Role of Renal Metabolism in Risk to Toxic Chemicals

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The kidneys are capable of carrying out extensive oxidation, reduction, hydrolysis, and conjugation reactions. Renal cortex has high activities of cytochrome P450 and glutathione (GSH) S-transferase. In contrast, renal medulla has high activity of prostaglandin synthetase, which can catalyze co-oxidation of xenobiotics. While these pathways are found in many tissues and at higher activities than in kidney, several key enzymes of the mercapturic acid pathway are found at especially high activities in cells of the renal proximal tubule. Investigations over the last two decades demonstrated that GSH conjugation is not only a mechanism for detoxification of reactive electrophiles. Rather, metabolism of GSH S-conjugates to the corresponding cysteine S-conjugates represents a branch point: cysteine S-conjugates may be metabolized by the cysteine S-conjugate N-acetyltransferase to mercapturic acids, which are nontoxic and are excreted, or they may be substrates for the pyridoxal phosphate-dependent cysteine conjugate β-lyase, which catalyzes either a β-elimination or a transamination reaction to produce unstable thiols. These thiols rearrange to form potent acylating species that can covalently bind to cellular macromolecules, thereby producing cytotoxicity, mutagenicity, and carcinogenicity. In addition to the β-lyase, two other renal enzymes, L-2- amino (2-hydroxy) acid oxidase and cysteine conjugate S-oxidase, can bioactivate chemicals to produce nephrotoxic species. Several halogenated alkanes and alkenes are bioactivated by these pathways. These findings show that mammalian kidney is highly active in bioactivation of xenobiotics. Although the properties of the corresponding enzymes in humans may differ, it is clear that renal metabolism can be a critical determinant of risk to chemical injury. — Environ Health Perspect 102(Suppl 1):75–79 (1994)

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Introduction

The traditional view of renal function is that the kidneys act as filters to remove toxic waste products from the blood via glomerular filtration. Reabsorption and secretion processes on plasma membranes of the epithelial cells allow useful metabolites and electrolytes to be conserved and waste products to be excreted. In addition to these basic functions, the kidneys are also active metabolically, particularly with respect to drug metabolism. One factor that complicates study of renal drug metabolism is nephron heterogeneity, which is expressed as differences in metabolism, transport, morphology, and physiologic function in the various cell populations. While the liver has been the focus of most drug metabolism studies and is quantitatively the most important site of metabolism for most xenobiotics, the kidneys are also capable of carrying out extensive oxidation, reduction, hydrolysis, and conjugation reactions (1,2). Enzyme systems similar to those present in liver and other extrarenal tissues are involved in renal drug metabolism (Table 1). An important difference between the kidney and other tissues, however, is that many of the drug metabolism enzyme systems are differentially distributed among the nephron cell populations (3–5). For example, cytochrome P450 is found exclusively in renal cortex, and prostaglandin synthetase, which catalyzes co-oxidation of several drugs and xenobiotics, is found in the medulla. As a consequence of this heterogeneity, a given metabolic pathway may be undetectable or detectable at very low activities in whole kidney homogenates but may be observable at significant rates when specific nephron cell types are employed as a biological source. Thus, renal metabolism of many chemicals is localized to specific cell types. Although other tissues also exhibit heterogeneity, few do so to the same extent as the kidneys.

Table 1. Drug metabolism enzymes in kidney.

| Phase I enzymes                      | Phase II enzymes                      | Ancillary enzymes               |
|--------------------------------------|---------------------------------------|---------------------------------|
| Cytochrome P450                       | Esterases                             | GSH peroxidase                  |
| Microsomal FAD-containing monoxygenase| N-Acetyltransferase                   | Catalase                        |
| Alcohol and aldehyde dehydrogenases  | GSH S-transferase                     | NADPH:Quinone oxidoreductase    |
| Epoxide hydrolase                     | Thiol S-methyltransferase             | NADPH-generating pathways       |
| Prostaglandin synthetase             | UDP-Glucuronosyltransferases          | Superoxide dismutase            |
| Monoamine oxidase                    | Sulfoxyltransferases                  | GSSG reductase                  |

Abbreviations: FAD, flavin adenine dinucleotide; GSH, reduced glutathione; GSSG, glutathione disulfide; UDP, uridine 5'-diphosphate; NADPH, reduced nicotinamide adenine dinucleotide phosphate.

Table 2. Factors contributing to nephrotoxicity.

