



INTRODUCTION

- **Diuretic** – agent that increases urine volume
- **Natriuretic** – agent that increases urinary sodium excretion
- **Aquaretic** – agent that increases excretion of solute free water

PRINCIPLES OF DIURETIC EFFECTS

- Interference with Na^+ reabsorption at one nephron site interferes with other renal functions linked to it
- Increased flow and Na^+ delivery to distal nephron stimulates K^+ (and H^+) secretion
- Diuretics act only if Na^+ reaches their site of action. The magnitude of the diuretic effect depends on the amount of Na^+ reaching that site
- Diuretic actions at different nephron sites can produce synergism

All, EXCEPT **spironolactone**, act from the luminal side of the tubular cellular membrane

RENAL TUBULE TRANSPORT MECHANISMS

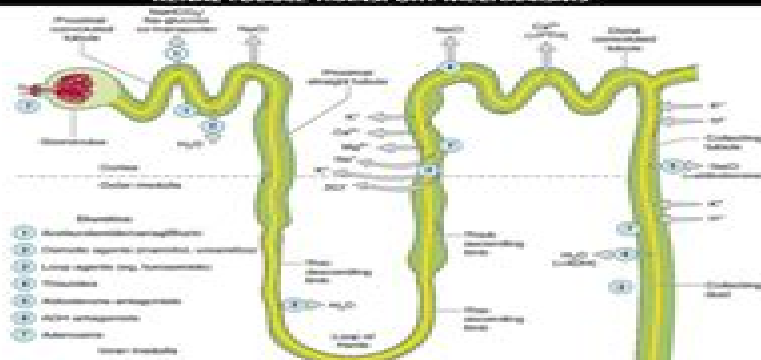


FIGURE 15-1 Tubule transport systems and sites of action of diuretics. ACE, angiotensin-converting enzyme; PTH, parathyroid hormone.

Proximal Convoluted Tubule

- Reabsorbs Na^+ (66%), NaHCO_3 (85%), K^+ (65%), glucose, amino acid & water (50%)
- Potassium reabsorbed via paracellular pathway
- Water reabsorbed passively maintaining osmolality in nearly constant level
- **Na^+/H^+ exchanger (NHE3)** – it initiates the reabsorption of NaHCO_3
- **Sodium-glucose cotransporter, isoform 2 (SGLT2)** – is responsible for reabsorbing much of the glucose that is filtered by the glomeruli
Inhibitors of SGLT2 have been approved to treat **diabetes mellitus**.
- **Carbonic anhydrase inhibitors** – blocks NaHCO_3 reabsorption
- **Adenosine receptor antagonist** – blocks NaCl reabsorption

Loop of Henle

- Pumps Na^+ , K^+ & Cl^- out of the lumen into the interstitium
- Provides the concentration gradient for the countercurrent concentrating mechanism
- **Thick ascending limb (TAL)** – it is the **diluting segment**

It follows the thin limb of Henle's loop, actively **reabsorbs NaCl** from the lumen (about 25% of the filtered sodium), but unlike the proximal tubule and the thin descending limb of Henle's loop, it is nearly **impermeable to water**

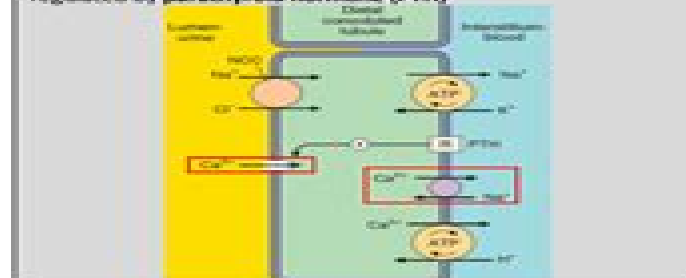
Salt reabsorption in the TAL therefore **DILUTES** the tubular fluid. Medullary portions of the TAL contribute to medullary hypertonicity and thereby also play an important role in concentration of urine by the collecting duct

- **$\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter** (called **NKCC2** or **NKCC1**) – is the NaCl transport system in the luminal membrane of the TAL
- Secondary reabsorption of Ca^{2+} and Mg^{2+} also happens here

