

FIGURE 3-11

Diagnostic approach to hypokalemia: hypokalemia due to renal losses with metabolic alkalosis. The urine chloride value is helpful in distinguishing the causes of hypokalemia. Diuretics are a common cause of hypokalemia; however, after discontinuing diuretics, urinary potassium and chloride may be appropriately low. Urine diuretic screens are warranted for patients suspected of surreptitious diuretic abuse. Vomiting results in chloride and sodium depletion, hyperaldosteronism, and renal potassium wasting. Posthypercapnic states are often associated with chloride depletion (from diuretics) and sodium avidity. If hypercapnia is corrected without replacing chloride, patients develop chloride-depletion alkalosis and hypokalemia.

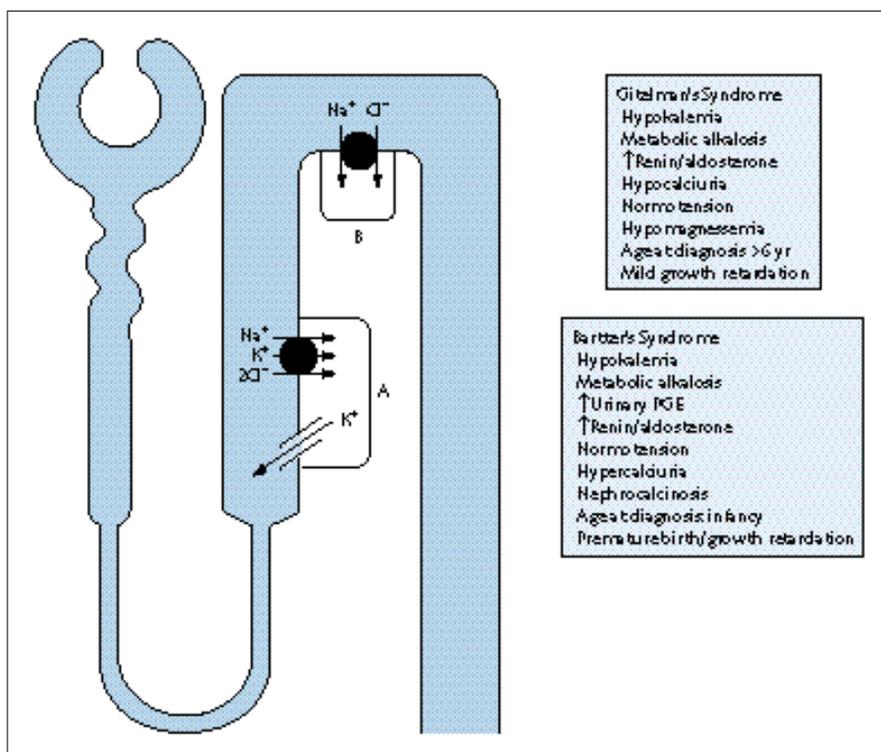


FIGURE 3-12

Mechanisms of hypokalemia in Bartter's syndrome and Gitelman's syndrome. **A**, A defective $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ cotransporter in the thick ascending limb (TAL) of Henle's loop can account for virtually all features of Bartter's syndrome. Since approximately 30% of filtered sodium is reabsorbed by this segment of the nephron, defective sodium reabsorption

results in salt wasting and elevated renin and aldosterone levels. The hyperaldosteronism and increased distal sodium delivery account for the characteristic hypokalemic metabolic alkalosis. Moreover, impaired sodium reabsorption in the TAL results in the hypercalciuria seen in these patients, as approximately 25% of filtered calcium is reabsorbed in this segment in a process coupled to sodium reabsorption. Since potassium levels in the TAL are much lower than levels of sodium or chloride, luminal potassium concentrations are rate limiting for $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ co-transporter activity. Defects in ATP-sensitive potassium channels would be predicted to alter potassium recycling and diminish $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ cotransporter activity. Recently, mutations in the gene that encodes for the $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ cotransporter and the ATP-sensitive potassium channel have been described in kindreds with Bartter's syndrome. Because loop diuretics interfere with the $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ cotransporter, surreptitious diuretic abusers have a clinical presentation that is virtually indistinguishable from that of Bartter's syndrome. **B**, Gitelman's syndrome, which typically presents later in life and is associated with hypomagnesemia and hypocalciuria, is due to a defect in the gene encoding for the thiazide-sensitive $\text{Na}^+\text{-Cl}^-$ cotransporter. The mild volume depletion results in more avid sodium and calcium reabsorption by the proximal nephrons.

