trimethoprim in AIDS)

$$\text{TTKG} = K_{CD} / K_{\text{plasma}}$$

$$\text{TTKG} = \frac{K_U * \text{osm}_p}{K_p * \text{osm}_U}$$

Transtubular potassium gradient

TTKG is a measurement of net K^+ secretion by the distal nephron after correcting for changes in urinary osmolality and is often used to determine if hyperkalemia is caused by aldosterone deficiency/resistance or if the hyperkalemia is secondary to nonrenal causes

$$TTKG = (K_u/K_s) \times (S_{osm}/U_{osm})$$

where K_u and K_s are the concentration of K^+ in urine and serum, respectively and U_{osm} and S_{osm} are the osmolalities of urine and serum, respectively.

TTKG value	Indication
6–12	Normal
> 10	Suggests normal aldosterone action and an extrarenal cause of hyperkalemia
< 5–7	Suggests aldosterone deficiency or resistance
After 0.05 mg 9 α -fludrocortisone	
> 10	Hypoaldosteronism is likely
No change	Suggests a renal tubule defect from either K^+ -sparing diuretics (amiloride, triamterene, spironolactone), aldosterone resistance (interstitial renal disease, sickle cell disease, urinary tract obstruction, pseudohypoaldosteronism type I), or increased distal K^+ reabsorption (pseudohypoaldosteronism type II, urinary tract obstruction)

Pseudohypoaldosteronism

- Hereditary: mutation in MR
- Acquired: obstruction, CIN, ATN, amyloidosis
- Type 2 : Gordon syndrome: CL shunt
- activation mutation in thiazide sensitive Na channel

hyperkalemia, hypertension, decreased renin activity

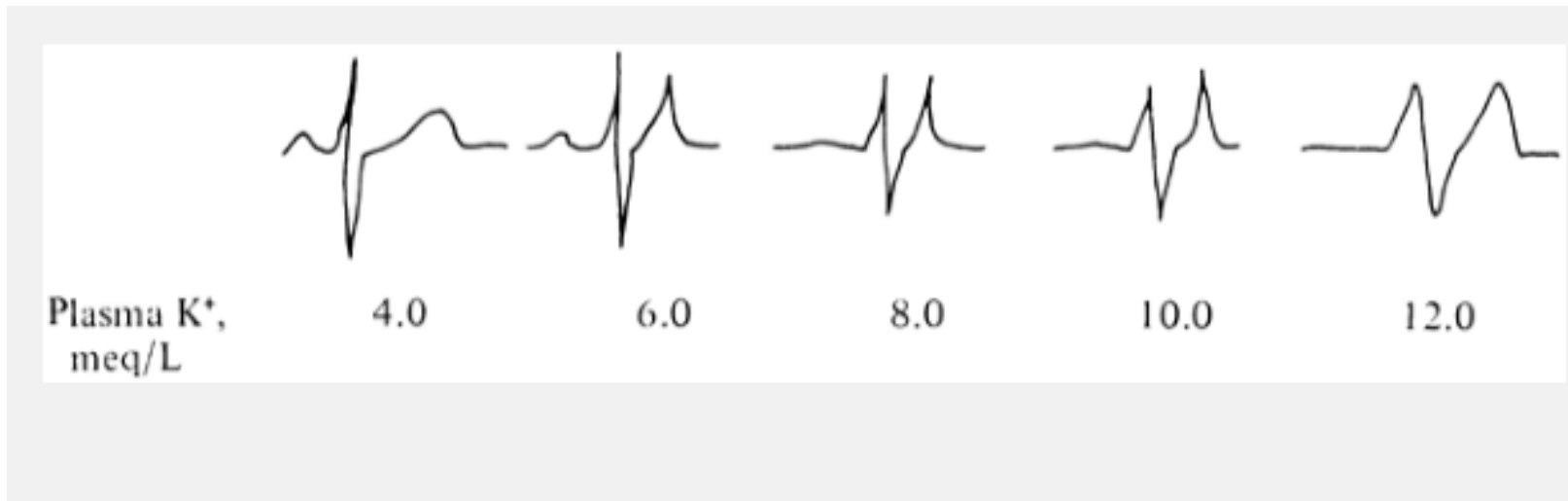
Drug and hyperkalemia

- ACEIs , ARB , DRI ,MRA
- OCP (progesterone)
- NSAIDs
- CNI
- Enac blockers : amiloride
pentamidin
trimetoprim

symptoms

- **Muscle weakness**: decreased cell membrane excitability
- **cardiac arrhythmia**: rapid depolarization and delayed repolarization

