

Diminished uric acid excretion could theoretically result from decreased glomerular filtration, decreased tubular secretion, or enhanced tubular reabsorption. Decreased urate filtration does not appear to cause primary hyperuricemia but does contribute to the hyperuricemia of renal insufficiency. Although hyperuricemia is invariably present in chronic renal disease, the correlation among serum creatinine, urea nitrogen, and urate concentrations is poor. Extrarenal clearance of uric acid increases as renal damage becomes more severe.

Many agents that cause hyperuricemia exert their effects by stimulating reabsorption rather than inhibiting secretion. This stimulation appears to occur through a process of “priming” renal urate reabsorption through the sodium-dependent loading of proximal tubular epithelial cells with anions capable of *trans*-stimulating urate reabsorption. The sodium-coupled monocarboxyl transporters SMCT1 and 2 (SLC5A8, SLC5A12) in the brush border of the proximal tubular cells mediate sodium-dependent loading of these cells with monocarboxylates. A similar transporter, SLC13A3, mediates sodium-dependent influx of dicarboxylates into the epithelial cell from the basolateral membrane. Some of these carboxylates are well known to cause hyperuricemia, including pyrazinoate (from pyrazinamide treatment), nicotinate (from niacin therapy), and the organic acids lactate, β -hydroxybutyrate, and acetoacetate. The mono- and divalent anions then become substrates for URAT1 and OAT4, respectively, and are exchanged for uric acid from the proximal tubule. Increased blood levels of these anions result in their increased glomerular filtration and greater reabsorption by proximal tubular cells. The increased intraepithelial cell concentrations lead to increased uric acid reabsorption by promoting URAT1-, OAT4-, and OAT10-dependent anion exchange. Low doses of salicylates also promote hyperuricemia by this mechanism. Sodium loading of proximal tubular cells also provokes urate retention by reducing extracellular fluid volume and increasing angiotensin II, insulin, and parathyroid hormone release. Additional OAT1, OAT2, and OAT3 are involved in the movement of uric acid through the basolateral membrane, although the detailed mechanisms are still being elucidated.