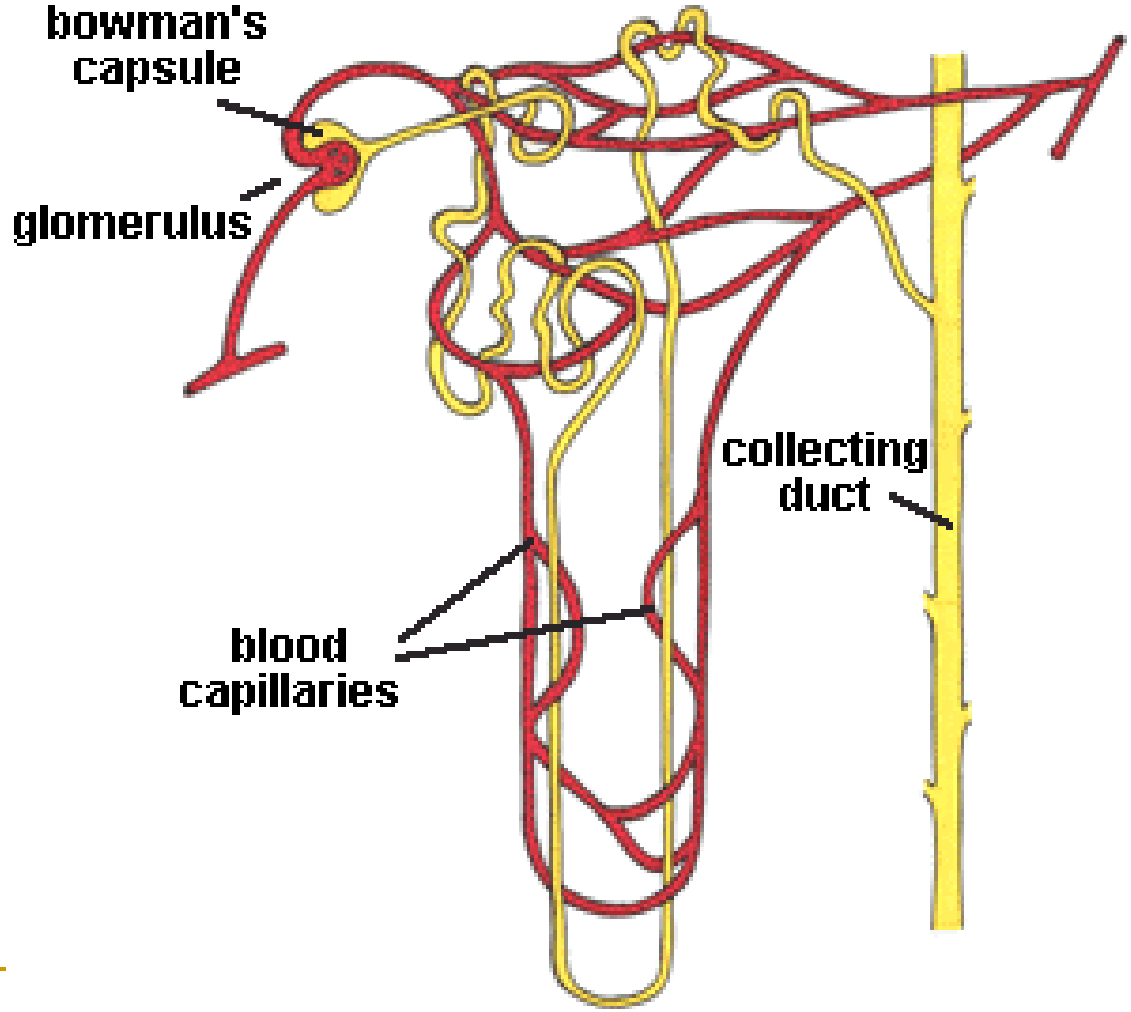
Diuretics

Excretion of Water and Electrolytes

Background

- Primary effect of diuretics is to increase solute excretion, mainly as NaCl
- Causes increase in urine volume due to increased osmotic pressure in lumen of renal tubule.
- Causes concomitant decrease in extra-cellular volume (blood volume)
- Certain disease states may cause blood volume to increase outside of narrowly defined limits
  - Hypertension
  - Congestive heart failure
  - Liver cirrhosis
  - Nephrotic syndrome
  - Renal failure
- Dietary Na restriction often not enough to maintain ECF and prevent edema → diuretics needed

Review of Kidney Structure



Types of diuretics and therapeutic uses

- Carbonic anhydrase inhibitors (work in proximal tubule)
  - Cystinuria (increase alkalinity of tubular urine)
  - Glaucoma (decrease occular pressure)
  - Acute mountain sickness
  - Metabolic alkalosis
- Osmotic diuretics (proximal tubule, loop of Henle)
  - Acute or incipient renal failure
  - Reduce preoperative intraocular or intracranial pressure

Types of diuretics and therapeutic uses

- **Loop diuretics** (ascending limb of loop)
  - Hypertension, in patients with impaired renal function
  - Congestive heart failure (moderate to severe)
  - Acute pulmonary edema
  - Chronic or acute renal failure
  - Nephrotic syndrome
  - Hyperkalemia
  - Chemical intoxication (to increase urine flow)

