THE SMALL INTESTINE AS A XENOBIOTIC-METABOLIZING ORGAN

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The mammalian small intestine serves principally as the site for absorption of nutrients, water, and both beneficial and potentially harmful xenobiotics. However, it has become apparent over the past 20 years, and most notably during the past 10 years, that an array of metabolic machinery is also expressed in this organ (Kaminsky and Fasco, 1992; Lin et al., 1999; Doherty and Charman, 2002; Ding and Kaminsky, 2003). Both phase I and phase II metabolic enzymes are expressed, together with associated transporters. In this minireview we discuss some of the most prominent phase I and II enzymes in the metabolic systems in the small intestine. The transporters, despite their importance for the fate of enterocyte- absorbed xenobiotics, are beyond the scope of this minireview (Suzuki and Sugiyama, 2000).

The morphology of the small intestine plays a major role in this organ’s metabolic competency, with several anatomic and physiologic features contributing. Among these are: the considerable length of the small intestine (7 m in humans and 90 cm in the rat) (Iatropoulos, 1986) divided proximally to distally into the duodenum, jejunum, and ileum; the distribution of the metabolically competent epithelium as a monolayer of enterocytes; and the amplification of the luminal surface of the small intestine by numerous finger-like projections of enterocyte-lined villi and, at their bases, buried crypts. Together these features provide an expansive surface for xenobiotic absorption, with enterocyte-lined villi and, at their bases, buried crypts. Together these features provide an expansive surface for xenobiotic absorption, with a consequent substantial potential for first-pass metabolism. Enterocytes have a very limited life span; after the division of stem cells in the crypt base, migration up to the crypt surface in humans takes 4 days and in rodents, 3 days. The cells then migrate to the villous tip, where they are sloughed off and excreted, a passage of 3 days in humans and 2 days in rodents (Iatropoulos, 1986). The shortness of the enterocyte life span diminishes the potential of metabolic enzyme-inducing agents in the small intestine to produce increased metabolic rates in the enterocytes for an extended length of time. Additionally, any lesions produced by covalent binding of bioactivated xenobiotics to enterocyte macromolecules will be short-lived, as a consequence of the sloughing off and excretion of the affected enterocytes.

Hypotheses that the small intestine plays an important role in first-pass metabolism of orally ingested xenobiotics are supported by the expression of numerous metabolic enzymes in the organ, the positioning of the small intestine as the first site of exposure of xenobiotics to metabolic systems, and the large surface area available in the small intestine for absorption of the xenobiotics. However, in humans, assessments of the relative contributions of the liver and small intestine to first-pass metabolism of xenobiotics have been difficult to make. It has been suggested that a deeper understanding must await the successful development of methods to decouple hepatic and small intestinal first-pass metabolism (Doherty and Charman, 2002). Two recent reviews have focused on the relative importance of the small intestine and the liver for first-pass metabolism (Lin et al., 1999; Doherty and Charman, 2002). The authors suggested that the greater overall weight of the human liver (~1.5 kg) relative to that of the small intestine (~0.7 kg), which when combined with the P4501 concentrations and the microsomal protein contents provide for a greater overall metabolic capacity for the liver, and the potential of absorbed systemic xenobiotics to undergo countercurrent exchange (diffusion from intestinal villous arterioles to venules without access to the enterocytes), would strongly favor the liver (Lin et al., 1999). The possibly greater role of the liver than the small intestine in first-pass metabolism does not, however, detract from the capability of the small intestine to directly metabolize orally ingested xenobiotics prior to systemic uptake, and thus to block uptake.