ECG changes in hyperkalemia



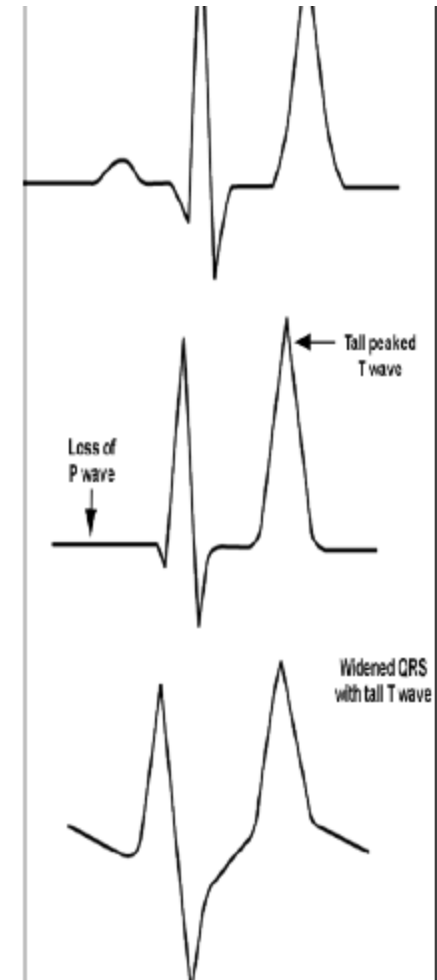
ECG changes in hyperkalemia

tall peaked T waves (5.5–6.5 mM)

a loss of P waves (6.5–7.5 mM)

a widened QRS complex (7.0–8.0 mM)

a sine wave pattern (>8.0mM).



Treatment of hyperkalemia

mechanism	therapy	dose	onset	duration
Antagonize membrane effect	calcium	10cc 10% solution over 10min	1-3min	30-60min
Cellular shift	insulin	Regular insulin 10 unit + 25gr glucose	30min	4-6hr
Cellular shift	B2 agonist	Nebuized Albutrol 10mg	30min	2-4hr
K removal	Sodium polystyrenesulfonate	30-60gr po	1-2hr	4-6hr
K removal	hemodialysis		immediate	Until dialysis completed

binding potassium in the lumen of the GI tract

- Sodium Polystyrene Sulfonate (SPS)

A cation-exchange polymer that exchanges sodium for potassium

- Patiromer

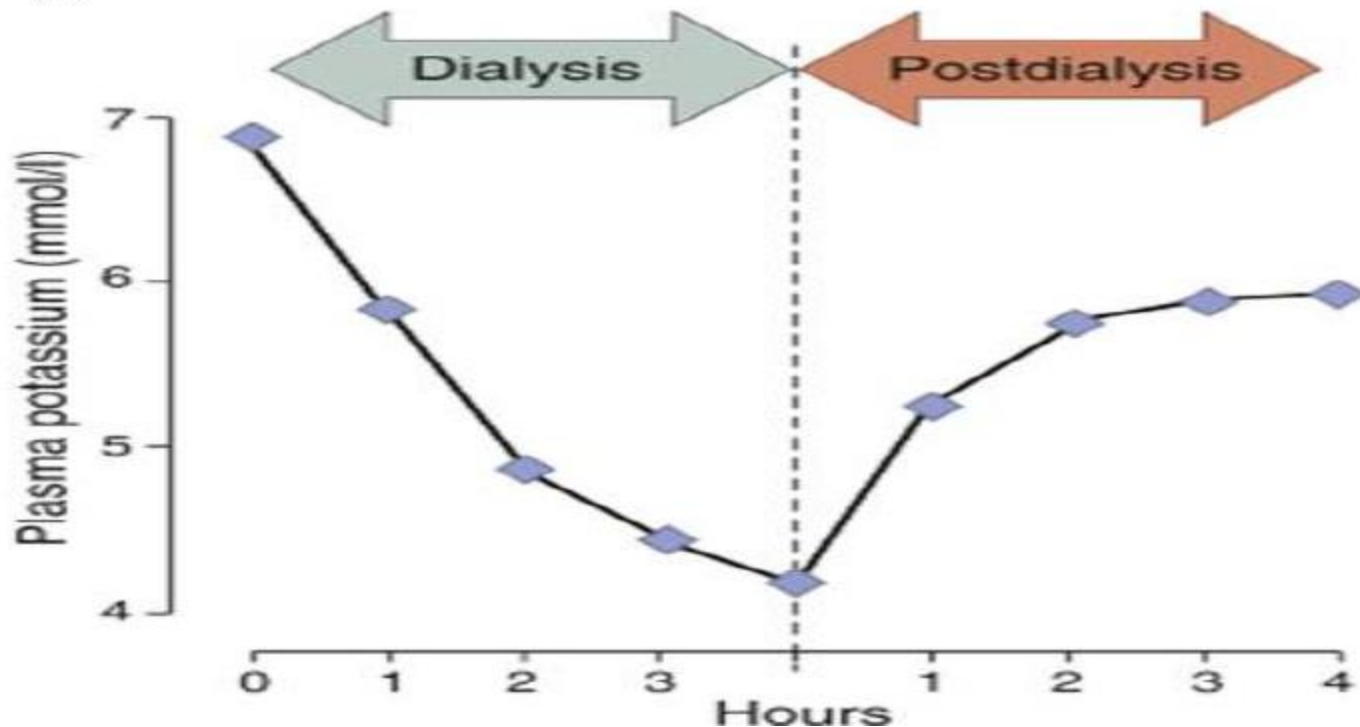
nonabsorbed potassium-binding polymer

- Sodium Zirconium Cyclosilicate (ZS-9)

an insoluble, nonabsorbed compound designed to capture potassium ions.

Emergency dialysis

is a final recourse for unresponsive hyperkalemia with renal failure.



The end