1. High renal blood flow. Kidneys comprise 1% of total body weight but receive 25% of cardiac output.
2. Concentration of chemicals in intraluminal fluid.
3. Reabsorption, secretion, or both of chemicals through tubular cells.
4. Biotransformation of protoxicants to reactive intermediates.
5. Proximal tubules as specific targets: membrane (brush-border, basal-lateral) transport systems, high content of bioactivation enzymes.
6. Medullary thick ascending limb: poor oxygenation of medulla, susceptibility to hypoxic injury.

From the brief discussion above, it should be apparent that the kidneys can metabolize drugs efficiently. In many cases, metabolism yields a product that is more toxic than the parent compound. Because of this bioactivation and because of several other factors (Table 2), the kidneys are often target organs for many toxic chemicals. This
target organ specificity can be attributed to the basic characteristics of renal physiology such as high blood flow, glomerular filtration, and a large array of membrane transport systems for organic molecules. Nephron heterogeneity also comes into play because the various cell populations are differentially susceptible to chemical and pathological injury (6).

Renal drug metabolism pathways and their role in bioactivation have been reviewed by several groups during the last decade (1,2,7–12). The primary focus of this article will be to consider pathways of renal metabolism, particularly the glutathione (GSH) conjugation pathway, that contribute to xenobiotic toxicity and are thus important factors in risk assessment. Metabolism of GSH S-conjugates of numerous halogenated hydrocarbons to cysteine S-conjugates provides a branch point in the pathway. Several alternative routes that generate toxic metabolites are available. Understanding how these different pathways are integrated and regulated is critical to understanding what role renal metabolism can play in risk assessment.

**Glutathione-dependent Activation of Xenobiotics**

The mercapturic acid pathway illustrates several principles that are critical to understanding how renal metabolism plays a role in risk to chemical injury (13,14). Metabolism of GSH and of GSH S-conjugates is a complex process involving the sequential action of several enzymes localized in various tissues (Figure 1). The pattern of this interorgan pathway is determined primarily by the selective tissue distribution of membrane transport proteins and of the enzymes catalyzing the pathway. Although most mammalian tissues have GSH S-transferase activity, the liver has the highest levels in the body and is quantitatively the most important site of GSH conjugate formation (15). In rats, rabbits, and mice, hepatocytes contain minimal activities of γ-glutamyl transferase, which is the only enzyme that can hydrolyze the γ-glutamyl peptide bond of GSH and GSH S-conjugates (15). Liver cells actively extrude GSH and GSH S-conjugates into plasma and bile for translocation to kidney and small intestine, respectively. The GSH S-conjugates that are secreted into bile are degraded to cysteine S-conjugates by γ-glutamyl transferase and dipeptidases, which are present at relatively high levels in biliary epithelium (16). Metabolites from the small intestinal epithelium are returned to the liver via the portal vein (enterohepatic circulation). Ultimately, metabolites that are primarily in the form of either cysteine or N-acetylcysteine S-conjugates (although some GSH S-conjugates are also present) are delivered via the circulation to the kidneys. The presence of glomerular filtration and active transport systems on both brush-border and basolateral plasma membranes produces high intracellular concentrations of these conjugates (17–21).

Once inside the renal epithelial cell, the ultimate toxic metabolite is generated. The prevailing view, therefore, is that GSH conjugation occurs in the liver but the reactions that are critical to generation of toxicity occur within the target organ. A study by Koob and Dekant (22), however, suggests that intrarenal formation of the GSH S-conjugate of hexafluoropropene is directly associated with nephrotoxicity and that the GSH S-conjugate formed in the liver is excreted in the bile and does not reach the kidneys and, therefore, does not cause nephrotoxicity. This finding suggests that the exact pattern of interorgan metabolism may vary, possibly depending on the chemical properties of the particular chemical. In any case, however, the ultimate toxic metabolite must be generated by intrarenal metabolism.

After the GSH S-conjugate is metabolized to the corresponding cysteine S-conjugate, either extrarenally or intrarenally, several alternative reactions are possible (Figure 2). The cysteine S-conjugate may be N-acetylated to form the mercapturic acid. Mercapturates generally are highly polar, chemically stable, and excreted. However, most mammalian cells, including renal cells, have deacetylase activities that can regenerate the cysteine S-conjugate. For many compounds, the cysteine