A reoccurring theme from studies of human small intestinal xenobiotic metabolism is the interindividual variability in expression of phase I and II metabolic enzymes, frequently in marked excess of the variability of the same enzymes in the liver (Paine et al., 1997; Strassburg et al., 2000). Although known polymorphisms in the coding and noncoding regions of the relevant genes could account for some of the variability in enzyme activity and expression, this is unlikely to differentially affect the small intestine and liver. The mechanisms for the small intestinal variability in expression are not known. A possible contributor could reside in the genetics of the villous columnar enterocytes. The enterocytes are derived from multipotent stem cells that reside in the crypts. The enterocytes, which form columns on each villus, can be derived from more than one crypt stem cell, each with differing levels of expression of a particular gene (Wong et al., 2000). The possibility of this being a factor in interindividual variability in small intestinal metabolic enzyme expression awaits further study. Another possibility is that the intestinal P450s have been differentially induced in different individuals by dietary and environmental factors. CYP3A4 has, in fact, been demonstrated to be induced in human small intestine by rifampicin (Kolars et al., 1992).

1 Abbreviations used are: P450, cytochrome P450; RT-PCR, reverse transcriptase-polymerase chain reaction; BNF, β-naphthoflavone; PB, phenobarbital; PCN, pregnenolone 16α-carbonitrile; DEX, dexamethasone; Ah, aryl hydrocarbon; BAP, benzo[a]pyrene; GST, glutathione S-transferase; UGT, UDP-glucuronosyltransferase.
Phase I Metabolism

The preeminent phase I metabolic enzymes are the P450 superfamily, with the CYP1, 2, and 3 families being the major contributors to xenobiotic metabolism (Anzenbacher and Anzenbacherová, 2001). This discussion will be confined to the P450s. In the small intestine, the expressed P450s could have a protective function by blocking the systemic uptake of xenobiota.

Human Small Intestine P450 Expression

Early studies on human small intestine P450 expression identified CYP3A as the predominant subfamily in the enterocytes (Watkins et al., 1987; Peters and Kremers, 1989; de Waziers et al., 1990). These and other studies are probably limited in their capacity to detect the full complement of P450 expression because of the inability, in contrast to rodent studies, to obtain samples exposed to inducing agents, and the limited life span of the enterocytes in vivo. Despite the previously discussed probability that hepatic first-pass metabolic capacity exceeds that of the small intestine in humans, the ability of small intestinal metabolism to block systemic uptake of orally ingested xenobiota remains an important role. The best evidence of a role for small intestinal metabolism of xenobiota is available for CYP3A4, which contributes substantially to the first-pass metabolism of high-turnover CYP3A4 substrate drugs (Paine et al., 1996).

The most extensive characterization of human small intestinal P450 expression was conducted recently, using enterocytes eluted from small intestines from 10 individuals by an EDTA-containing buffer. This method of enterocyte preparation produces only villous enterocytes, without crypt cell contamination (Zhang et al., 1999b). RT-PCR of these enterocyte preparations revealed the expression of CYP1A1, 1B1, 2C, 2D6, 2E1, 3A4, and 3A5 mRNAs but was unable to detect CYP1A2, 2A6, 2A7, 2B6, 2F1, 3A7, and 4B1 mRNAs. However, immunoblot analysis revealed only CYP3A4, 1A1 (in two of eight intestines tested), and 2C proteins, whereas CYP1B1, 2E1, 2D6, and 3A5 proteins were not detectable. CYP2D6 has, however, been detected by Western immunoblot and metoprolol metabolism in another study (de Waziers et al., 1990). We subsequently used metabolic activities to confirm the results of an earlier study (de Waziers et al., 1990). Expression of CYP2C9 and of CYP2C19 was demonstrated by activities of diclofenac 4’-hydroxylase and mephenytoin 4’-hydroxylase, respectively. Interindividual variability was 18-fold for CYP2C9 and 17-fold for CYP2C19, for the 10 intestines investigated, and the individuals’ activity levels did not correlate, thus eliminating sample preparation as being a cause of the variability in activities. On the basis of 6β-testosterone hydroxylase activity, CYP3A4 activities varied 7-fold for these 10 small intestinal preparations, although in larger populations, much greater variability has been observed. The basis for such variability probably resides in the pathways of regulation of CYP3A4, rather than in genetic polymorphisms leading to structural P450 protein variants (Guengerich, 1999; Goodwin et al., 2002).

