Potassium Disorders

Normal Potassium Balance

100 mEq K+

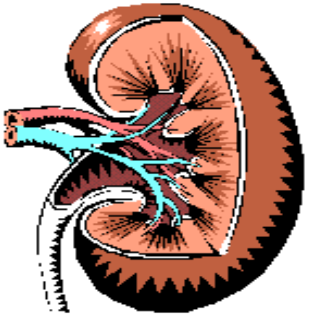
RBC
~250

Extracellular fluid
65 mEq

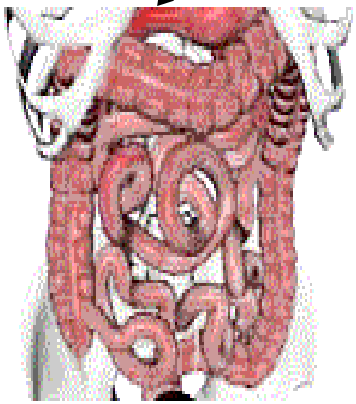
Muscle
~2500

Liver
~250

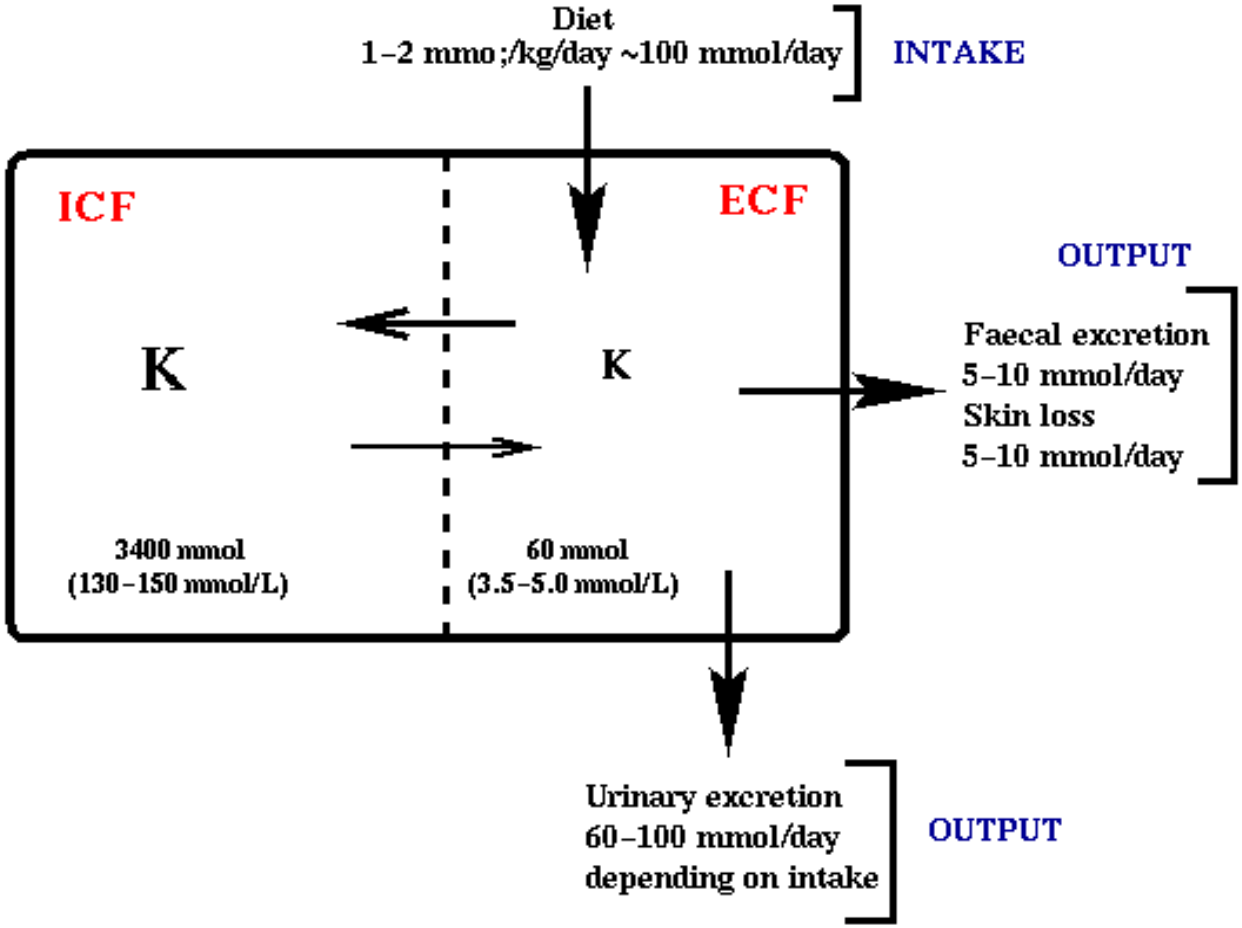
Bone
~500



90-95
mEq



5-10 mEq

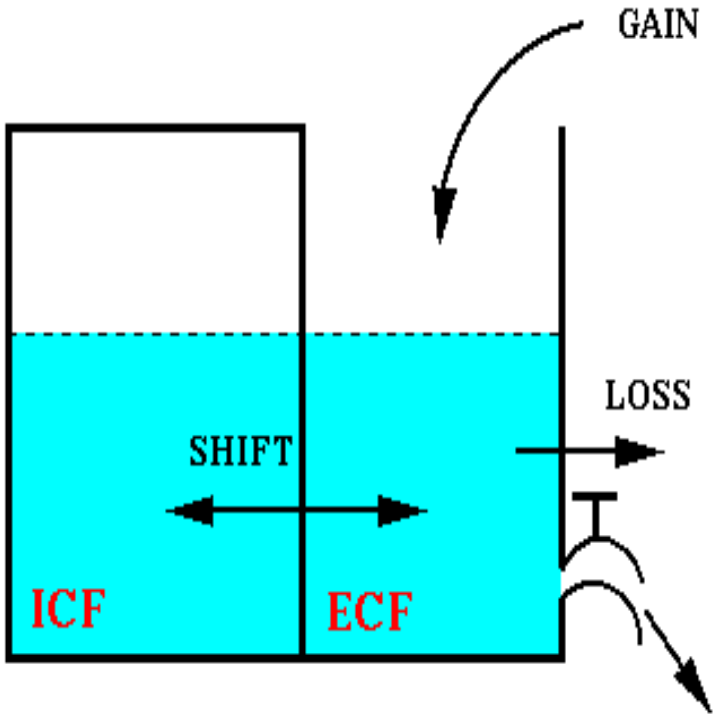


ECF [K^{+}] Dependent upon:-

- **K Intake/Load**
- **Redistribution between ECF and ICF**
- **Output**

Plasma [K^{+}] is a poor indicator of total body K^{+}

ECF/Plasma [K^+] dependent upon: -



- **Loss or gain of total body K^+**
- **Shift into or out of cells**
  - hormonal controllers
  - reciprocal movements of H^+
- **Losses via Kidney/Skin/Gut**

Extra-renal K^+ Homeostasis: Shift/Redistribution

- **4 major factors: -**
  - Hormones
  - Acid base status
  - Plasma tonicity
  - Plasma [K^+]

Distribution of K+ between cells and ECF: Physiologic

<u>Factors that maintain K+ distribution:</u>

- Plasma [K+] – passive outward diffusion
- Na+-K+ ATPase (3 out : 2 in)
- Catecholamines: impact ATPase & insulin
  - Alpha-receptors impair cellular entry
  - Beta 2-receptors promote entry
- Insulin – indirect incr ATPase, indep of glucose
- Exercise: release from cells, up to 2mEq/L

