

Role of Bioactivation Reactions in Chemically Induced Nephrotoxicity

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1 OVERVIEW OF RENAL STRUCTURE AND FUNCTION: TOXICOLOGICAL IMPLICATIONS

The kidneys are uniquely sensitive to toxicants because they receive and filter a large quantity of blood relative to their weight. On average, the two kidneys receive 25% of the cardiac output, while comprising only about 1% of total body weight. This fact, along with the presence of a myriad of plasma membrane transport proteins, which can result in a high degree of accumulation and concentration of chemicals within the tubular epithelial cells, and drug metabolism enzymes that can result in bioactivation of inert or nontoxic chemicals, contribute to the susceptibility of the kidneys. The major function of the kidneys is to excrete waste products while maintaining total body electrolytes, water, and acid–base balance. Thus, the kidneys are the primary organs responsible for maintaining the constancy of the internal environment. They accomplish this task by three general mechanisms: (i) glomerular filtration, (ii) tubular reabsorption, and (iii) tubular secretion. Although the focus of this chapter is on the role of metabolism in chemically induced nephrotoxicity, it is important to appreciate the role that normal renal physiology plays in the intoxication process.

The mammalian kidney is a complex organ that possesses structural divisions at both the whole organ level and the level of the nephron, which is the basic functional unit of the kidney. A detailed consideration of renal physiology and morphology is beyond the scope of this chapter. However, some key points will be made as they critically impact renal handling of drugs and patterns of chemically induced injury that are observed. Interested readers are referred to a variety of reviews and other publications that discuss renal physiology and nephron structure in greater depth (e.g. Horster, 1978; Jacobson, 1981; Walker and Valtin, 1982; Guder and Ross, 1984; Brenner, 1996; Guder, Wagner and Wirthensohn, 1986; Sands and Verlander, 2005).

At the whole organ level, the kidney is subdivided into cortex and medulla, with the latter being further divided into outer and inner stripes of the outer medulla and inner medulla or papilla. Each of these zones is comprised of distinctive cell types and