transport of celiprolol in Caco-2 cells is five times greater than apical-to-basal and is inhibited by Pgp substrates, organic cations, and organic anions (152). These transport systems remain to be elucidated but may be similar to the transport systems responsible for the secretion of xenobiotics by the kidney.

6. RENAL TRANSPORT

6.1. Overview of Renal Excretion

The kidney comprises over 1 million nephrons, the functional unit of the organ. Each nephron executes the three distinct mechanisms of renal drug excretion: filtration, secretion, and reabsorption. Approximately 25% of blood flow perfusing the kidney (450–600 mL/min) is filtered at the glomerulus. The driving force for this process is hydrostatic pressure resulting in a glomerular filtration rate of ≈100 mL/min. However, filtration is restrictive to only unbound, low molecular weight compounds. In addition to filtration, transport systems are present in the proximal tubule of the nephron that secretes drug into the urine across the tubular cell. The transport systems exhibit broad substrate specificity and, consequently, represent a potential site of clinically significant drug interactions. While filtration and secretion serve to excrete drug into the urine, the homeostatic function of the kidney can result in significant reabsorption of drug from the urine into the body. Tubular reabsorption is thought to be primarily a passive process, the extent of reabsorption being both urine flow rate and urine pH dependent. However, active transport systems also exist for the reabsorption of endogenous (e.g., glucose) and exogenous compounds. The transport systems involved in renal drug excretion are discussed in what follows. A number of excellent reviews of renal transport of acids and bases can be found in the literature (26–33).

6.2. Organic Cation Transport

Organic cations are transported by the proximal tubule via a multistep process, as depicted in Fig. 5. Consistent with other organ systems, the kidney efficiently secretes a wide range of positively charged medications and their metabolites. Uptake from the blood into the tubular cell proceeds by facilitated diffusion, the driving force being the electrochemical gradient across the basolateral membrane (inside negative potential difference). At least two distinct organic cation transporters have been identified on the basolateral membrane, OCT1 and OCT2 (153,154).

Once inside the tubular cell, intracellular sequestration can result in extensive drug accumulation. In addition to binding cytosolic proteins, organic cations can also accumulate in vesicular compartments (e.g., endosomes and lysosomes). The acidic pH of these organelles can