![Figure 1](image-url) Interorgan processing of GSH S-conjugates. Scheme showing the interaction of metabolic pathways in lung, liver, intestine, and kidney in overall processing of chemicals (RX) by GSH conjugation. Arrows with underlined compartments (i.e., bile, plasma, etc.) indicate the route by which metabolites are translocated between organs. Abbreviations: RX, parent compound; RSG, GSH S-conjugate; RSCys, cysteine S-conjugate; RSNAcCys, N-acetylcysteine S-conjugate (= mercapturic acid); RS⁻, reactive thiolate anion generated in kidney that produces nephrotoxicity; RSCH₃, trimethyl derivative.
**Figure 2.** Pathways of GSH S-conjugate metabolism. Scheme showing the mercapturic acid pathway and the alternative reactions possible for glutathione S-conjugates and cysteine S-conjugates. Abbreviations: RX, parent compound; HX, leaving group; RSG, GSH S-conjugate; RSCys, cysteine S-conjugate; RSCysNac, N-acetylcysteine S-conjugate (mercapturate); GSTase, glutathione S-transferase; GTase, γ-glutamyltranspeptidase; DPase, dipeptidase; NAcTase, cysteine S-conjugate N-acetyltransferase; DeAcase, deacetylase; β-Lyase, S-oxidase, HAO, cysteine conjugate β-lyase; S-oxidase, cysteine conjugate S-oxidase, HAO, l-2-hydroxy (2-amino) acid oxidase.

*S*-conjugate is a substrate for renal enzymes generating reactive metabolites that produce toxicity. The localization of transport systems that deliver the conjugates to kidney cells and the presence of enzymes that act on these conjugates within those cells determines the target site specificity of injury. It should be noted, however, that some GSH or cysteine S-conjugates do not require further metabolism to exert toxicity. Rather, these conjugates are chemically unstable and form reactive episulfonium ions that can bind covalently to cellular macromolecules and produce toxicity (23). 1,2-Dihaloethanes produce nephrotoxicity and nephrocarcinogenicity by this mechanism. Although both the GSH and the cysteine S-conjugate can alkylate cellular macromolecules (24), it is not known which conjugate is 1,2-dichloroethane's primary alkylating agent in vivo.

**Cysteine Conjugate β-Lyase-dependent Bioactivation**

Several haloalkyl or haloalkenyl cysteine S-conjugates are substrates for a pyridoxal phosphate-dependent enzyme found in renal cytosol and mitochondria. This enzyme cleaves the carbon–sulfur bond, thereby generating a reactive, sulfur-containing compound (25–27). All the conjugates that are substrates have the common chemical property of possessing a good leaving group on the β-carbon atom, hence the name β-lyase. Cytosolic β-lyase has been purified to homogeneity from rat kidney (28), from bovine kidney (29), and from human kidney (30).

The renal cystolic enzyme is identical to glutamine transaminase K (28). This suggests that the β-lyase, in addition to catalyzing a β-elimination reaction (Figure 3, reaction 1a), might also catalyze a transamination reaction (Figure 3, reaction 1b) to generate the corresponding 2-keto acid (31,32). This hypothesis was correct. Additionally, the observation that an addition of exogenous 2-keto acids both stimulated the β-lyase activity and potentiated the cytotoxicity of S-(1,2-dichlorovinyl)-L-cysteine (DCVC) in isolated rat kidney cells indicated that the keto acid/amino acid status could have a regulatory function (31). Detailed studies with renal subcellular fractions (31) and with purified β-lyases (28–30) showed that the pyridoxal phosphate moiety on the enzyme can get trapped in the pyridoxamine phosphate form in the absence of a keto acid acceptor. The best keto acid acceptors are those with relatively hydrophobic substituents on the β-carbon such as 2-keto-4-methylbutyrate, phenylpyruvate, and 2-keto octanoate (28,31). In either the case of β-elimination or transamination, the ultimate toxic metabolite is the same, as the keto acid analogue is chemically unstable and spontaneously releases the reactive thiolate.

Although the kidney is the target organ, β-lyase activity is also present in liver, where it is a catalytic property of kynureninase (32). A significant amount of β-lyase activity is also present in the intestinal microflora (33). This emphasizes that other factors besides the presence of the β-lyase in kidney cells are necessary to determine the tissue and cell type specificity of cysteine S-conjugate toxicity. As discussed above, membrane transport processes and the presence of detoxification pathways are two other important factors in susceptibility to injury.

β-Lyase activity is also present in renal mitochondria (25–27). The function and regulation of the mitochondrial activity is more complex than that of the cytosolic form, as there appears to be at least two mitochondrial β-lyases, one on the outer membrane (26) and one in the matrix compartment that is identical with matrix glutamine transaminase K (34). There is some evidence suggesting that the multiple β-lyases have different substrate specificities toward both cysteine S-conjugates and 2-keto acids (31,34).
Abbreviations:
- flavin mononucleotide (FMN),
- conjugates, and
- molecular oxygen.