Other P450s have been reported to be expressed in the human small intestine, including CYP2S1 (Rylander et al., 2001), CYP4F12, which catalyzes the antihistaminic ebastine’s metabolism (Hashizume et al., 2001), and CYP2J2, which catalyzes arachidonic acid and ebastine metabolism (Zeldin et al., 1997).

The reported inhibition of the metabolic function of human small intestinal CYP3A4 by grapefruit juice has provided an approach to investigate this function in vivo. Grapefruit juice, when administered together with either of the calcium antagonists nifedipine and felodipine, increases the plasma concentration of the drug (Bailey et al., 1991). The metabolism of coumarin, cyclosporine, ethinylestradiol, midazolam, terfenadine, and verapamil (for reviews, see Ameer and Weintraub, 1997; Fuhr, 1998), as well as that of saquinavir (Kupfer-schmidt et al., 1998; Eagling et al., 1999) and erythromycin (Kanazawa et al., 2001), was also shown to be decreased by grapefruit juice.

The grapefruit-mediated decrease in substrate metabolism was determined to occur through a mechanism-based inactivation of enterocyte CYP3A4, possibly by a furanocoumarin constituent of grapefruit juice (Schmiedlin-Ren et al., 1997). Through the use of small intestinal biopsies and an erythromycin breath test, it was determined that orally ingested grapefruit juice did not affect hepatic CYP3A4 activity but did decrease small intestinal CYP3A4 levels by 62%, without any corresponding change in the enterocyte CYP3A4 mRNA levels (Lown et al., 1997). A recent study showed that at least six furanocoumarins in grapefruit juice contribute to the inhibition of CYP3A4 and that a combination of competitive and mechanism-based inhibition occurs (Guo et al., 2000).

Rat and Mouse Small Intestinal P450 Expression

Early studies on P450 expression and on their metabolic activities in rat small intestine have been reviewed previously (Kaminsky and Fasco, 1992). These and subsequent studies revealed that several P450s are expressed in the rat small intestine, including CYP1A1, 2B, 2C, 2D6, and 3A (Kaminsky and Fasco, 1992; Fasco et al., 1993; Zhang et al., 1996), although the complement of intestinal P450s is more restricted than that expressed hepatically. CYP2C11, 2E1, and 1A2 expression was not detected in early studies of the small intestine (de Waziers et al., 1990; Shimizu et al., 1990; Wortelboer et al., 1992). However, CYP2E1 was reported to be inducible, by a post-transla-tional mechanism, in rat small intestine by ethanol (Roberts et al., 1994). The many contradictions in the published data on intestinal P450 composition were presumed to be partly due to the differences in the procedures used to prepare enterocyte microsomes (Kaminsky...
and amine, aminopyrine, family have been indicated to have catalytic activity with benzphetamine from retinal. However, few xenobiotic substrates have been expressed in rat small intestine (Zhang et al., 1997a, 1998, 1999a). In addition, CYP2C was detected in untreated rats at low levels. In contrast, several P450 mRNA forms that are expressed in the liver were not detected in the enterocytes of untreated or induced rats, including CYP2B1, 2B2, 2E1, 3A2, and 4A1. CYP1A2 mRNA was detectable only in BNF-induced rat small intestine, at levels that did not result in any detectable translation.

Induction of the small intestinal P450s can affect the metabolic fate of many ingested xenobiotics. The most prominent inducible form in rat small intestine is CYP1A1 (Fasco et al., 1993; Zhang et al., 1996). This form probably is not constitutively expressed, but is inducible by constituents of commonly used rat chow and, consequently, is readily detected in rat small intestinal preparations in the absence of administration of known inducing agents (Rosenberg, 1991; Kaminsky and Fasco, 1992). Inducing agents such as BNF, however, can induce small intestinal CYP1A1 up to 17-fold (Fasco et al., 1993; Zhang et al., 1996) in rats on a normal chow diet. The inducibility of CYP1A1 diminishes markedly along the length of the small intestine from the duodenum to the ileum and is affected by the route of administration of the inducing agent. Thus, intestinal CYP1A1 is more sensitive to orally administered BNF, whereas induction of hepatic CYP1A1 is more sensitive to i.p. administered BNF (Zhang et al., 1996). The time courses of hepatic and intestinal CYP1A1 induction by BNF were compared quantitatively at the protein and mRNA levels after a single dose of BNF treatment (Zhang et al., 1997b). Intestinal CYP1A1 protein was detectable earlier, and for a shorter duration, than was hepatic CYP1A1. In another study, differences in the expression of CYP1A forms in liver and small intestine, their inducibility by 3-methylcholanthrene, and the effects of various levels of CYP1A1/1A2 on caffeine metabolism were investigated (Spatzengger et al., 2000). Differences in the expression of CYP1A1 and CYP1A2 in the two tissues led to significant differences in the contributions of the various enzymes involved in the biotransformation of caffeine.