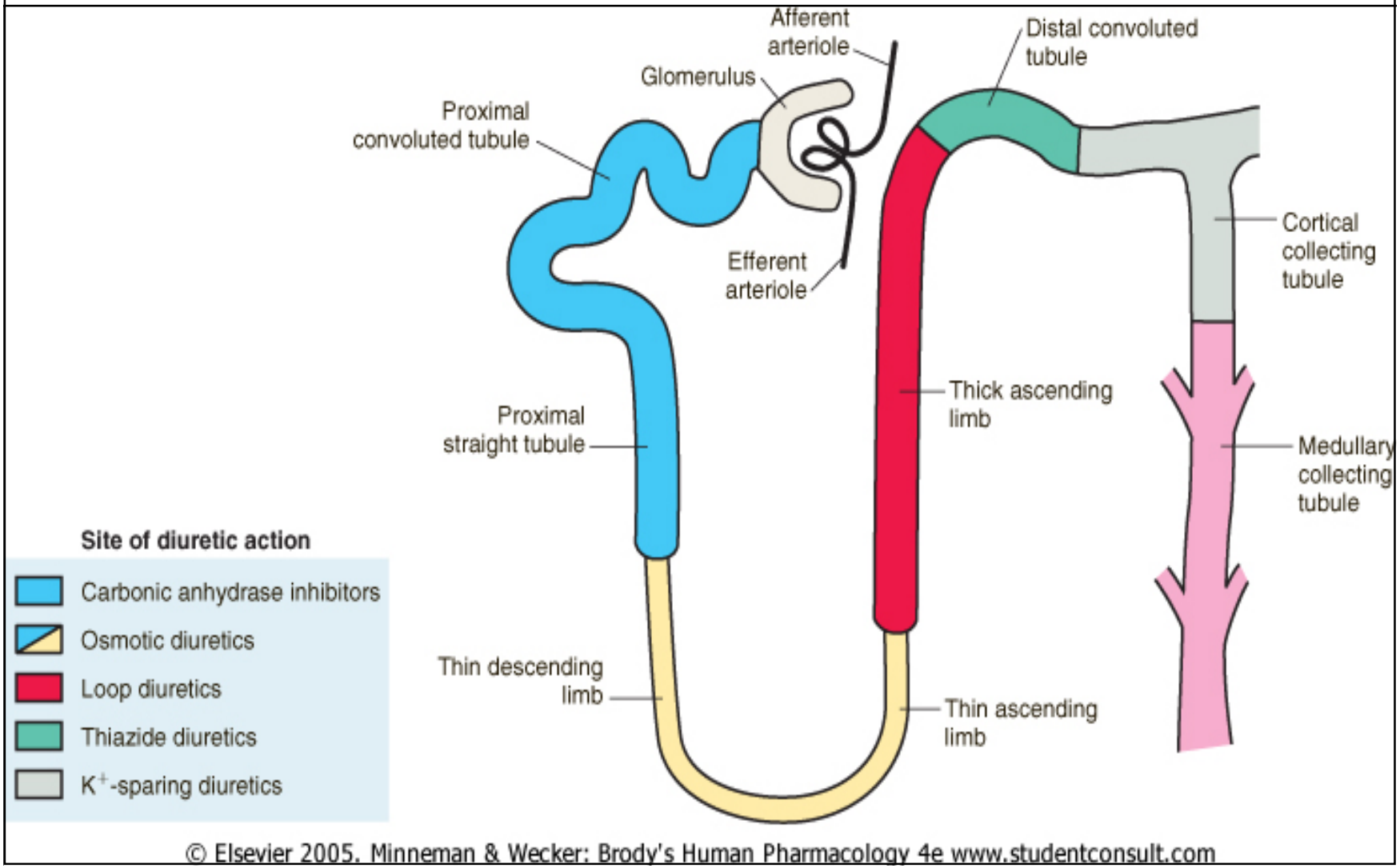
Types of diuretics and therapeutic uses

- **Thiazide diuretics** (distal convoluted tubule)
  - Hypertension
  - Congestive heart failure (mild)
  - Renal calculi
  - Nephrogenic diabetes insipidus
  - Chronic renal failure (as an adjunct to loop diuretic)
  - Osteoporosis

Types of diuretics and therapeutic uses

- **Potassium-sparing diuretics** (collecting tubule)
  - Chronic liver failure
  - Congestive heart failure, when hypokalemia is a problem
- **Osmotic agents** (proximal tubule, descending loop of Henle, collecting duct)
  - Reduce pre-surgical or post-trauma intracranial pressure
  - Prompt removal of renal toxins
  - One of the few diuretics that do not remove large amounts of Na^+
  - Can cause hypernatremia