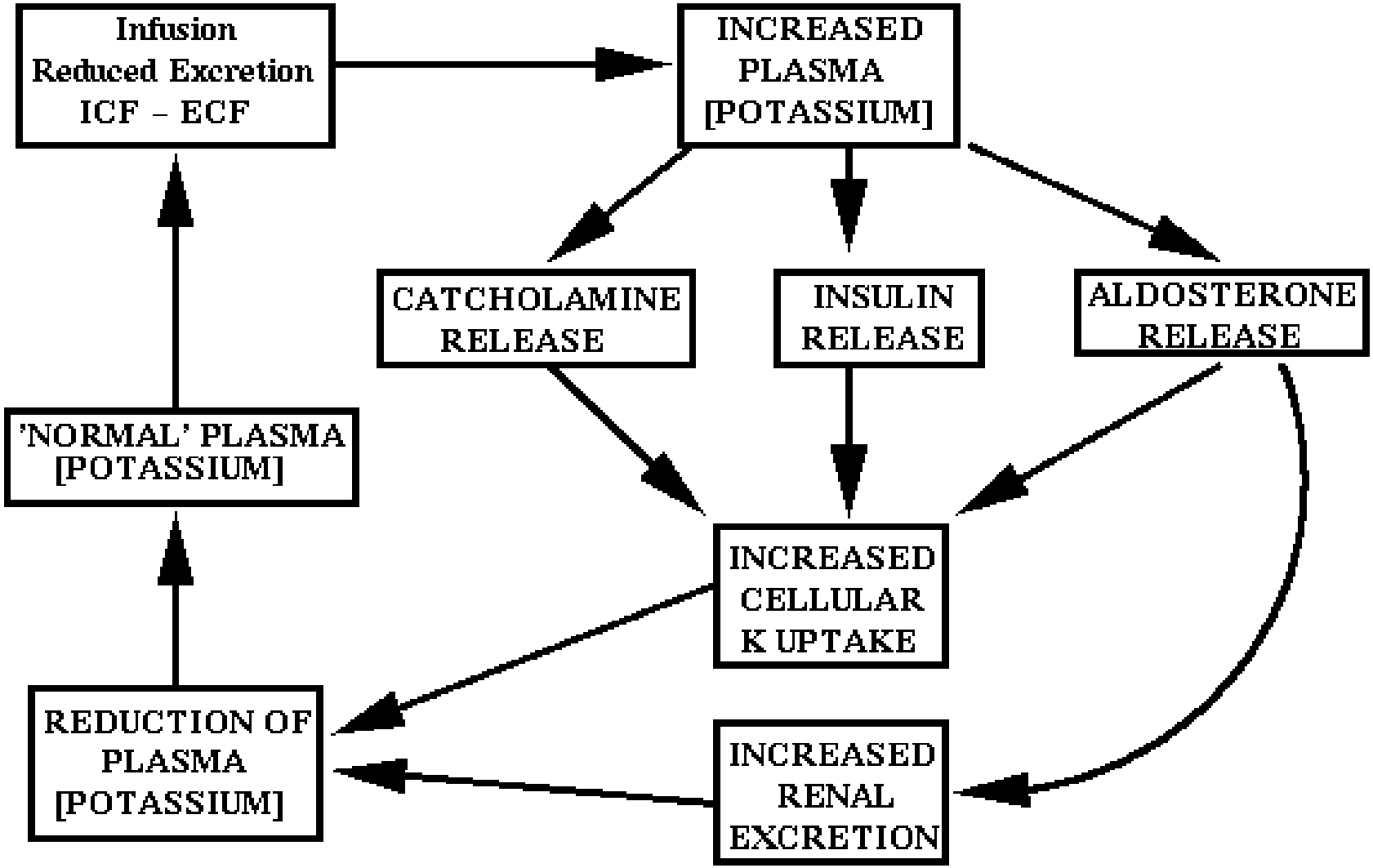
Distribution of K+ between cells and ECF: Pathologic

- Extracellular pH
  - Entry of H+ causing K+ to exit
  - Variable increase of 0.2 – 1.7 mEq/L of ex.cell K+ for each 0.1 fall in pH
  - More common in non-organic acid MA (organic anions easily taken up by cell)
- Hyperosmolality
  - 0.4-0.8 mEq/l incr in K+ for each 10 mosm/k elevation in effective plasma osmolality (solvent drag & gradient)
- Rate of cell breakdown

B

Acute	
Factor	Effect on potassium
Insulin	Enhanced cell uptake
β-Catecholamines	Enhanced cell uptake
α-Catecholamines	Impaired cell uptake
Acidosis	Impaired cell uptake
Alkalosis	Enhanced cell uptake
External potassium balance	Loose correlation
Cell damage	Impaired cell uptake
Hyperosmolality	Enhanced cell efflux

Chronic	
Factor	Effect on ATP pump density
Thyroid	Enhanced
Adrenal steroids	Enhanced
Exercise (training)	Enhanced
Growth	Enhanced
Diabetes	Impaired
Potassium deficiency	Impaired
Chronic renal failure	Impaired


Infusion
Reduced Excretion
ICF – ECF
INCREASED
PLASMA
[POTASSIUM]
CATCHOLAMINE
RELEASE
INSULIN
RELEASE
ALDOSTERONE
RELEASE
'NORMAL' PLASMA
[POTASSIUM]
INCREASED
CELLULAR
K UPTAKE
REDUCTION OF
PLASMA
[POTASSIUM]
INCREASED
RENAL
EXCRETION

Mineralocorticoids (Aldosterone):-

- **Produced by Zonae Glomerulosa of the Adrenal cortex :-**
- **Release stimulated by:-**
  - **Activation of Renin/Angiotensin system:-**
    - **Volume sensors, JGA etc.**
  - **Direct effect of K^+ on adrenal.**
- **Effects of Aldosterone:-**
  - **Exchange of Na^+ for K^+ or H^+ with net loss of K^+ and gain of sodium.**

Mineralocorticoids (Aldosterone):-

- **Sites of action:**
  - Distal renal tubule
  - Colon
  - Sweat Glands
- **In renal failure, the colon is an important site for K^+ regulation**
- **Cortisol has mineralocorticoid activity**

Acid/Base

- **Metabolic Acidosis ↑ [K+]: -**
  - Inhibition of renal tubular K^+ secretion
  - Shift of K^+ from ICF to ECF

- **Metabolic Alkalosis ↓ [K^+]**

Hypertonicity and Potassium

Hypertonicity

- **Movement of H_2O and K^+ from ICF to ECF**
  - **Particular problem in presence of insulin deficiency.**

Plasma [K^+]

Stimulates ATPase

Stimulates hormonal release

Summary

ECF [K^+] depends upon: -

Intake

Redistribution: ECF and ICF

–Hormones

–Acid base status

–Plasma tonicity

–Plasma [K^+]

Output

Kidney

Sweat glands

Gut (colon)

Renal Handling of K^+

600 mmol/day

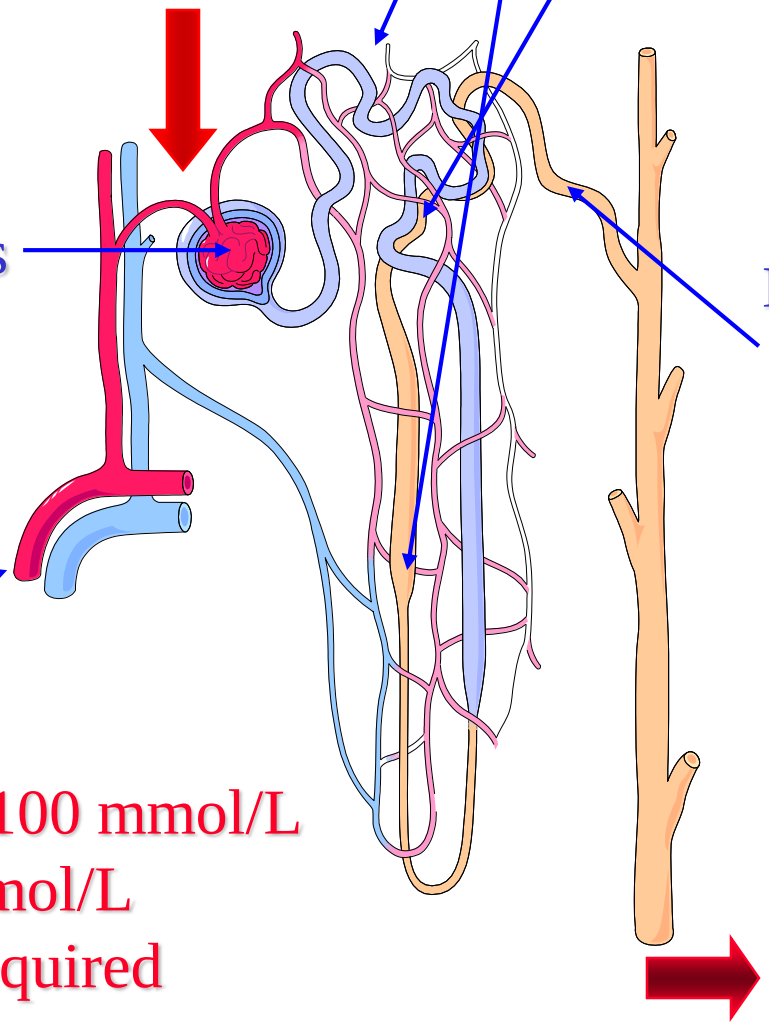
K^+ Filtered

Proximal Tubule (60-70%)