The inducibility of CYP2B1/2 and CYP3A3s in the intestine and liver has been studied in rats following PB, DEX, or PCN treatment (Kaminsky and Fasco, 1992). Studies using the RT-PCR technique led to the conclusion that only CYP2B1, and not CYP2B2, is present in rat small intestine, where it can be induced by PB (Traber et al., 1990; Zhang et al., 1996). With the development of form-specific antibodies, it has been possible to determine that CYP3A1, and not CYP3A2, is expressed in rat small intestine (Debri et al., 1995). This has been further confirmed by RT-PCR analysis (Zhang et al., 1996). More recently, a new CYP3A form was isolated from rat enterocytes that shares 97% similarity with CYP3A9 (Gushchin et al., 1999). The ready inducibility of P450s by drugs can lead to drug-drug interactions. The expression of CYP3A and CYP1A1, as well as their associated enzyme activities in rat small intestine, was decreased by 5-fluorouracil, a widely used antineoplastic agent, leading to drug interactions with administered nifedipine (Yoshisue et al., 2001).

Recent studies identified P450 expression more specifically in mouse enterocytes: CYP1A1 was identified following its induction by BNF (Torronen et al., 1994) and by a polychlorinated biphenyl mixture, but only in Ah receptor-positive mice (Cummings and Schut, 1995); CYP3A was detected in mouse small intestine by erythromycin and cyclosporine activities and by immunoblot analysis (Berg-Candolfi et al., 1996); CYP1A, CYP2B, CYP2C, and CYP3A proteins were demonstrated to be induced in mouse small intestine by a food contaminant, imazalil (Muto et al., 1997); and CYP24 mRNA was induced in mouse small intestine by 1,25-dihydroxyvitamin D3 (Yoshimura et al., 1998). In one recent report, antibodies to rat CYP1A1, 2C, 2D, 2E1, and 3A were used to probe P450 protein expression in the small intestine of untreated mice. Two immunoreactive bands were detected with the anti-CYP3A antibody, suggesting the expression of two CYP3A forms, but no positive bands were detected with the other antibodies, possibly because of inadequate sensitivity (Emoto et al., 2000a). The presence of CYP3A protein and testosterone 6β-hydroxylase activities in the upper and middle sections of mouse small intestine was further confirmed in an everted sac experimental model of first-pass small intestinal metabolism (Emoto et al., 2000b). In addition, a CYP2J protein, presumably CYP2J6, was identified to be predominantly expressed in mouse small intestine and was induced by pyrazole (Xie et al., 2000). Furthermore, CYP2C40 was identified as the major CYP2C2 in mouse intestinal tract (Tao et al., 2000).

In an effort to characterize the mouse small intestinal P450s more systematically and accurately, we recently investigated the forms of P450s expressed in mouse small intestine and their inducibility, with use of qualitative RT-PCR, real-time quantitative RT-PCR, and immunoblot analysis (Zhang et al., 2003). Many mRNA forms, including CYP1A1, 1B1, 2B9, 2B10, 2B19, 2B20, 2C9, 2C8, 2C40, 2E1, 3A11, 3A13, 3A16, 3A25, and 3A44, were identified, whereas several others, including CYP1A2, 2A, 2C37, 2C39, and 2F2, were not detected in the enterocytes of untreated mice (Zhang et al., 2003). CYP1A1 mRNA was markedly induced by BNF; all five forms of CYP3A mRNA were induced by DEX treatment; CYP2B9, CYP2B10, and CYP2B20 mRNAs were induced, whereas CYP2B9 mRNA levels were diminished by PB treatment; CYP2C29 and CYP2C40 mRNAs were also induced by PB, whereas CYP2C38 mRNA showed no induction. At the protein level, CYP1A1, 2B, 2C, and 3A were detected in enterocytes from untreated mice, and these proteins were inducible by BNF (CYP1A1), PB (CYP2B and 2C), and DEX (CYP3A). In addition, CYP2B, 2C, and 3A from untreated animals and CYP1A1 from induced mice were all expressed at high concentration at the proximal end of the small intestine and decreased distally.