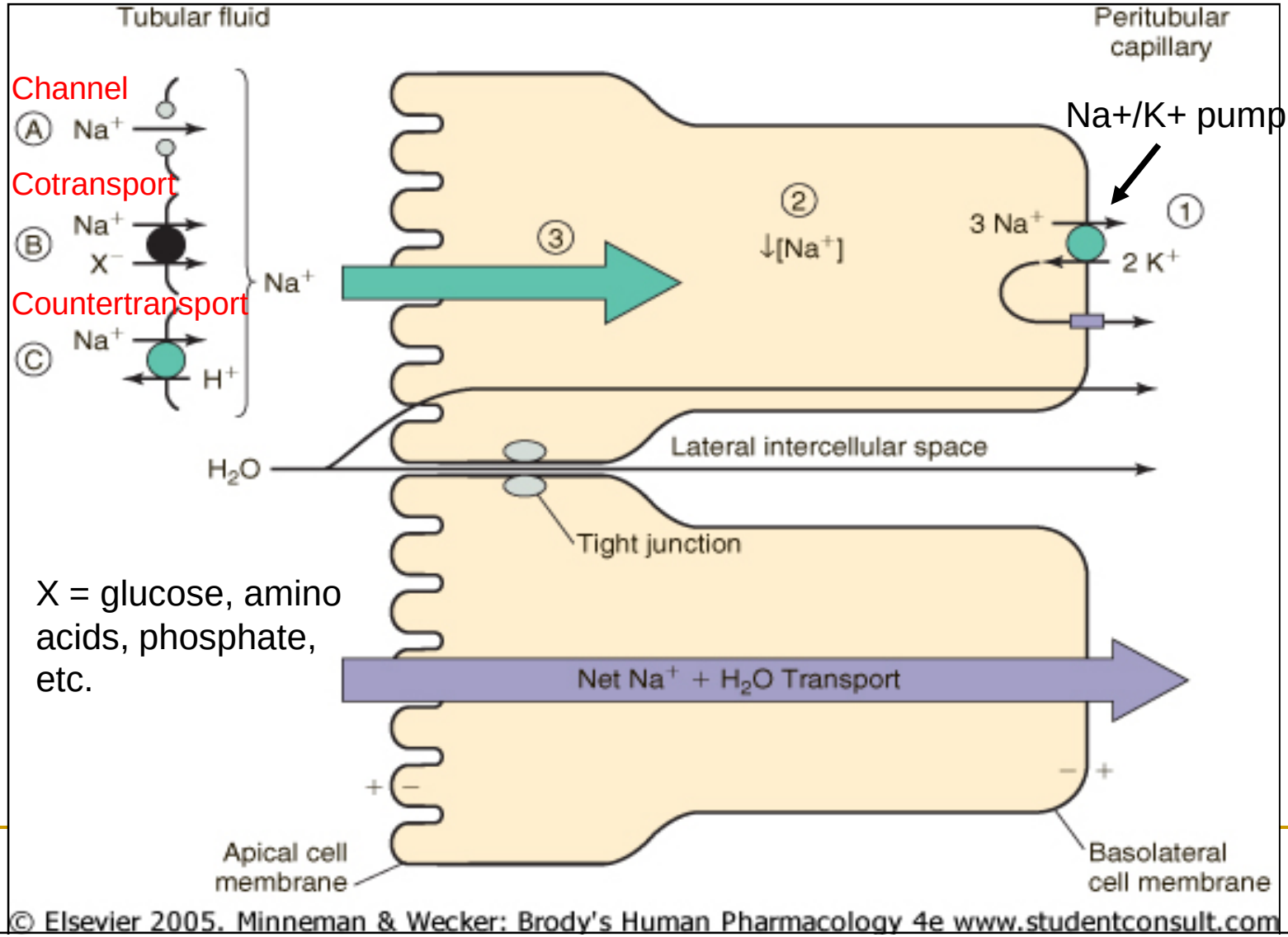
Nephron sites of action of diuretics



Background to Mechanisms of Action of Diuretics

- Previously told that reabsorption, secretion occurred along renal tubule but not *how* this was accomplished
- Movement from tubular fluid through renal epithelial cells and into peritubular capillaries accomplished by three transport mechanisms after cell interior is polarized by Na+/K+ pump
  1. Channels
     - formed by membrane proteins
     - Allows only sodium to pass through
  2. Cotransport
     - Carrier mediated
     - Simultaneously transports both Na+ and other solute (Cl-, glucose, etc) from tubular lumen into renal epithelial cell
  3. Countertransport
     - Carrier mediated
     - Transports Na in, another solute (H+) out of renal epithelial cell
- Water moves transcellularly in permeable segments or via tight junctions between renal epithelial cells