Ascending Loop of Henle (20-30%)

Distal tubule: 10% remaining

100% K^+ Reabsorbed



Glomerulus

Renal artery

Distal Tubule = Fine tuning. Aldosterone K^+/H^+ for Na^+

K^+ Renal Cells = >100 mmol/L

Extracellular = 4mmol/L

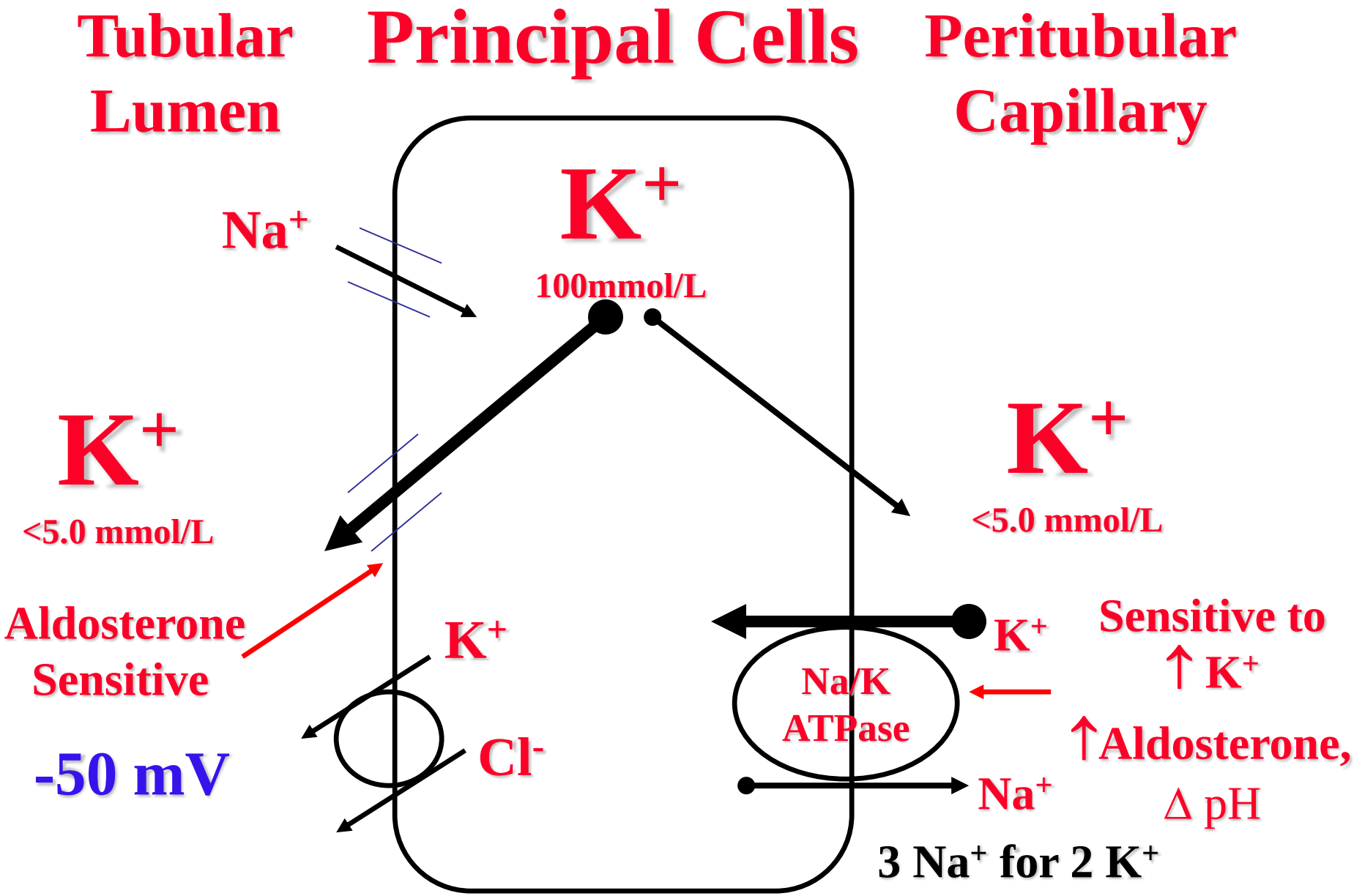
Active transport Required

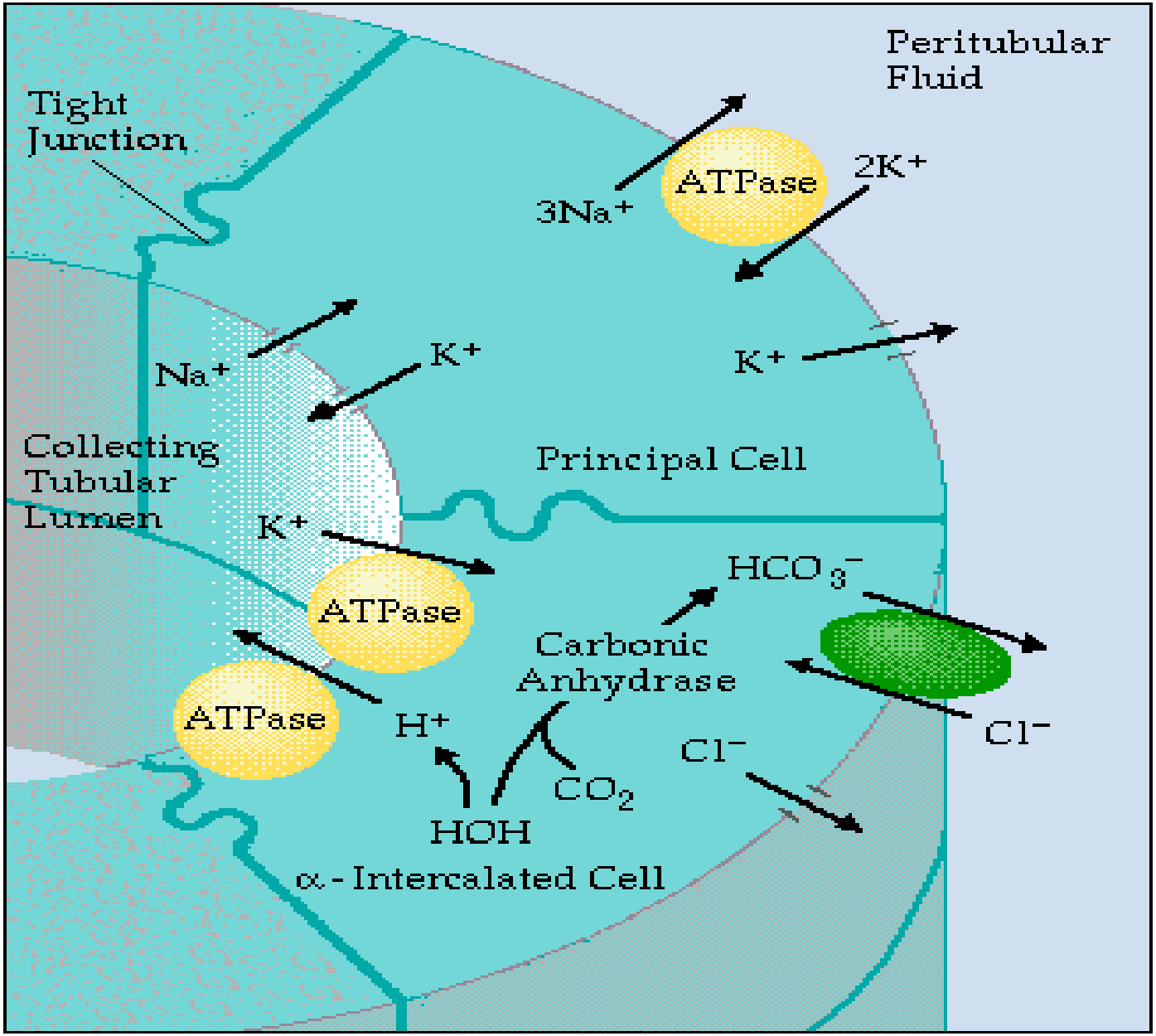
100 mmol/day K^+ excreted (10-20%)