Studies on P450-mediated in vivo toxicity or mutagenicity in the small intestine are scarce. In one study, the mutagenicity of BAP in mouse small intestine was investigated through the use of the Dib-I locus assay (Brooks et al., 1999). Administration of BAP by oral and
i.p. routes had markedly different effects on the number of \textit{Dlb-1} mutations and on the pattern of induction of CYP1A1. Oral BAP treatment resulted in a decrease in the number of mutations, when compared with the i.p. route. Studies in Ah receptor-nonresponsive versus Ah receptor-responsive mice indicated that induction of CYP1A1 was associated with increased numbers of \textit{Dlb-1} mutations.

**Phase II Metabolism.**

Conjugation of xenobiotics and xenobiotic metabolites in the small intestine has the potential to facilitate their excretion to the lumen of the intestine. It is thus tempting to attribute the low incidence of human small intestinal cancer to the high levels of expression of phase II enzymes in small intestinal enterocytes, relative to expression levels in other organs of the gastrointestinal tract. Although several authors have proposed this relationship, very few data exist to support it.

**Glutathione S-Transferase**

GSTs show patterns of expression similar to those of the P450s in the human small intestine; expression levels decrease from proximal to distal small intestine, have a high degree of interindividual variation, and are very high relative to levels in other organs in the gastrointestinal tract (Coles et al., 2002). The most prominently expressed GSTs in the human small intestine are GSTP1, GSTA1, and GSTA2. GSTT1-1, with high activity toward dichloromethane, has also been detected in human small intestine (Juronen et al., 1996). In a comparison of human small intestinal and hepatic GSTA1-1 using busulfan as a substrate, very similar \(K_{m}/V_{\text{max}}\) values were obtained, implying that the enzyme functions similarly in the two environments (Gibbs et al., 1998).

Could these enterocyte GSTs protect against xenobiotic-mediated carcinogenesis of the small intestine? There is some supportive, but indirect, evidence. Human GST levels in the gastrointestinal tract correlate inversely with cancer risk (Van Lieshout et al., 1998b). Several dietary compounds that reduce gastrointestinal cancer rates in rats were tested for their ability to induce GST. As an example, sulforaphane analog compound 30 induced GST \(\alpha\), \(\mu\), and \(\pi\) in rat small intestine, a possible explanation for its anticarcinogenic effects (Van Lieshout et al., 1998b). In similar studies, nonsteroidal anti-inflammatory drugs increased expression levels of rat small intestinal GST, and this was mirrored for GSTT1-1 by a range of anticancer drugs. It was thus hypothesized that gastrointestinal, including small intestinal, GST plays a protective role against carcinogenesis in this system (Van Lieshout et al., 1998a). Further support for a protective role for small intestinal GST is provided by the observation that celiac disease leads to small intestinal villous atrophy, with a decreased expression of GST (Wahab et al., 2001), a possible explanation for increased cancer risk in celiac disease patients. Also, GST expression levels are significantly higher in the A/J mouse small intestine than in the carcinogenesis-susceptible colon (Guo et al., 2002).