Electrolyte Transport Mechanisms



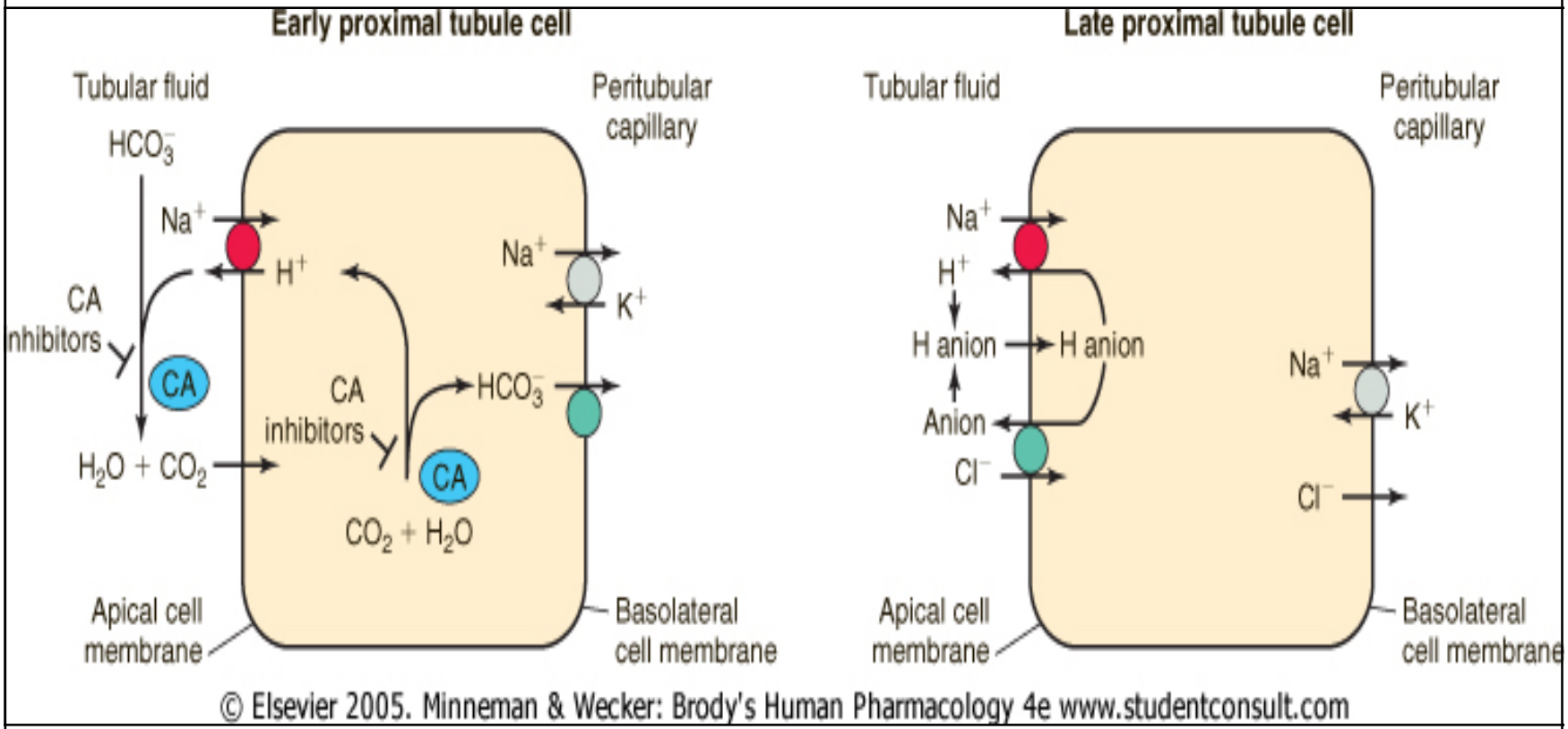
Mechanisms of Action: Carbonic anydrase inhibitors

- CAIs work on cotransport of Na^+, HCO_3^- and Cl^- that is coupled to H^+ countertransport
- Acts to block carbonic anhydrase (CA),

1. CA converts $HCO_3^- + H^+$ to $H_2O + CO_2$ in tubular lumen
2. CO_2 diffuses into cell (water follows Na^+), CA converts $CO_2 + H_2O$ into $HCO_3^- + H^+$
3. H^+ now available again for countertransport with Na+, etc)
4. Na^+ and HCO_3^- now transported into peritubular capillary

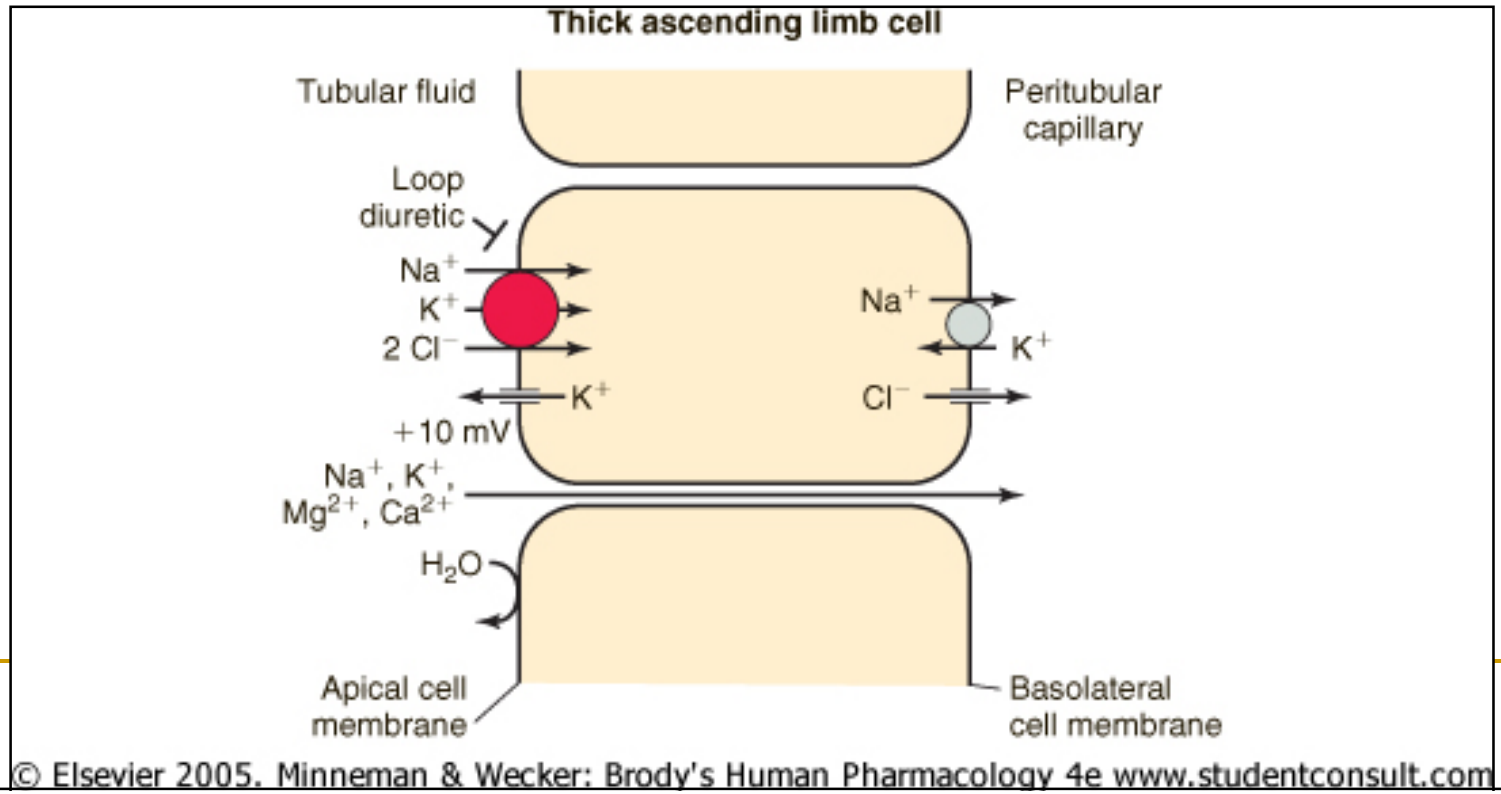
- CA can catalyze reaction in either direction depending on relative concentration of substrates