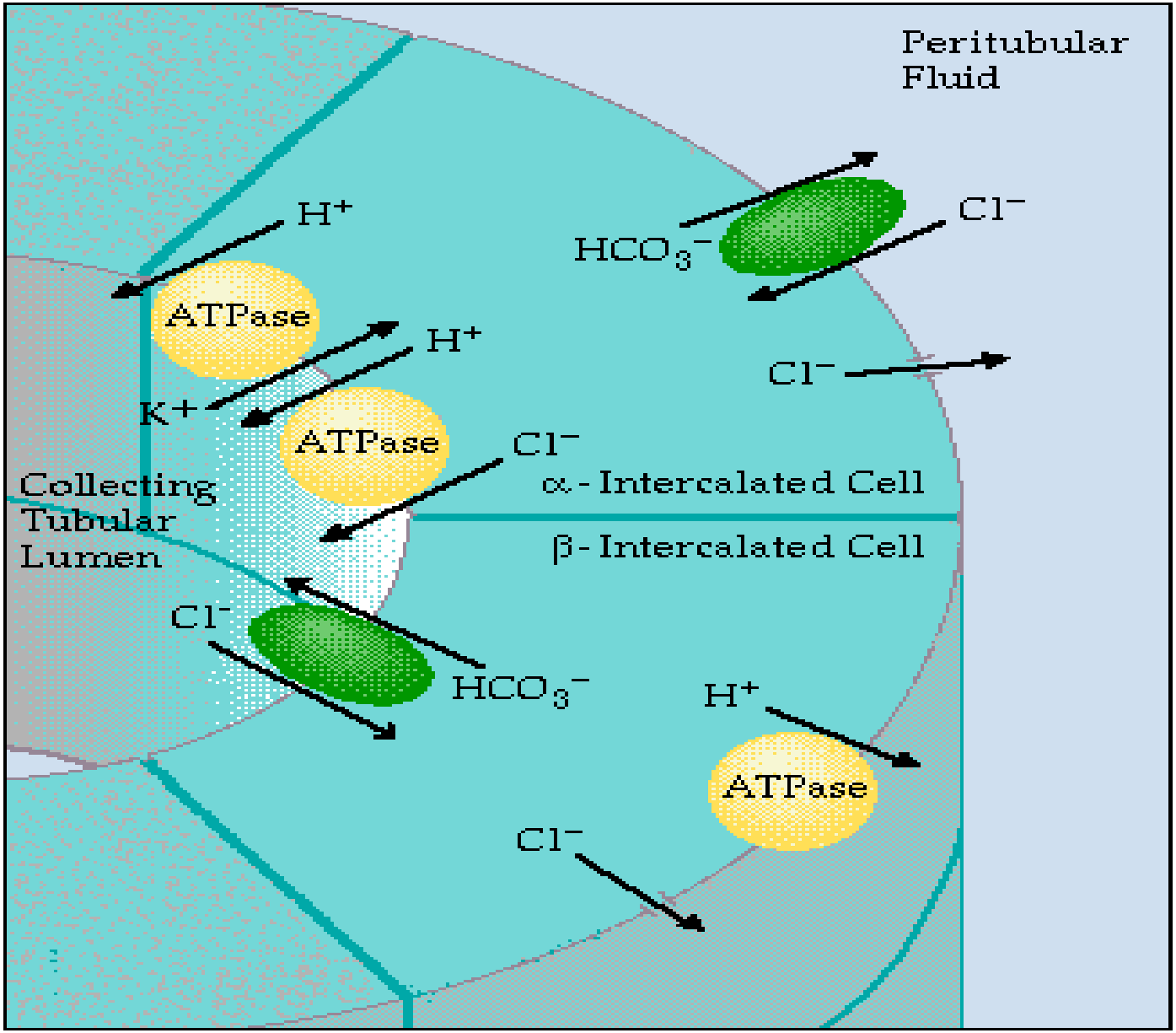
Distal Tubule and Potassium

Distal Tubular secretion influenced by:-

- **K^+ Intake**
- **Acid-base status**
- **Rate of fluid delivery to distal tubule (Washout)**
- **Mineralocorticoids (Aldosterone)**


Tubular Lumen
Principal Cells
Peritubular Capillary
Na+
K+
100mmol/L
K+
<5.0 mmol/L
K+
<5.0 mmol/L
Aldosterone Sensitive
K+
Cl-
-50 mV
Na/K ATPase
K+
Na+
Sensitive to ↑ K+
↑Aldosterone, Δ pH
3 Na+ for 2 K+


Peritubular
Fluid
Tight
Junction
ATPase
3Na+
2K+
Na+
K+
K+
Collecting
Tubular
Lumen
Principal Cell
K+
HCO3−
ATPase
Carbonic
Anhydrase
ATPase
H+
Cl−
Cl−
CO2
HOH
α - Intercalated Cell


Peritubular
Fluid
H+
ATPase
H+
K+
ATPase
Cl−
HCO3−
Cl−
Cl−
α - Intercalated Cell
β - Intercalated Cell
Collecting
Tubular
Lumen
Cl−
HCO3−
H+
ATPase
Cl−

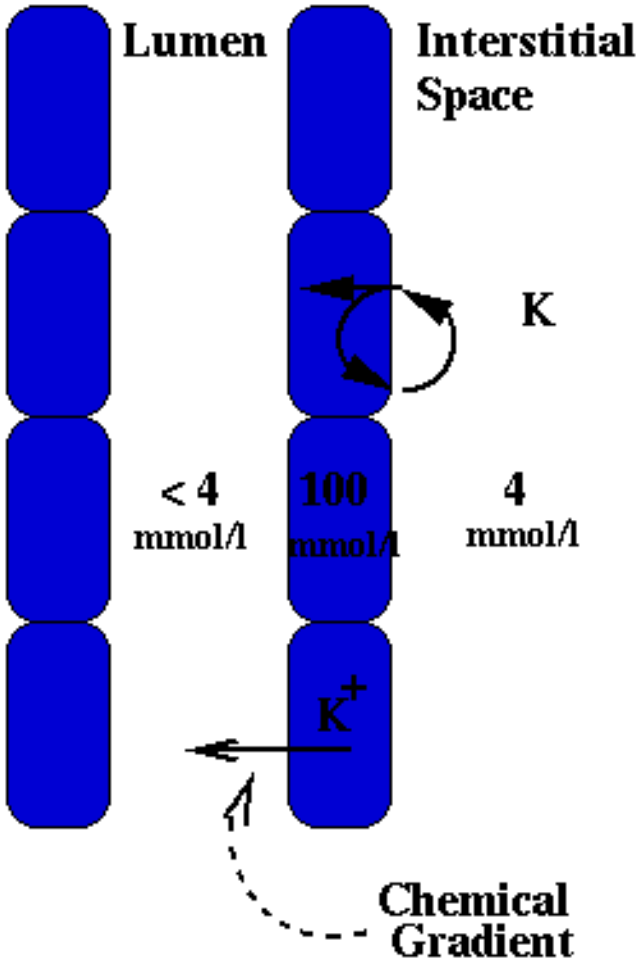
Factors favouring K+ secretion

- **Increased Na^+ reabsorption**
  - Exchange
- **Increased intra-cellular K^+**
  - Concentration gradient
- **Decreased H^+ secretion.**
  - Aldosterone
  - Electrochemical gradient.

K^+ Intake High

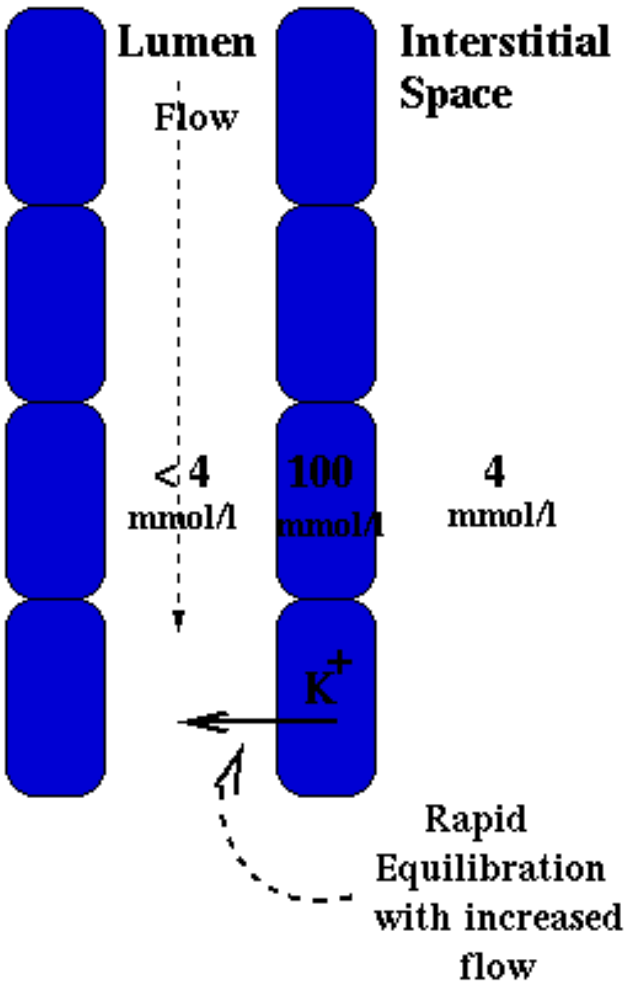
High

- Stimulates renal cell uptake and secretion of K^+.
- Stimulation of aldosterone secretion.