Figure 4. Renal metabolism of cysteine S-conjugates by L-2-hydroxy (2-amino) acid oxidase (HAO). Reactions: 1, HAO; 2, retro-Michael reaction. Abbreviations: R, haloalkyl or haloalkenyl group; E-FMN, flavin mononucleotide form of HAO.

Alternative Bioactivation Enzymes for Cysteine S-Conjugates

Rat kidney cytosol and peroxisomes contain an L-2-hydroxy (2-amino) acid oxidase (HAO) that can also metabolize cysteine S-conjugates (Figure 4). The HAO contains flavin mononucleotide as a cofactor and catalyzes the oxidation of L-2-amino acids and L-2-hydroxy acids to the corresponding iminium ions and 2-oxo acids, respectively, with concomitant reduction of molecular oxygen to hydrogen peroxide (35). In mammalian species besides the rat, the enzyme acts strictly on L-2-hydroxy acids. This pathway, which has been demonstrated to function in the bioactivation and cytotoxicity of several cysteine S-conjugates and analogues in isolated rat kidney cells (36) and with purified β-lyase (28), may only be of relevance to studies in the rat because humans lack the activity.

Sausen and Elfarra (37) have recently described an additional enzyme, a cysteine conjugate S-oxidase, that metabolizes cysteine S-conjugates to the corresponding sulfoxides (Figure 5, reaction 1). The sulfoxide can rearrange and, via a retro-Michael reaction (Figure 5, reaction 2), produce a sulfenic acid that can covalently bind to cellular macromolecules. The enzyme activity is dependent on reduced nicotinamide adenine dinucleotide phosphate and oxygen, and contains a flavin cofactor. Differences in tissue distribution, substrate specificity, and other biochemical properties suggest that the S-oxidase is distinct from the microsomal flavin-containing monooxygenase.

Although sulfoxidation may be a major pathway for generation of terminal oxidation products of cysteine S-conjugates in vivo, the sulfoxide of DCVC is a potent nephrotoxin (38) and is highly reactive toward nucleophiles such as GSH (39). The quantitative importance of this pathway in cysteine S-conjugate nephrotoxicity is unknown at present.

Figure 5. Renal metabolism of cysteine S-conjugates by cysteine S-oxidase. Reactions: 1, cysteine S-oxidase; 2, retro-Michael reaction. Abbreviation: R, haloalkyl or haloalkenyl group.

Figure 6. Strategies for elucidation of renal bioactivation and nephrotoxicity mechanisms. Scheme showing processes whose roles in the nephrotoxicity of reduced glutathione and cysteine S-conjugates have been studied. Abbreviations: RS-G, GSH S-conjugate; RS-C, cysteine S-conjugate; RSNAcC, mercapturate; RSMeC, methylcysteine S-conjugate; GlyGly, glycylglycine; PhenGly, L-phenylalanyl-L-glutamate; GGTase, γ-glutamyltransferase; HAO, L-2-hydroxy (2-amino) acid oxidase.

Strategies for Demonstration of Role of Bioactivation Pathways in Nephrotoxicity

To demonstrate the requirement for the bioactivation reactions described above, particularly the β-lyase, the strategy has been to imply specific enzyme inhibitors, cosubstrates, and nonmetabolizable analogues and then examine effects on toxicity, both in vivo and in vitro (Figure 6). The dependence of membrane transport via the probenecid-sensitive organic anion transport system has been shown by the ability of probenecid to prevent or diminish toxicity. Specific inhibitors of γ-glutamyltransferase (i.e., acivicin), of the dipeptidase (i.e., 1,10-phenanthroline or phenylalanine glycinic), the β-lyase (i.e., aminooxyacetic acid), of HAO (i.e., hydroxybutynoate), and the S-oxidase (i.e., methimazole) have shown a direct dependence of generation of a reactive metabolite and consequent nephrotoxicity in vivo, cytotoxicity in vitro, or nephrocarcinogenicity on these reaction processes. It is clear, then, that with the exception of those S-conjugates that form reactive episulfonium ions, other nephrotoxic cysteine S-conjugates must be metabolized to produce toxicity.

Conclusions

The concept of metabolism as a means by which many chemicals are biotransformed to reactive and toxic species is critical for an understanding of most types of chemical-induced nephrotoxicity. Mammalian kidney possesses numerous enzymatic reactions that can bioactivate chemicals. Several bioactivation and detoxification pathways are present simultaneously and compete for the same substrates. An important consideration is species differences. While not as much information is available about drug metabolism in human tissues, many of the principles discovered in experimental animals are applicable. Care must be used in extrapolating data from animals to humans when assessing risk.

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