Disorders of Potassium Metabolism

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Potassium, the most abundant cation in the human body, regulates intracellular enzyme function and neuromuscular tissue excitability. Serum potassium is normally maintained within the narrow range of 3.5 to 5.5 mEq/L. The intracellular-extracellular potassium ratio (K_i/K_e) largely determines neuromuscular tissue excitability [1]. Because only a small portion of potassium is extracellular, neuromuscular tissue excitability is markedly affected by small changes in extracellular potassium. Thus, the body has developed elaborate regulatory mechanisms to maintain potassium homeostasis. Because dietary potassium intake is sporadic and it cannot be rapidly excreted renally, short-term potassium homeostasis occurs via transcellular potassium shifts [2]. Ultimately, long-term maintenance of potassium balance depends on renal excretion of ingested potassium. The illustrations in this chapter review normal transcellular potassium homeostasis as well as mechanisms of renal potassium excretion.

With an understanding of normal potassium balance, disorders of potassium metabolism can be grouped into those that are due to altered intake, altered excretion, and abnormal transcellular distribution. The diagnostic algorithms that follow allow the reader to limit the potential causes of hyperkalemia and hypokalemia and to reach a diagnosis as efficiently as possible. Finally, clinical manifestations of disorders of potassium metabolism are reviewed, and treatment algorithms for hypokalemia and hyperkalemia are offered.

Recently, the molecular defects responsible for a variety of diseases associated with disordered potassium metabolism have been discovered [3–8]. Hypokalemia and Liddle's syndrome [3] and hyperkalemia and pseudohypoaldosteronism type I [4] result from mutations at different sites on the epithelial sodium channel in the distal tubules. The hypokalemia of Bartter's syndrome can be accounted for by two separate ion transporter defects in the thick ascending limb of Henle's loop [5]. Gitelman's syndrome, a clinical variant of Bartter's

CHAPTER 3

syndrome, is caused by a mutation in an ion cotransporter in a completely different segment of the renal tubule [6]. The genetic mutations responsible for hypokalemia in the syndrome of apparent mineralocorticoid excess [7] and glucocorticoid-remediable aldosteronism [8] have recently been elucidated and are illustrated below.

Overview of Potassium Physiology

PHYSIOLOGY OF POTASSIUM BALANCE: DISTRIBUTION OF POTASSIUM

ECF 350 mEq (10%)	ICF 3150 mEq (90%)
Plasma 15 mEq (0.4%)	Muscle 2650 mEq (76%)
Interstitial fluid 35 mEq (1%)	Liver 250 mEq (7%)
Bone 300 mEq (8.6%)	Erythrocytes 250 mEq (7%)
$[K^+]$ = 3.5–5.0 mEq/L	$[K^+]$ = 140–150 mEq/L
Urine 90–95 mEq/d	Urine 90–95 mEq/d
Stool 5–10mEq/d	Stool 5–10mEq/d
Sweat < 5 mEq/d	Sweat < 5 mEq/d

FIGURE 3-1

External balance and distribution of potassium. The usual Western diet contains approximately 100 mEq of potassium per day. Under normal circumstances, renal excretion accounts for approximately 90% of daily potassium elimination, the remainder being excreted in stool and (a negligible amount) in sweat. About 90% of total body potassium is located in the intracellular fluid (ICF), the majority in muscle. Although the extracellular fluid (ECF) contains about 10% of total body potassium, less than 1% is located in the plasma [9]. Thus, disorders of potassium metabolism can be classified as those that are due 1) to altered intake, 2) to altered elimination, or 3) to deranged transcellular potassium shifts.

FACTORS CAUSING TRANSCELLULAR POTASSIUM SHIFTS

Factor	Δ Plasma K^+
Acid-base status	
Metabolic acidosis	
Hyperchloremic acidosis	↑↑
Organic acidosis	↔
Respiratory acidosis	↑
Metabolic alkalosis	↓
Respiratory alkalosis	↓
Pancreatic hormones	
Insulin	↓↓
Glucagon	↑
Catecholamines	
β-Adrenergic	↓
α-Adrenergic	↑
Hyperosmolarity	↑
Aldosterone	↓, ↔
Exercise	↑

FIGURE 3-2

Factors that cause transcellular potassium shifts.