Increased fluid delivery to lumen causes increased K+ excretion: -

- Wash out.
  - diuretics
  - poorly absorbed anions
  - osmotic diuresis

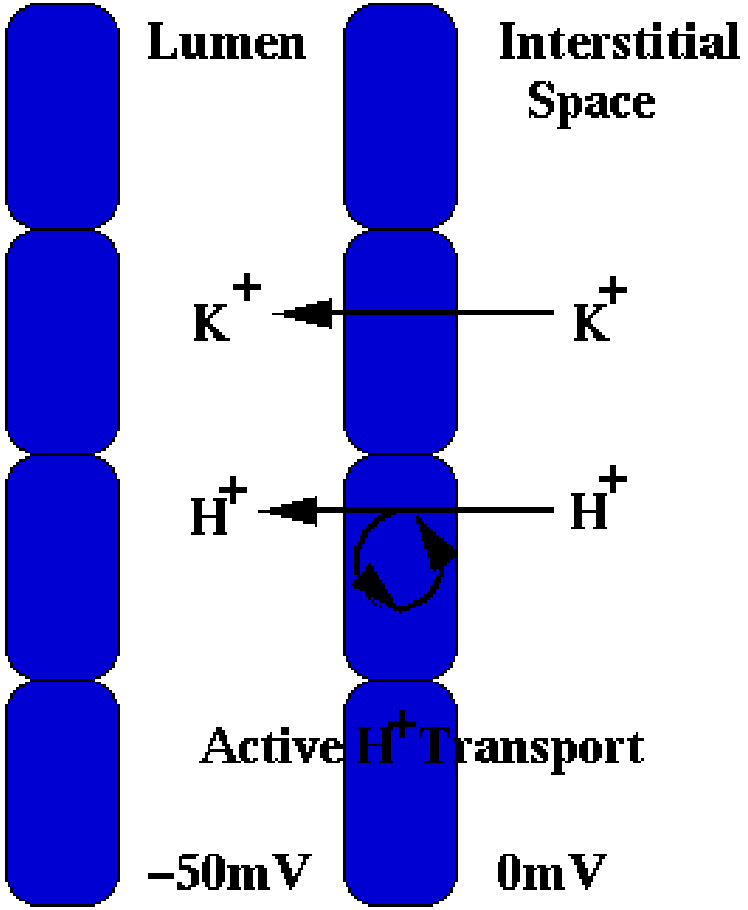


Electrochemical Gradient: -

- Distal tubule actively secretes H^+
- K^+ and H^+ are neutralising the same electrical gradient