Site of Action of CAIs



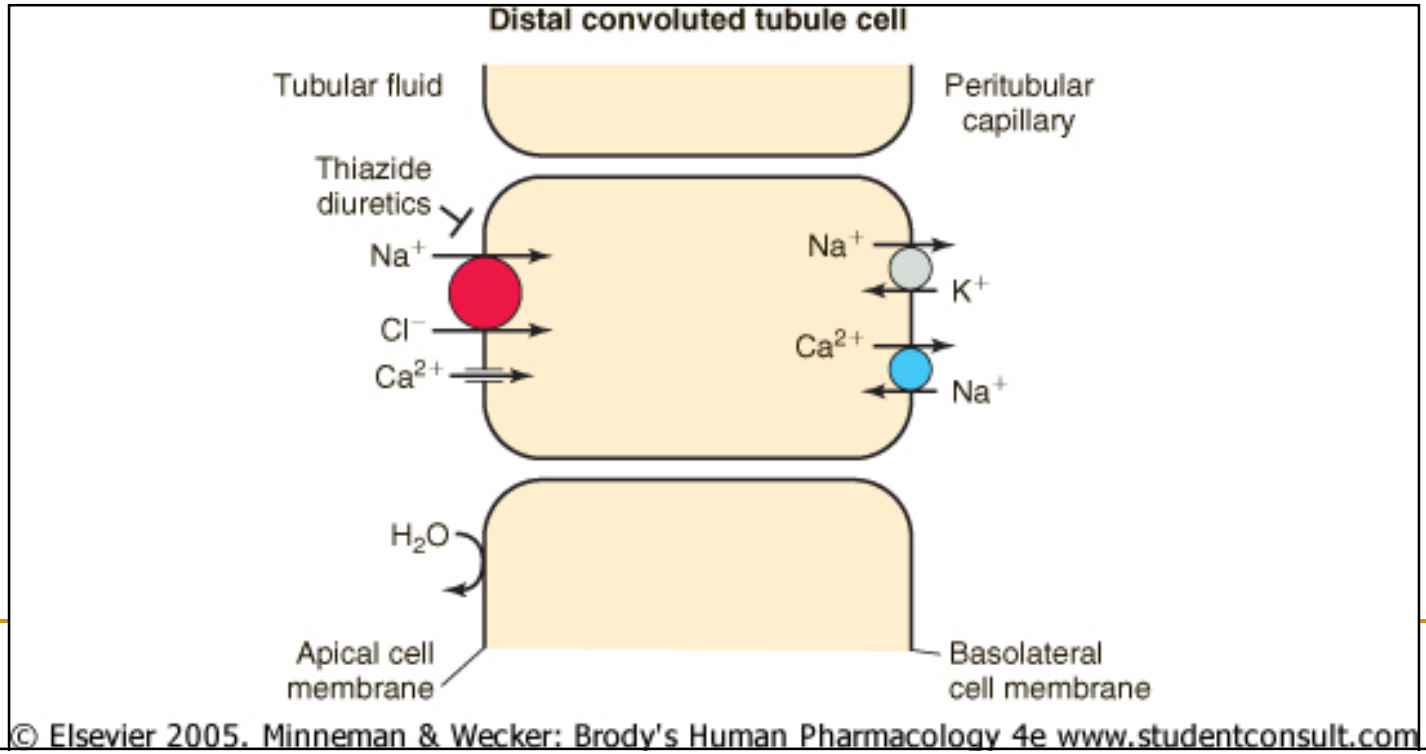
Mechanisms of Action: Loop diuretics

- No transport systems in descending loop of Henle
- Ascending loop contains Na^+ - K^+ - $2Cl^-$ cotransporter from lumen to ascending limb cells
- Loop diuretic blocks cotransporter → Na^+, K^+, and Cl^- remain in lumen, excreted along with water