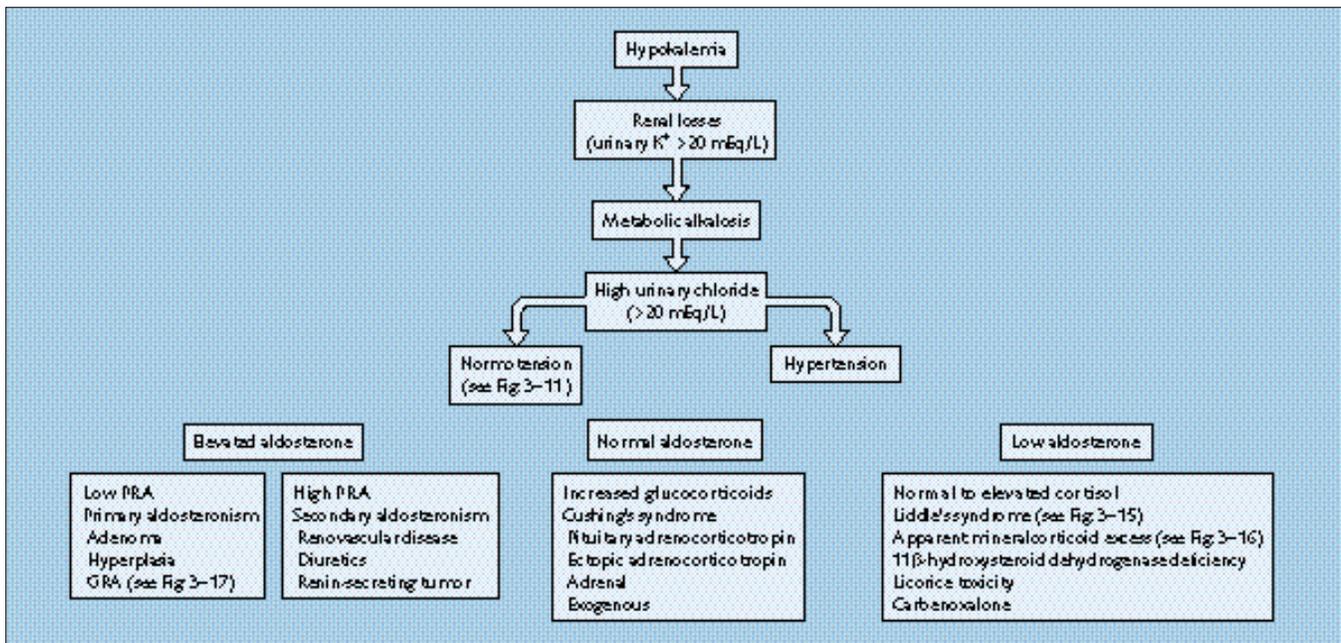


FIGURE 3-13

Diagnostic approach to hypokalemia: hypokalemia due to renal losses with hypertension and metabolic alkalosis.

CHARACTERISTICS OF HYPOKALEMIA WITH HYPERTENSION AND METABOLIC ALKALOSIS

| | Aldosterone | Renin | Response to Dexamethasone |
|--|-------------|-------|---------------------------|
| Primary aldosteronism | ↑ | ↓ | — |
| 11 β-hydroxysteroid dehydrogenase deficiency | ↓ | ↓ | + |
| Glucocorticoid remediable aldosteronism | ↑ | ↓ | + |
| Liddle's syndrome | ↓→ | ↓ | — |

FIGURE 3-14

Distinguishing characteristics of hypokalemia associated with hypertension and metabolic alkalosis.