Acidosis Causing

Hyper-kalaemia

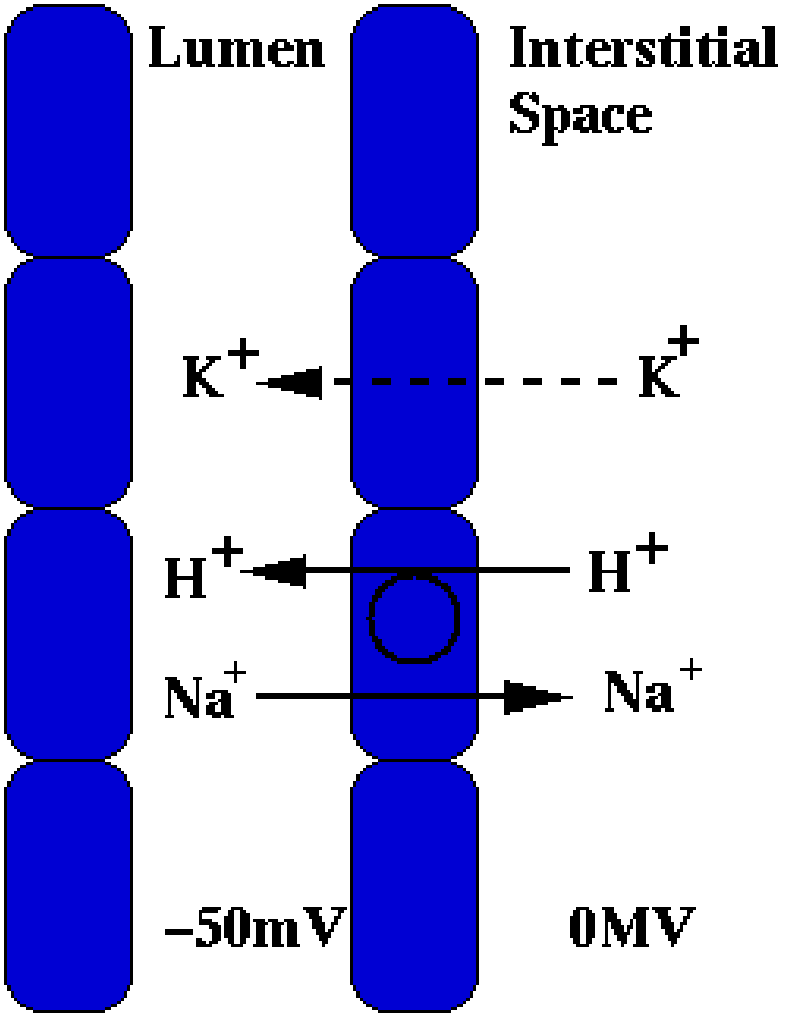


At low pH more H^+ exchanged for Na^+: -

- **reduces electrical gradient and reduces K^+ excretion**

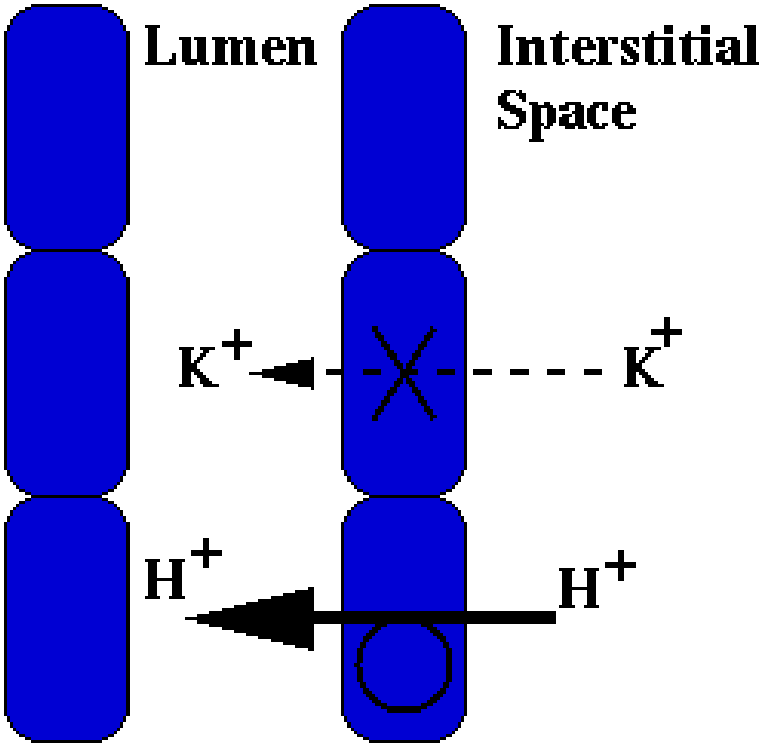
Acidosis Causing

Hyperkalaemia



Effect of High [H^+] upon Renal K^+ excretion and ECF [K^+]: -

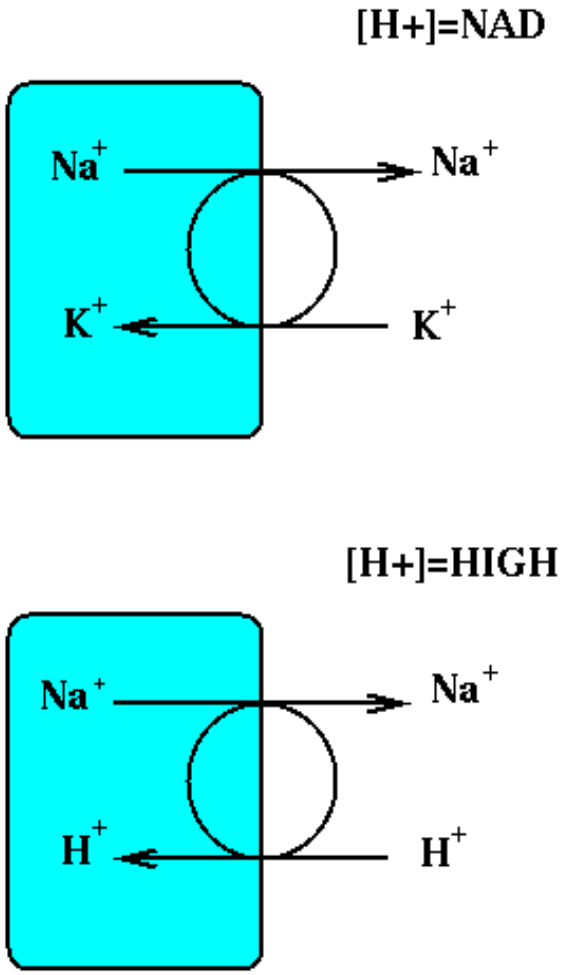
- Acidotic patients will have high [H^+] and high rates of delivery of H^+ to the kidney
- H^+ load blocks K^+ excretion therefore ECF [K^+] rises.
- In alkalosis, the converse is true



High blood [H^+] = High blood [K+]

Extra-Renal

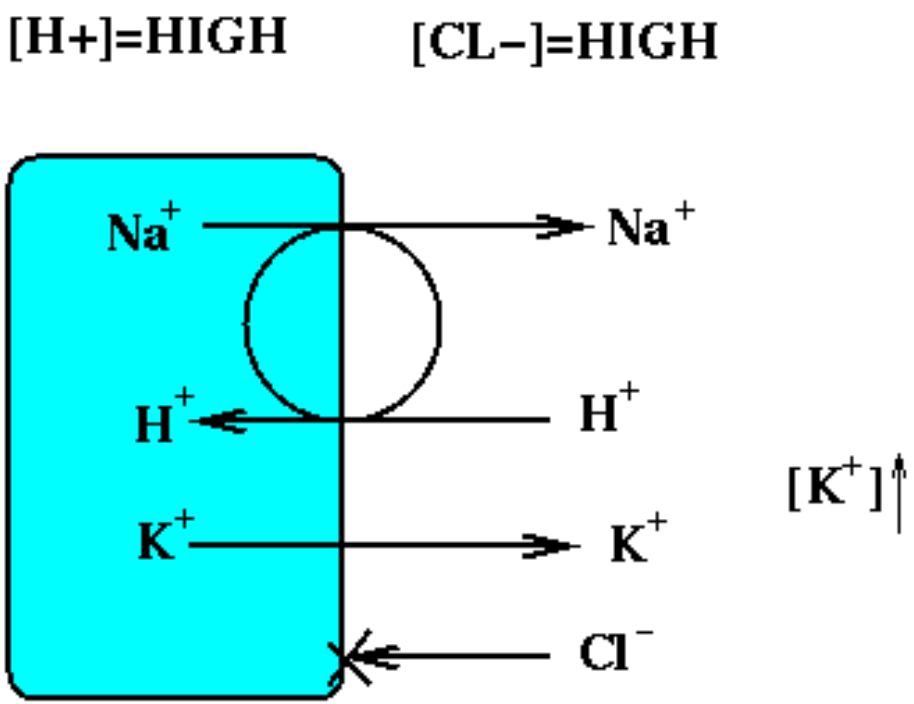
Inter-relationship between ECF [H^+] and [K^+].



- ECF [H^+] affects K+ entry into cells
- Acidosis:
  - H^+ enters cells (ICF) instead of K^+
  - Kidney = loss of H+ rather than K^+
  - [K^+] rises in ECF = hyperkalaemia

More K+ lost if acidosis is hyper-chloraemic.

- Cl^- cannot pass membrane to maintain neutrality therefore K+ lost instead
- If acidaemia due to organic acids, (lactic, ketoacids) both cation and anion pass membrane therefore no additional K^+ loss



Low = ↑ ECF [K^+]

ECF [K+] ↑
Resting Potential ↓
Excitability ↑

ECF **ICF**

+ Cell Membrane -
+ -
+ -
+ -
+ -
+ -

Threshold potential –30mV

Resting potential –80mV

ECF [K+] ↓
Resting Potential ↑
Excitability ↓

Excitation Threshold

$[K+]^{ICF}$: $[K+]^{ECF}$
<= 35 : 1

$[K+]^{ICF}$: $[K+]^{ECF}$
>= 35 : 1

$[K+]^{ICF}$: $[K+]^{ECF}$
35 : 1

High = ↓ ECF [K^+]

Etiology of Hyperkalemia

- Increased intake
- Movement from cells into extracellular fluid
- Decreased urinary excretion
- Combinations of above

Movement from cells into extracellular fluid (1)

- Pseudohyperkalemia
  - Movement of K+ out of cells during or after blood drawing
    - Hemolysis
    - Fist clenching (local exercise effect)
    - Marked leukocytosis
- Metabolic acidosis – non organic acids
- Insulin deficiency
- Hyperosmolality
- Beta blockade

Movement from cells into extracellular fluid (2)

- Tissue catabolism
  - Trauma
  - Cytotoxic agents (TLS)
  - Severe hypothermia
- Severe exercise
- Digitalis overdose
- Hyperkalemic periodic paralysis
- Post cardiac surgery
- Succinylcholine
- Arginine

Hypoaldosteronism

- Decreased activity of renin-angiotensin system
  - Hyporeninemic hypoaldosteronism (T4 RTA)
  - NSAIDS, ACE-I, CSA
- Primary decrease in adrenal synthesis
  - Adrenal insufficiency, CAH, heparin
- Aldosterone resistance
  - K+sparing diuretics, trimethoprim, CSA
  - pseudohypoaldosteronism

Decreased urinary excretion

- Renal failure – if diet OK, not until GFR < 25 ml/min
- Effective circulating volume depletion
- Hypoaldosteronism
- Selective K+ secretory defects

Diagnosis of hypoaldosteronism

- Discontinue potential drugs
- AM plasma renin activity, aldo, and cortisol
  - Premedicate with lasix 20-40mg prior pm and am of blood draw can increase specificity
- TTKG
  - Indirect clinical estimate of the tubular K+ concentration at the end of the cortical collecting duct
  - Must have adequate urine Na+ delivery and flow

Use of TTKG

- Indirect clinical assessment of K+ concentration at end of the CCT
    - >7 = nonrenal, adequate aldosterone
    - <3 = c/w hypoaldosteronism

Hyperkalaemia: Causes

Factitious

- Improper collection
- Haematological disorders

Increased input

- Oral
- IV therapy

Altered distribution

- Acidemia
- insulin deficiency
- Crush Injury or haemolysis

Reduced excretion

- Renal Failure
- Mineralocorticoid deficiency (Addison's)
- Tubular defects

Drugs

- Potassium sparing diuretics (spiranolactone)
- Inappropriate use of K supplements with above