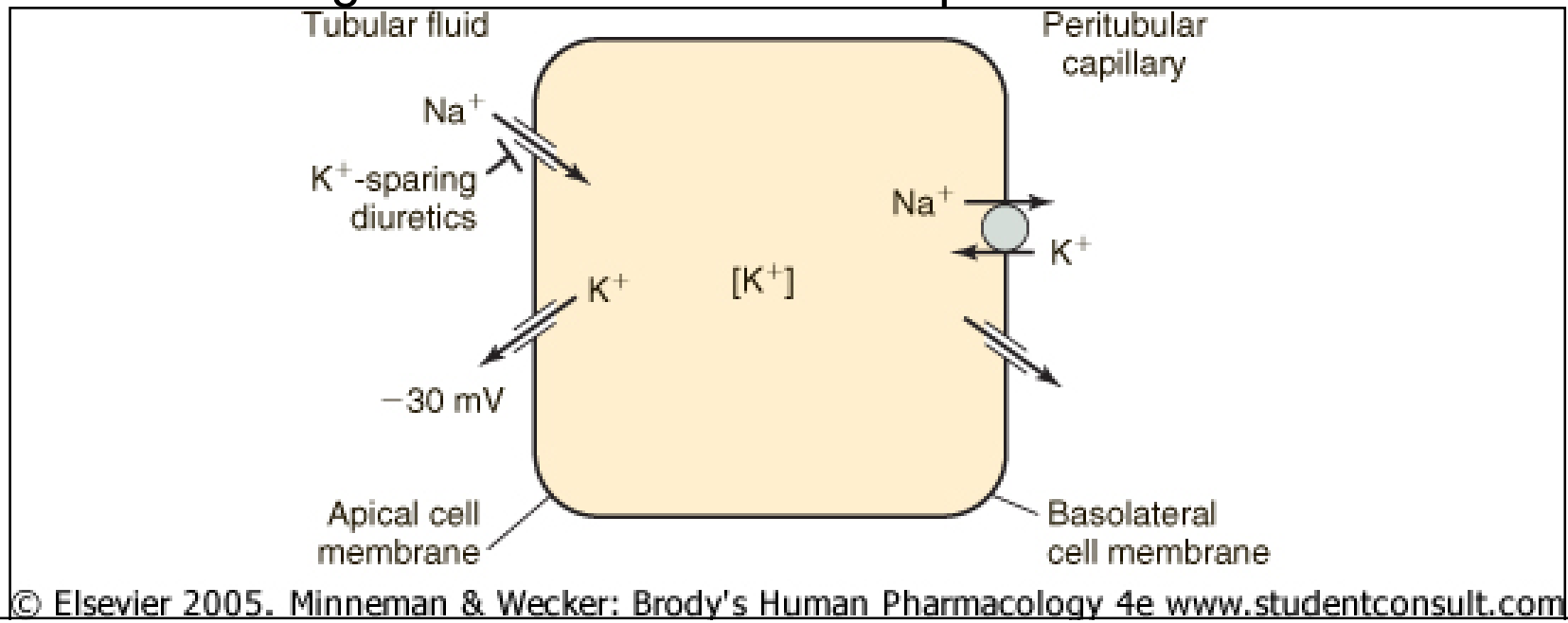
Mechanisms of Action: Thiazide Diuretics in the Distal Convoluted Tubule

- Less reabsorption of water and electrolytes in the distal convoluted tubule than proximal tubule or loop
- A Na^+ - Cl^- cotransporter there is blocked by thiazides