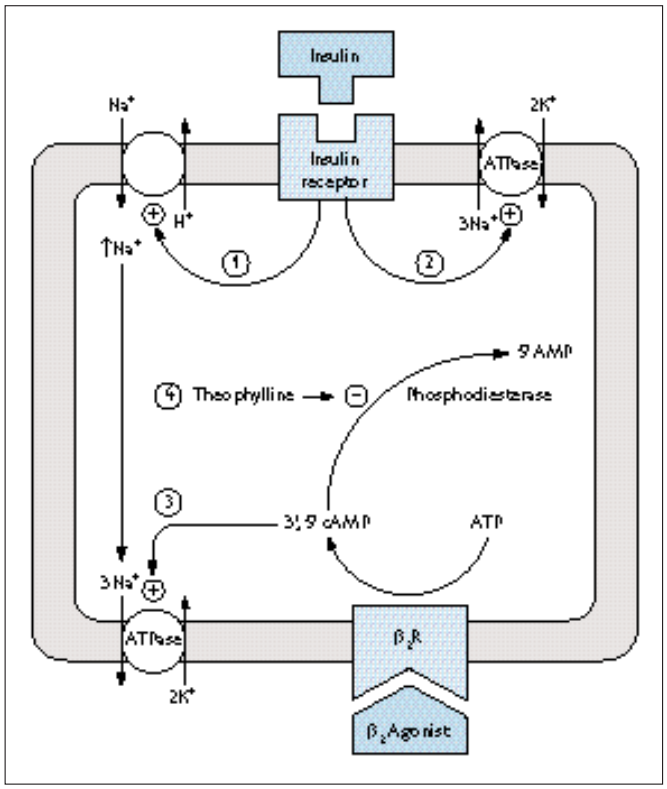

FIGURE 3-3

Extrarenal potassium homeostasis: insulin and catecholamines. Schematic representation of the cellular mechanisms by which insulin and β-adrenergic stimulation promote potassium uptake by extrarenal tissues. Insulin binding to its receptor results in hyperpolarization of cell membranes (1), which facilitates potassium uptake. After binding to its receptor, insulin also activates Na^+-K^+-ATPase pumps, resulting in cellular uptake of potassium (2). The second messenger that mediates this effect has not yet been identified. Catecholamines stimulate cellular potassium uptake via the β_2 adrenergic receptor (β_2R). The generation of cyclic adenosine monophosphate (3′, 5′ cAMP) activates Na^+-K^+-ATPase pumps (3), causing an influx of potassium in exchange for sodium [10]. By inhibiting the degradation of cyclic AMP, theophylline potentiates catecholamine-stimulated potassium uptake, resulting in hypokalemia (4).

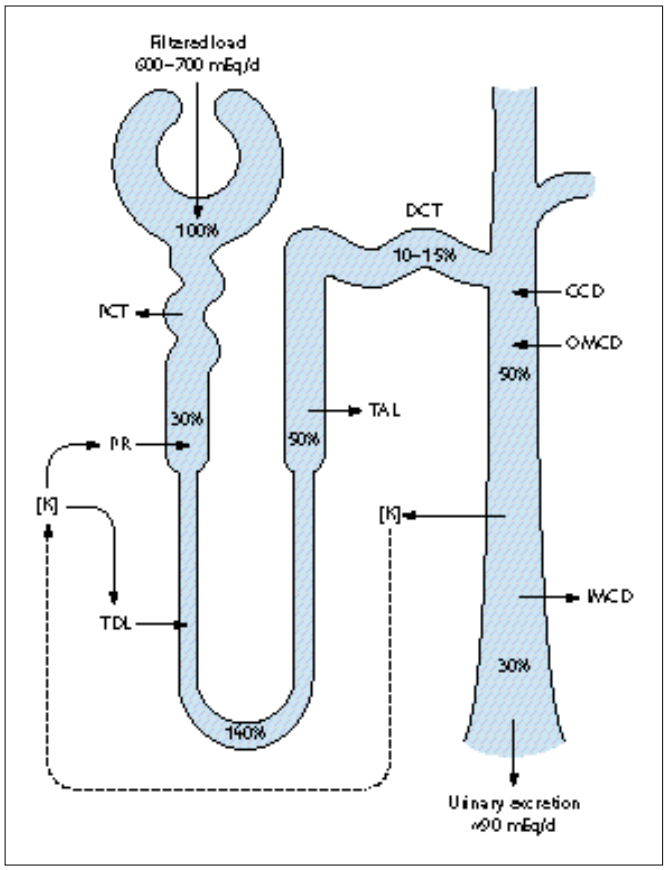

FIGURE 3-4

Renal potassium handling. More than half of filtered potassium is passively reabsorbed by the end of the proximal convolted tubule (PCT). Potassium is then added to tubular fluid in the descending limb of Henle's loop (see below). The major site of active potassium reabsorption is the thick ascending limb of the loop of Henle (TAL), so that, by the end of the distal convoluted tubule (DCT), only 10% to 15% of filtered potassium remains in the tubule lumen. Potassium is secreted mainly by the principal cells of the cortical collecting duct (CCD) and outer medullary collecting duct (OMCD). Potassium reabsorption occurs via the intercalated cells of the medullary collecting duct (MCD). Urinary potassium represents the difference between potassium secreted and potassium reabsorbed [11]. During states of total body potassium depletion, potassium reabsorption is enhanced. Reabsorbed potassium initially enters the medullary interstitium, but then it is secreted into the pars recta (PR) and descending limb of the loop of Henle (TDL). The physiologic role of medullary potassium recycling may be to minimize potassium "backleak" out of the collecting tubule lumen or to enhance renal potassium secretion during states of excess total body potassium [12]. The percentage of filtered potassium remaining in the tubule lumen is indicated in the corresponding nephron segment.