In light of the possible protective role of small intestinal GSTs, it is of interest to review some of the factors that regulate its expression. In the female rat, small intestinal (jejunal) GST expression is enhanced by lactation, probably through mediation of prolactin (Luquita et al., 1999). Small intestinal GST expression levels in rats increase markedly as a function of age (Jang et al., 1998). Many anticarcinogens, e.g., flavone, coumarin, and \(\alpha\)-angelica lactone, induce rat small intestinal GST \(\alpha\) and \(\mu\) isozymes (Nijhoff et al., 1993). GST expression in the rat jejunum is greater in males than in females, and testosterone is apparently a factor in this differential expression (Catania et al., 2000). Undernourishment during rat gestation, weaning, and growth and development produces a decrease (by 35–45%) in small intestinal GST, in contrast to increases in hepatic expression (Reen et al., 1999). These undernourishment-mediated changes were not reversed by subsequent normal nourishment. Similarly, 5-fluorouracil causes a broad decrease in rat small intestinal metabolic enzyme activities and protein levels, including GST, more effectively than it does for the corresponding hepatic enzymes (Yoshisue et al., 2001).

**UDP-Glucuronosyltransferases**

The role of human UGTs in drug metabolism, including the role of small intestinal UGT, has recently been reviewed (Fisher et al., 2001). Several UGTs were listed in this review as being expressed in the human small intestine: UGT1A1, 1A3, 1A4, 1A6, 1A10, 2B4, 2B7, 2B10, 2B11, and 2B15 (Fisher et al., 2001). Only UGT1A10, of this group, was reported to not be expressed in the liver also. In the rat, UGT1A2 and 1A3 are also selectively expressed in the small intestine (Gams et al., 2000).

Human UGT1A1 is the most highly expressed UGT in the small intestine, with activities even greater than in the liver (Fisher et al., 2000). Its expression is polymorphic, thereby giving rise to interindividual variability in its associated activity. Individuals with the UGT1A1 null variant are likely to undergo increased systemic uptake of those orally administered drugs involved in UGT conjugation (Strassburg et al., 2000). These authors also demonstrated marked interindividual variation in human small intestinal UGT1A, at the levels of gene expression, protein abundance, and catalytic activity, in contrast to hepatic expression, that was without significant interindividual variation. Such enhanced interindividual variability in small intestinal versus hepatic UGT levels is consistent with observations on human small intestinal P450 variability.

As is the case with GST expression, the markedly lower expression of UGT in the human colon relative to that in the small intestine has been hypothesized to be a factor in the differential susceptibility to carcinogenesis of the two organs (Frohlich et al., 1991). Support for this hypothesis is provided by studies in mice. Butylated hydroxyanisole decreases the carcinogenic potential of some xenobiotics, and its capacity to increase mouse small intestinal UGT activity has been suggested as a possible mechanism for this effect (Hjelle et al., 1985).

Investigation of small intestinal UGT regulation has been carried out primarily in rodents. The expression levels of rat UGT activity toward 3-hydroxybenzo[a]pyrene and 4-hydroxybiphenyl were highest in the villous tips and declined progressively toward the crypts. The former activity was enhanced by 3-methylcholanthrene and PB, whereas the latter activity was only enhanced by PB. In both cases, the crypt cell activities were induced to the greatest extent (Dubey and Singh, 1988). Similarly, the highest concentrations of UGTs in the human small intestine were detected in the villous tips (Peters et al., 1987). The major UGT1 form induced by 2-naphthoflavone in the rat small intestine is UGT1A7 (Kobayashi et al., 1998).

**Sulfotransferase**

Limited information is available on sulfotransferase expression in the human small intestine. Despite this, available data suggest that marked interindividual variability of expression occurs. By the use of a general sulfotransferase probe, it was demonstrated that marked sulfotransferase expression occurs in the human small intestine and that considerable interindividual variability exists in this expression (Windmill et al., 1997). A sulfotransferase, \(N\)-acetylglucosamine-6-sulfotransferase, has recently been characterized and demonstrated to be specifically expressed in the human small intestine and colon (Lee et al., 1999).

Estrogen and dehydroepiandrosterone sulfotransferases (SULT1E1...


Eagling VA, Profit L, and Back DJ (1999) Inhibition of the CYP3A4-mediated metabolism and tissue-selective chemical toxicity in the respiratory and gastrointestinal tracts.


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