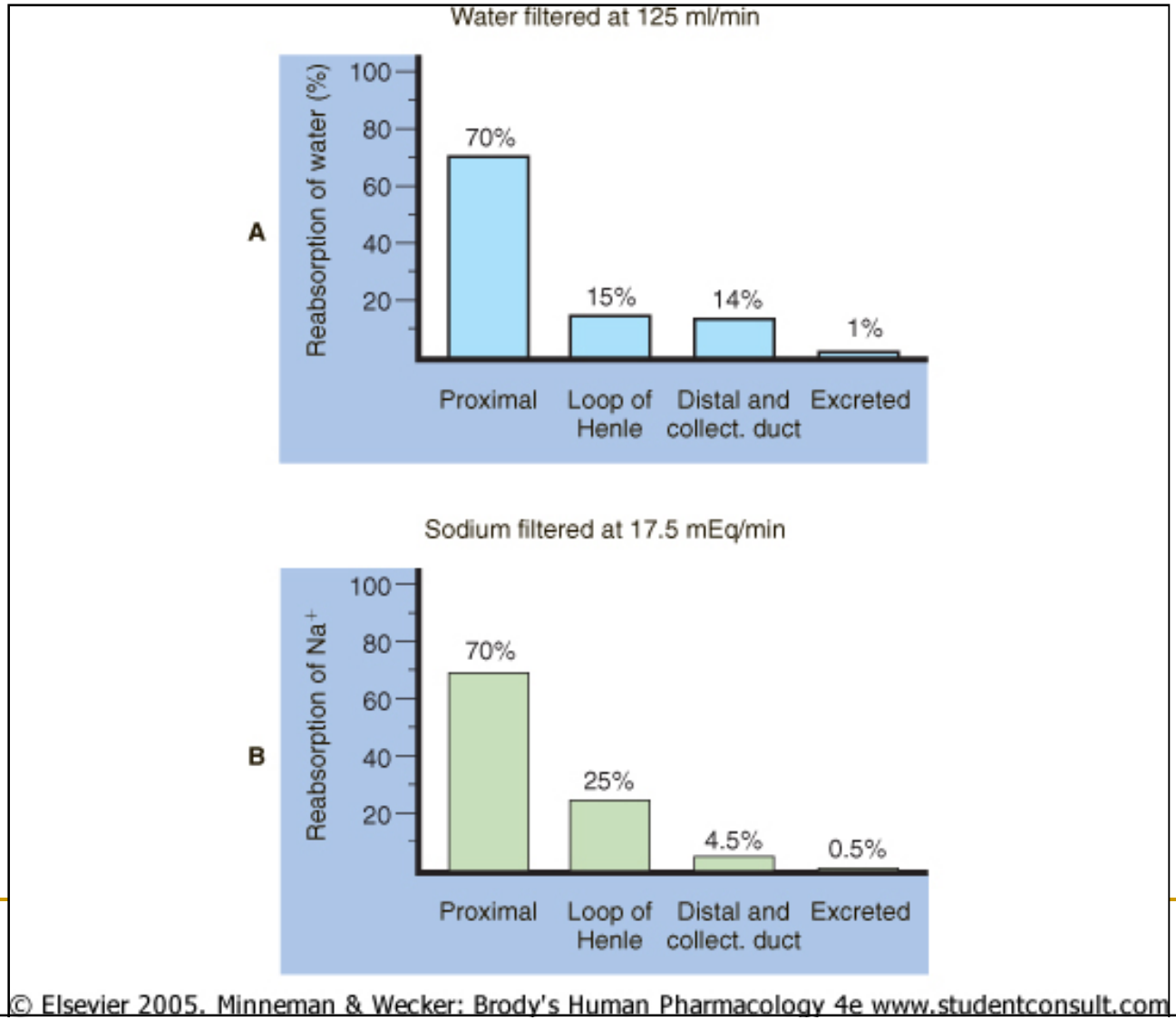


Mechanisms of Action: Collecting tubule and potassium-sparing diuretics

- Two cell types in collecting tubule
  1. Principal cells – transport Na, K, water
  2. Intercalated cells – secretion of H^+ and HCO_3
  3. Blocking Na+ movement in also prevents K^+ movement out



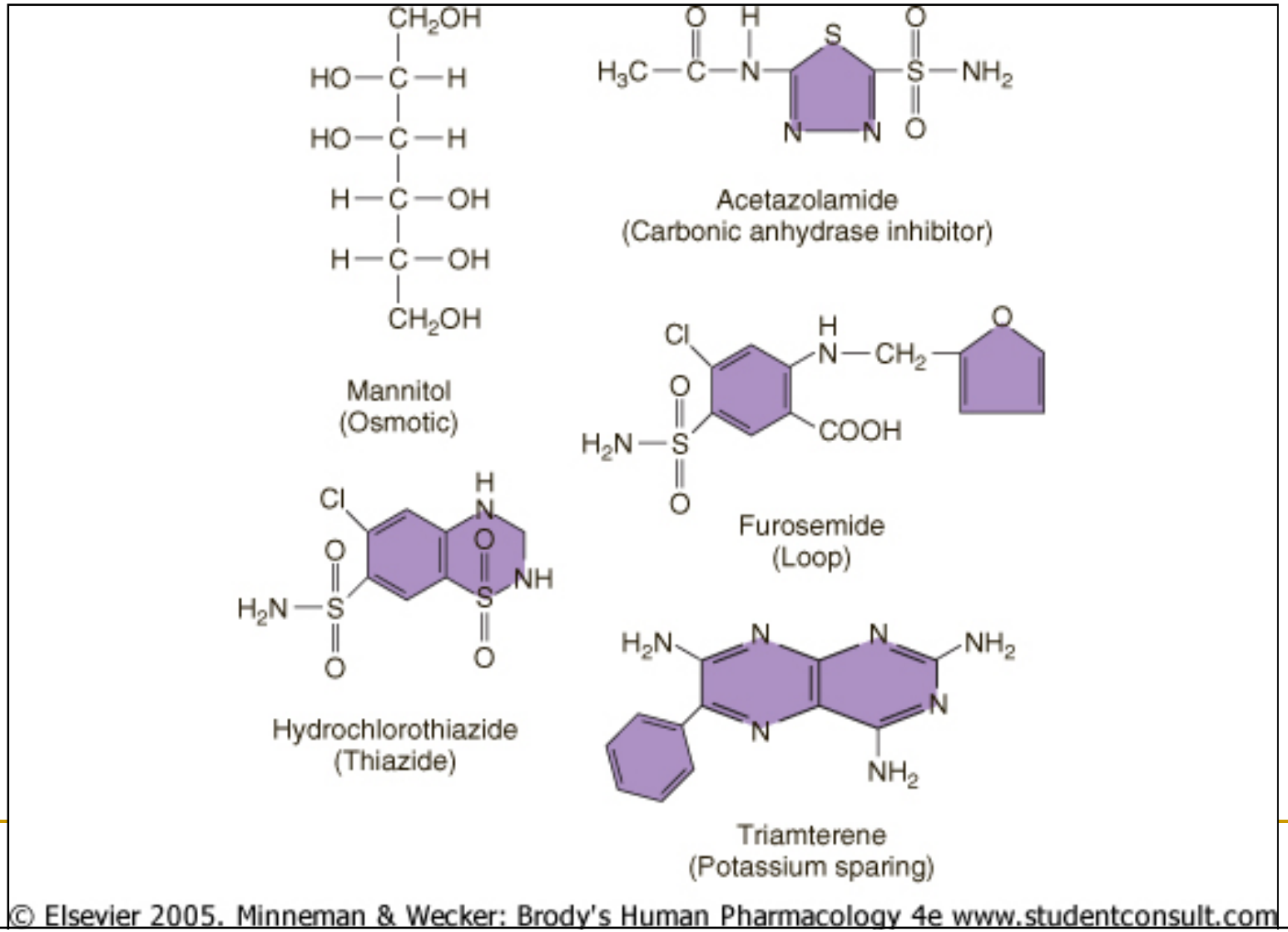
Summary of sites of renal reabsorption of filtrate



