toxicity. Furthermore, modulation of these transport systems can elicit changes in distribution, clearance, and bioavailability and, consequently, drug activity.

In this chapter, the membrane transporters that are involved in drug disposition will be presented. The impact of membrane transport on pharmacokinetics and drug activity will be discussed for individual organ systems (e.g., hepatobiliary, GI, kidney, CNS). A comparison of the experimental techniques used to study drug transport will also be provided. Finally, the implications of this topic for preclinical drug development will be summarized.

2. OVERVIEW OF MEMBRANE TRANSPORTERS

Table 1 summarizes the transporters that have been identified in the four major organ systems and will be discussed in this chapter (liver, kidney, intestine, CNS). Although Heidenhain (46) first proposed the phenomenon of drug transport in 1870, identification and characterization of membrane transporters have only evolved over the past 25 years (and continue to evolve). A general overview of each of these transport "families" is given in what follows. The role of these transporters in specific organs is described later in this chapter.

2.1. ATP-Binding Cassette Transporters

Mammalian cells possess membrane proteins that catalyze drug transport and enable cells to overcome toxicity by limiting intracellular drug concentrations. Multidrug resistance (MDR), a major challenge for cancer chemotherapy, is defined as when cells develop resistance to a broad range of structurally and functionally unrelated compounds. This resistance is generally produced upon exposure to a single substance (47). In 1976, Juliano and Ling (48) identified a plasma membrane protein that was overexpressed in colchicine-resistant tumor cells. This protein was called P-glycoprotein (Pgp). Today, Pgp is known to have a wide tissue distribution in the body (14,15,49,50).

P-glycoprotein belongs to a family of membrane transporters known as the ATP-binding cassette (ABC) superfamily (51). Comprehensive reviews of the ABC superfamily are provided in the literature (12). Two members of the ABC transporter family have been associated with MDR in human cancer cells: Pgp (MDR) and multidrug resistance-associated proteins (MRPs) (52). Two Pgp proteins have been identified in humans (MDR1 and MDR3) and three Pgps have been identified in mice (mdr1a, mdr1b, and mdr2). MDR1, mdr1a, and mdr1b are known to confer MDR (3). Although the mechanism is not completely known, these proteins presumably function as "hydrophobic vacuum cleaners," efficiently