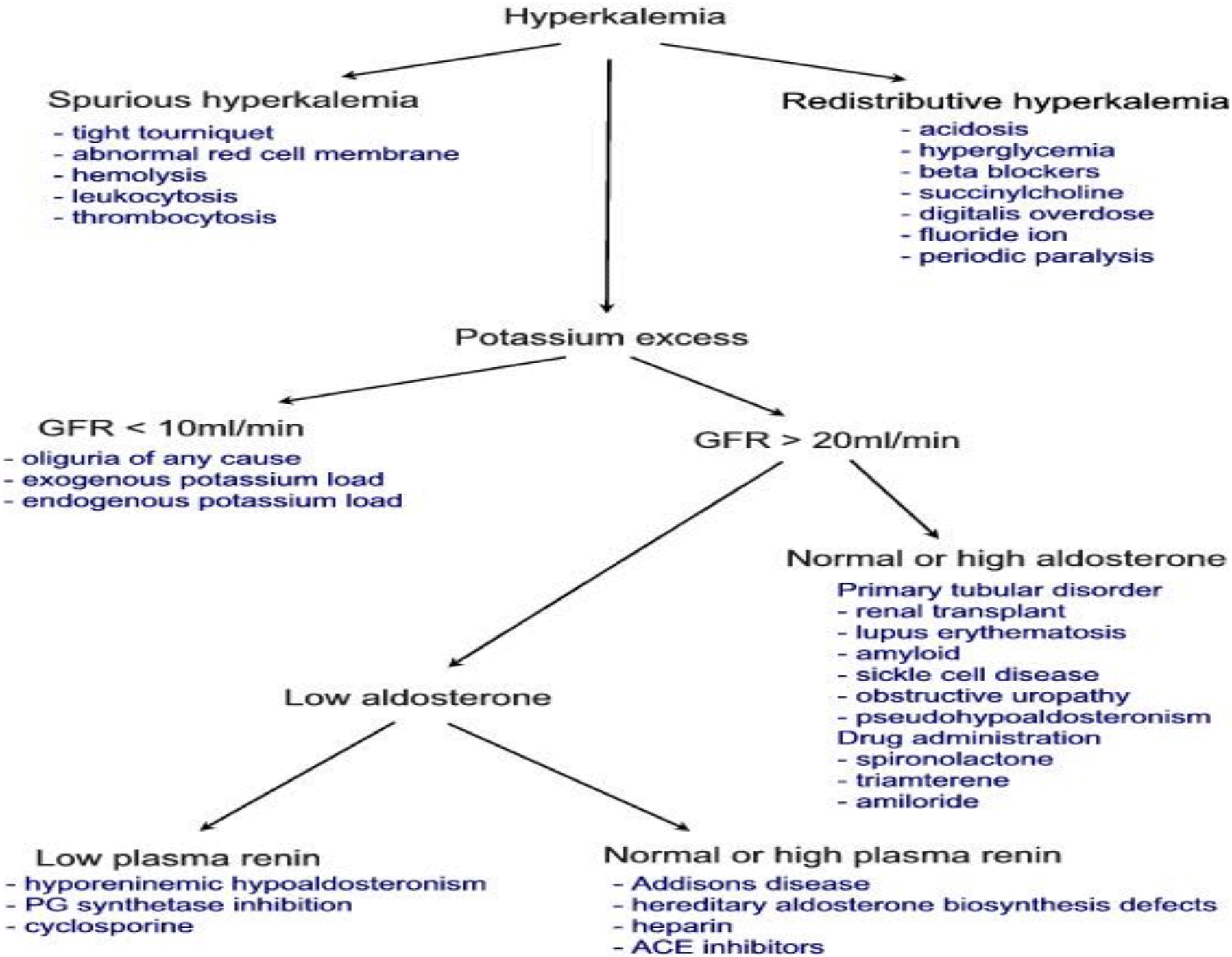
Hyperkalaemia

Most usual causes

- Decreased renal function
- Redistribution secondary to acidosis

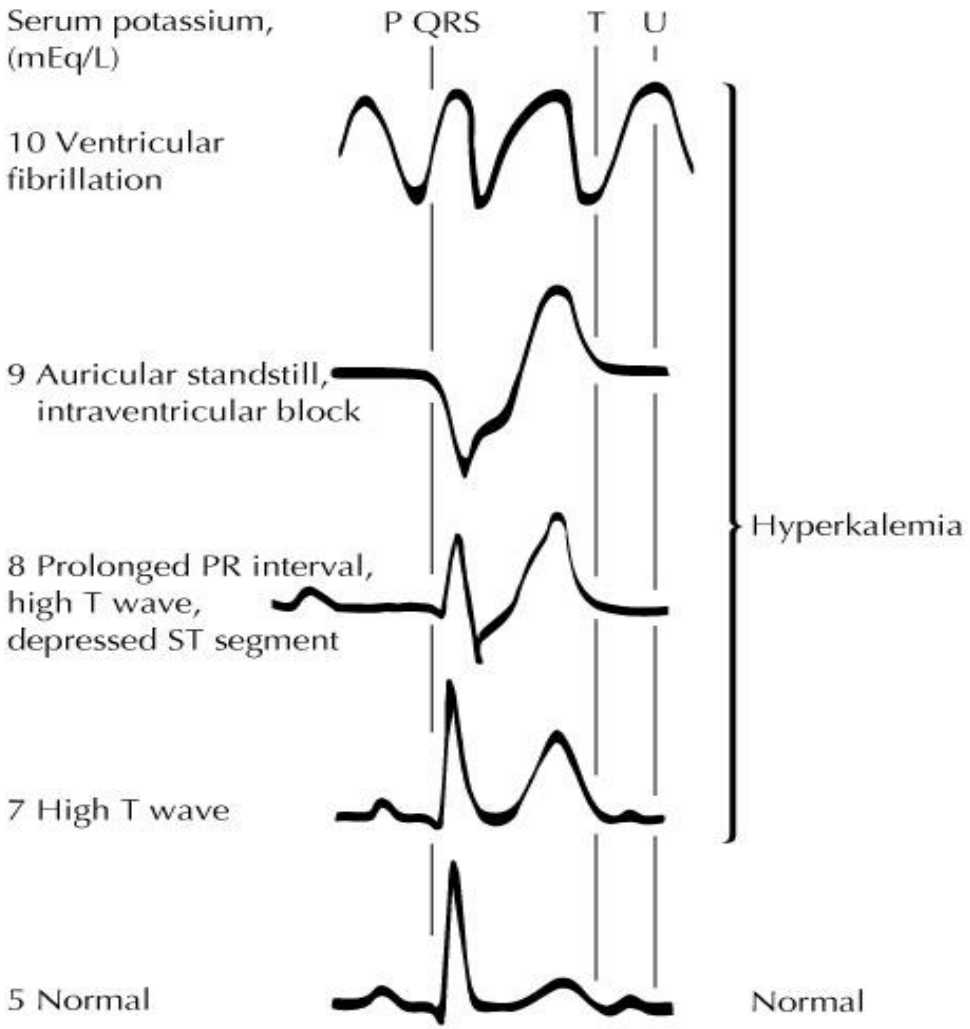
Consequences of Hyperkalaemia

- Neuromuscular - Weakness, parasthesia, paralysis
- Gastrointestinal - Nausea, vomiting, pain, ileus
- Cardiovascular - Conduction defects, arrhythmias, Cardiac arrest


Hyperkalemia
Spurious hyperkalemia
- tight tourniquet
- abnormal red cell membrane
- hemolysis
- leukocytosis
- thrombocytosis
Redistributive hyperkalemia
- acidosis
- hyperglycemia
- beta blockers
- succinylcholine
- digitalis overdose
- fluoride ion
- periodic paralysis
Potassium excess
GFR < 10ml/min
- oliguria of any cause
- exogenous potassium load
- endogenous potassium load
GFR > 20ml/min
Normal or high aldosterone
Primary tubular disorder
- renal transplant
- lupus erythematosis
- amyloid
- sickle cell disease
- obstructive uropathy
- pseudohypoaldosteronism
Drug administration
- spironolactone
- triamterene
- amiloride
Low aldosterone
Low plasma renin
- hyporeninemic hypoaldosteronism
- PG synthetase inhibition
- cyclosporine
Normal or high plasma renin
- Addisons disease
- hereditary aldosterone biosynthesis defects
- heparin
- ACE inhibitors

Signs & sxs of Hyperkalemia

- Muscle weakness – decr magnitude of resting MP
- Cardiac toxicity Enhanced by :
  - hypocalcemia
  - Acidemia
  - hypomagnesemia
  - Rapid onset



Treatment of Acute Hyperkalemia

1) Assess urgency
2) Stabilize myocardium: CaGluconate
3) Redistribute K+ from ECF to ICF

   Ins/D50, Albuterol (high dose), NaHCO3, ?diur
4) Remove K+ from body by Kayexalate, dialysis

Treatment of chronic hyperkalemia

- Limit intake! Easier said than done
  - 2 g/day
  - OTC that contain K+
- Avoid drugs that induce (NSAIDs!)
- Increase K excretion
  - Diuretics, avoid constipation, +/- kayexalate
- Avoid excessive volume depletion

Etiology of Hypokalemia

1) Decreased net intake
2) Increased entry into cells
3) Increased GI losses
4) Increased urinary losses
5) Increased sweat losses
6) Increased other losses (dialysis)

Decreased net intake

- Normal 100 mEq/d (40-120)
- Renal excretion as low as 5–20 mEq/d
- Thus, decreased intake rare cause, but increases susceptibility to hypokalemia
- Clay (non riverbed) ingestion can bind dietary K+ in gut, reducing absorption