Types and Names of Diuretics

Type	Example	Sites of Action
Osmotic agents	Mannitol	Proximal tubule Descending loop Collecting duct
Carbonic anydrase inhib.	Acetazolamide	Proximal tubule
Thiazides	Hydrochlorothiazide	Distal convoluted tubule
Loop diuretic	Ethacrynic acid Furosemide	Loop of Henle
K^+ - sparing	Spironolactone Amiloride	Collecting tubule

Structure of Classes of Diuretics



General Background of Diuretics

- Pattern of excretion of electrolytes (how much of which type) depends on class of diuretic agent
- Maximal response is limited by site of action
- Effect of two or more diuretics from different classes is additive or synergistic if there sites or mechanisms of action are different

Osmotic diuretics

- No interaction with transport systems
- All activity depends on osmotic pressure exerted in lumen
- Blocks water reabsorption in proximal tubule, descending loop, collecting duct
- Results in large water loss, smaller electrolyte loss → can result in hypernatremia

Carbonic anydrase inhibitors

- Block carbonic-anhydrase catalyzation of CO_2/ carbonic acid/carbonate equilibrium
- Useful for treating glaucoma and metabolic alkalosis but can cause hyperchloremic metabolic acidosis from HCO_3^- depletion

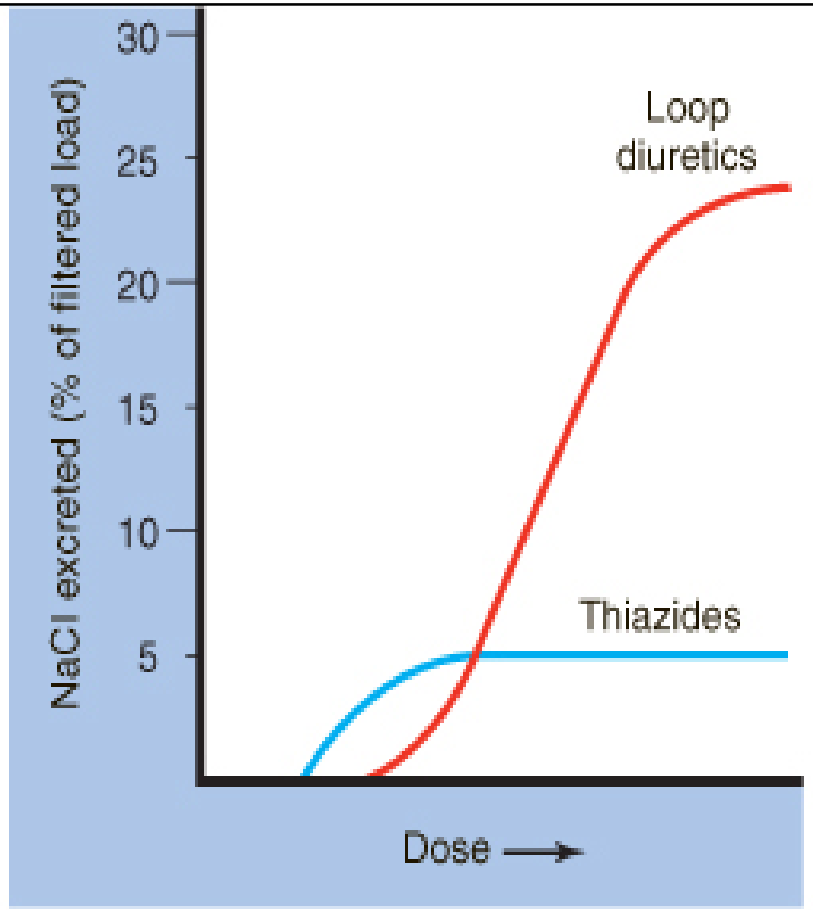
Loop diuretics

- Generally cause greater diuresis than thiazides; used when they are insuffficient
- Can enhance Ca^{2+} and Mg^{2+} excretion
- Enter tubular lumen via proximal tubular secretion (unusual secretion segment) because body treats them as a toxic drug
- Drugs that block this secretion (e.g. probenecid) reduces efficacy

Thiazide diuretics

- Developed to preferentially increase Cl^- excretion over HCO_3^- excretion (as from CAIs)
- Magnitude of effect is lower because work on distal convoluted tubule (only recieves 15% of filtrate)
- Cause decreased Ca excretion → hypercalcemia → reduce osteoporosis

Comparison of loop and thiazide diuretics



Potassium-sparing diuretics

- Have most downstream site of action (collecting tubule)
- Reduce K loss by inhibiting Na/K exchange
- Not a strong diuretic because action is furthest downstream
- Often used in combination with thiazide diuretics to restrict K loss