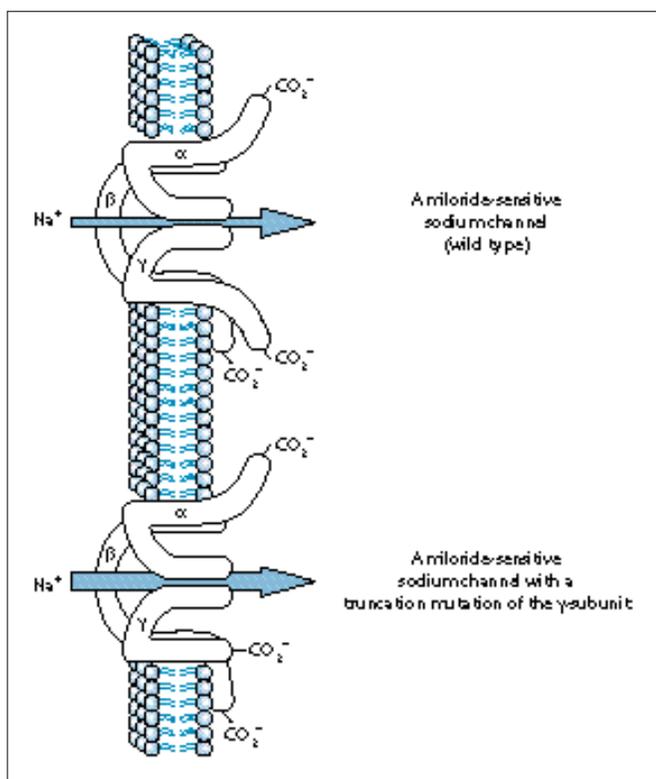


FIGURE 3-15

Mechanism of hypokalemia in Liddle's syndrome. The amiloride-sensitive sodium channel on the apical membrane of the distal tubule consists of homologous α , β , and γ subunits. Each subunit is composed of two transmembrane-spanning domains, an extracellular loop, and intracellular amino and carboxyl terminals. Truncation mutations of either the β or γ subunit carboxyl terminal result in greatly increased sodium conductance, which creates a favorable electrochemical gradient for potassium secretion. Although patients with Liddle's syndrome are not universally hypokalemic, they may exhibit severe potassium wasting with thiazide diuretics. The hypokalemia, hypertension, and metabolic alkalosis that typify Liddle's syndrome can be corrected with amiloride or triamterene or restriction of sodium.

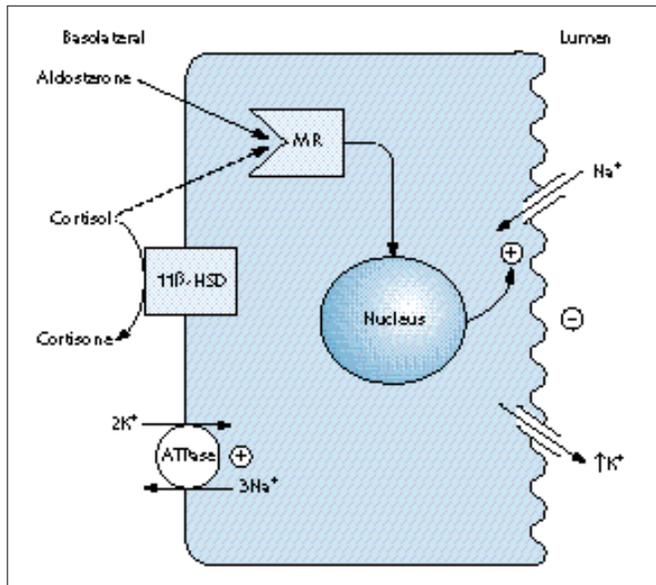


FIGURE 3-16

Mechanism of hypokalemia in the syndrome of apparent mineralocorticoid excess (AME). Cortisol and aldosterone have equal affinity for the intracellular mineralocorticoid receptor (MR); however, in aldosterone-sensitive tissues such as the kidney, the enzyme 11 β -hydroxysteroid dehydrogenase (11 β -HSD) converts cortisol to cortisone. Since cortisone has a low affinity for the MR, the enzyme 11 β -HSD serves to protect the kidney from the effects of glucocorticoids. In hereditary or acquired AME, 11 β -HSD is defective or is inactivated (by licorice or carbenoxalone). Cortisol, which is present at concentrations approximately 1000-fold that of aldosterone, becomes a mineralocorticoid. The hypermineralocorticoid state results in increased transcription of subunits of the sodium channel and the $\text{Na}^+\text{-K}^+\text{-ATPase}$ pump. The favorable electrochemical gradient then favors potassium secretion [7,15].