Increased Entry into Cells

- Elevated extracellular pH
  - H+ released from cellular buffers
  - K+ (and Na+) enters cells to preserve electroneutrality
- Increased availability of insulin
- Elevated beta-adrenergic activity

Increased Entry into Cells

- Periodic paralyis
  - Familial, autosomal dominant, onset up to 30y, severe
  - Acquired w/ thyrotoxicosis (eg Asian men)
  - Episodes ppt by
    - Rest post-exercise
    - Carbohydrate meal
    - Stress, cold
    - Administration of insulin or epinephrine
  - Sudden movement of K+ into cells, acute decr. [K+]
  - Plasma [K+] is normal between attacks

Increased Entry into Cells

- Treatment of anemia or neutropenia
  - Folate or B12 administration most common
- Pseudohypokalemia
  - Metabolically active cells take up K+ after blood is drawn
- Hypothermia
  - K+ entry , reversible with rewarming

Increased GI Losses

- Vomitting*
- Diarrhea
- Intestinal fistulas
- Tube drainage
- Loss of colonic secretions
  - Villous adenoma
  - Laxative abuse

Increased urinary losses

- Diuretics
  - Increased flow to K+ secretory sites
  - Enhanced secretion of aldosterone
- Bartter's or Gitelman's Syndrome
- Mineralocorticoid excess (or apparent…)
- Reabsorption of Na+ in presence of nonreabsorbable anion

Increased Urinary Losses…cont

- Renal Tubular Acidosis
- Salt-wasting nephropathies
- Ureterosigmoidostomy
- Amphotericin B
- Hypomagnesemia
- Polyuria

Hypokalaemia: Causes

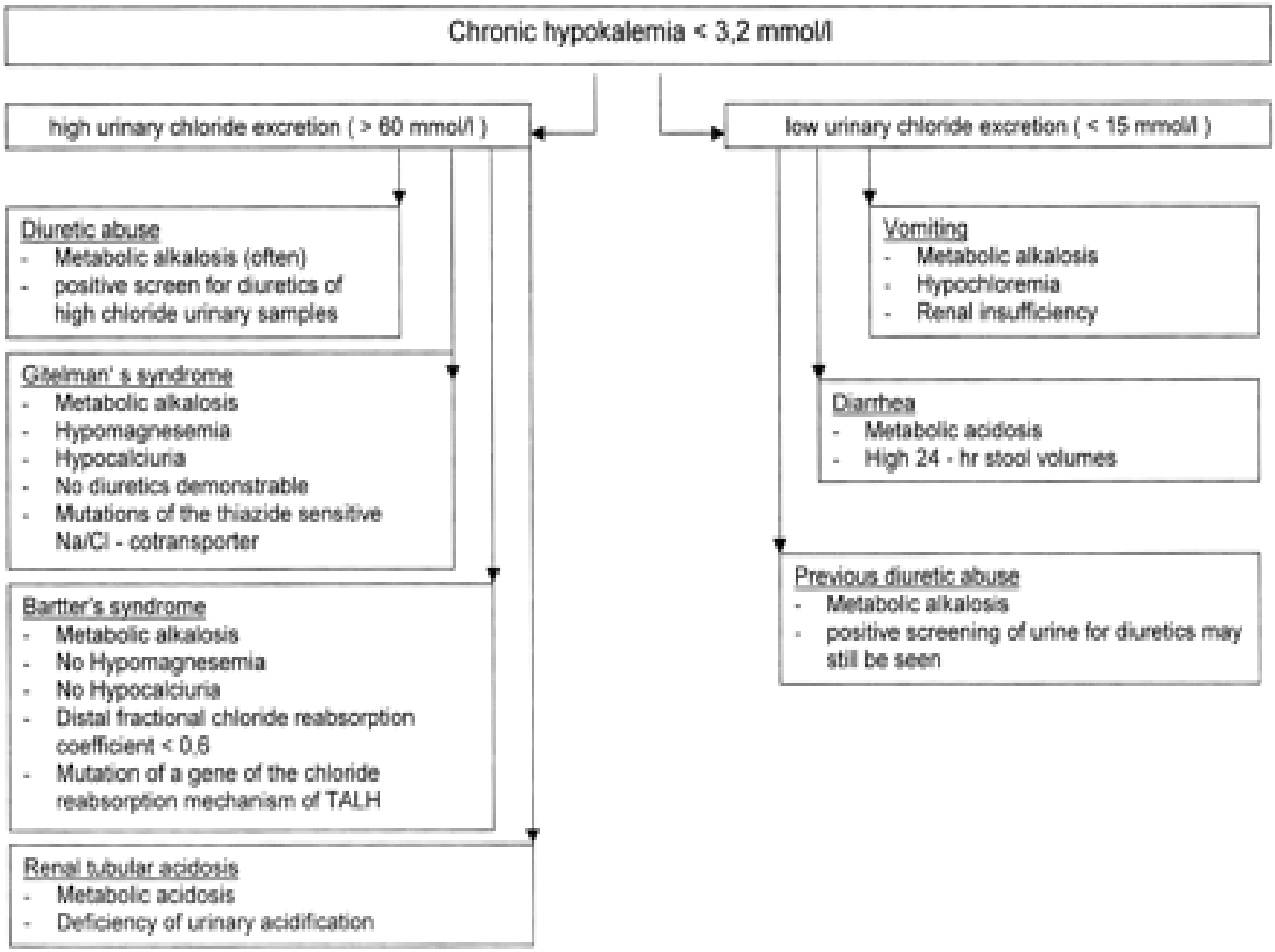
Most usual causes

- Excessive gastrointestinal or renal loss
- Hypomagnesamia on to watch for.

Consequences of Hypokalaemia

- **Skeletal muscle** - Weakness, paralysis
- **Gastrointestinal** - Paralytic Ileus
- **Kidney** - Impaired concentrating ability, Tubular defects
- **Cardiac** - Conduction defects, arrhythmias, Digoxin toxicity

Diagnostic guide for chronic hypokalemia



Hypokalemia and Hypertension

Urine K+ excretion

< 25 mEq/d

GI losses
Prior diuretic Rx

> 30mEq/d

Plasma renin activity

Low

Plasma aldosterone

High

Primary Hyperaldosteronism

Adrenal vein aldo +/- CT

Adenoma:
Do surgery

Hyperplasia:
K+ sparing diuretic

Low

Licorice
Liddle's
SAME
Other Mineralo-
corticoid

High or normal

Continued diuretic use
Renovascular HTN
Malignant HTN
Renin-secreting tumor
Cushing's Syndrome

Role of Cortisol

- Cortisol binds to mineralocorticoid receptor with equal avidity to aldosterone
- Conversion to cortisone by 11β-hydroxysteroid dehydrogenase prevents mineralocorticoid activity
- Cortisol acts as mineralocorticoid with:
  - Excess cortisol production: Cushing's
  - Impairment of 11β- : 'real'Licorice, Syndrome of AME

Work-up of hypokalemia

- H and P
  - Diarrhea
  - Vomitting
  - Diuretics
  - Periodic paralysis
  - Offending drugs
- Acid-base balance
- Urine potassium
  - >25-30 meq/d indicates renal losses
  - < 15 meq/L on spot usually r/o urine losses
    - Exception: polyuria, Una < 30-40 meq/L

Use of TTKG

- Transtubular potassium gradient

- < 2 = nonrenal, suspect GI cause
- > 4 = renal etiology

TABLE 4. FOODS WITH HIGH POTASSIUM CONTENT.

Highest content (>1000 mg [25 mmol]/100 g)
Dried figs
Molasses
Seaweed
Very high content (>500 mg [12.5 mmol]/100 g)
Dried fruits (dates, prunes)
Nuts
Avocados
Bran cereals
Wheat germ
Lima beans
High content (>250 mg [6.2 mmol]/100 g)
Vegetables
Spinach
Tomatoes
Broccoli
Winter squash
Beets
Carrots
Cauliflower
Potatoes
Fruits
Bananas
Cantaloupe
Kiwis
Oranges
Mangos
Meats
Ground beef
Steak
Pork
Veal
Lamb

Hypokalaemia: Treatment

Not urgent UNLESS complications

- Oral is preferable to IV therapy
- Deficits:
  - K = 3 mmol/L ~ 300 mmol
  - K = 2 mmol/L ~ 600 mmol

Oral treatment

- Normal intake + 60 mmol/day
- = 8 Slow K, or 10 Effervescent K

I.V. treatment

- 10 mmol/hr MAXIMUM
- DILUTE potassium ampules - NEVER straight from ampule> 40 mmol/L