Distal Convoluted Tubule

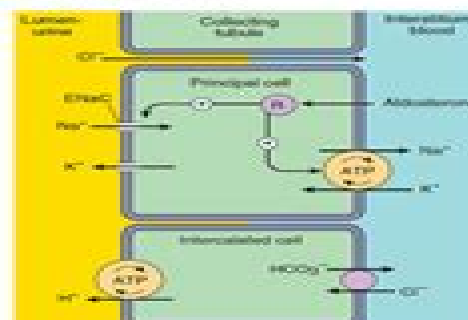
- Actively pumps Na^+ & Cl^- out of the lumen nephron
- 10% Na reabsorbed
- Impermeable to water
- NaCl reabsorption further dilutes the tubular fluid
- **Na^+/Cl^- cotransporter (NCC)** – is the NaCl transport in the DCT
- Ca^{2+} reabsorption

Ca^{2+} is actively reabsorbed by the DCT epithelial cell via an apical Ca^{2+} channel and basolateral $\text{Na}^+/\text{Ca}^{2+}$ exchanger. This is regulated by **parathyroid hormone (PTH)**



Collecting Tubule

- 2-5% NaCl reabsorption
- Final site of NaCl reabsorption
- Determines the final Na^+ concentration of the urine
- Tight regulator of body fluid volume
- Influenced by mineralocorticoids
- Important site of K^+ secretion



Principal Cells

- Major sites of Na^+ , K^+ , and water transport system
- Do not contain apical cotransport system for Na^+ and other ions
- Exhibits separate ion channels for Na^+ and K^+

Intercalated Cells (α & β)

- Primary sites of H^+ (α cells) or HCO_3^- (β cells) secretion



Renal Pharmacology

JS Bruner



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Table of Contents Renal Pharmacology

1. Understanding the eBook Renal Pharmacology
 - The Rise of Digital Reading Renal Pharmacology
 - Advantages of eBooks Over Traditional Books
2. Identifying Renal Pharmacology
 - Exploring Different Genres
 - Considering Fiction vs. Non-Fiction
 - Determining Your Reading Goals
3. Choosing the Right eBook Platform
 - Popular eBook Platforms
 - Features to Look for in an Renal Pharmacology
 - User-Friendly Interface
4. Exploring eBook Recommendations from Renal Pharmacology
 - Personalized Recommendations

- Renal Pharmacology User Reviews and Ratings
- Renal Pharmacology and Bestseller Lists
- 5. Accessing Renal Pharmacology Free and Paid eBooks
 - Renal Pharmacology Public Domain eBooks
 - Renal Pharmacology eBook Subscription Services
 - Renal Pharmacology Budget-Friendly Options
- 6. Navigating Renal Pharmacology eBook Formats
 - ePub, PDF, MOBI, and More
 - Renal Pharmacology Compatibility with Devices
 - Renal Pharmacology Enhanced eBook Features
- 7. Enhancing Your Reading Experience
 - Adjustable Fonts and Text Sizes of Renal Pharmacology
 - Highlighting and Note-Taking Renal Pharmacology
 - Interactive Elements Renal Pharmacology
- 8. Staying Engaged with Renal Pharmacology
 - Joining Online Reading Communities
 - Participating in Virtual Book Clubs
 - Following Authors and Publishers Renal Pharmacology
- 9. Balancing eBooks and Physical Books Renal Pharmacology
 - Benefits of a Digital Library
 - Creating a Diverse Reading Collection Renal Pharmacology
- 10. Overcoming Reading Challenges
 - Dealing with Digital Eye Strain
 - Minimizing Distractions
 - Managing Screen Time
- 11. Cultivating a Reading Routine Renal Pharmacology
 - Setting Reading Goals Renal Pharmacology
 - Carving Out Dedicated Reading Time
- 12. Sourcing Reliable Information of Renal Pharmacology
 - Fact-Checking eBook Content of Renal Pharmacology

- Distinguishing Credible Sources
- 13. Promoting Lifelong Learning
 - Utilizing eBooks for Skill Development
 - Exploring Educational eBooks
- 14. Embracing eBook Trends
 - Integration of Multimedia Elements
 - Interactive and Gamified eBooks

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