OXIDATIVE AND CONJUGATIVE METABOLISM OF XENOBIOTICS BY LIVERS OF CATTLE, SHEEP, SWINE AND RATS

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Summary

Homogenate preparations from fresh livers of cattle, sheep, swine and rats were assayed for microsomal cytochrome P-450 content, for mixed-function oxidase activities and for a wide array of conjugative activities using numerous xenobiotic substrates. Results show that hepatic enzymatic capabilities toward xenobiotics do not parallel phylogenetic classifications, thus strengthening the view that most of the comparative data available at present is more descriptive than predictive of relationships among species. Livestock species differed widely from rats in having lower activities of benzo(a)pyrene hydroxylase, glutathione S-transferase and acetyltransferase toward isoniazid and sulfamethazine and UDP-glucuronosyltransferase toward bilirubin. Acetyltransferase activities toward β-naphthylamine and 2-aminofluorene were not detected in livers of livestock species studied. Cattle livers were remarkably high in activities of styrene oxide hydrolase, ethoxyresorufin O-deethylase, 2-naphthol sulfotransferase and p-aminobenzoic acid acetyltransferase; but notably low in activity of glutathione-S-transferase toward sulfobromophthalein and 1,2-dichloro-4-nitrobenzene. Swine livers had low activity of glutathione-S-transferase toward four of six substrates and low acetyltransferase activity toward four of five substrates. Sheep livers generally were higher than cattle livers in sulfotransferase and UDP-glucuronosyltransferase activities and lower in acetyl- and glutathionyl-S-transferase.

Findings emphasize the risk of error in extrapolations among species and in extrapolations among substrates.

(Key Words: Biotransformations, Livers, Xenobiotics, Livestock Species, Rats.)

Introduction

Biomedical research depends on the usage of some species as models for others (NAS, 1970). Policies regulating drugs, additives to feeds and food, and dispersion of chemicals into the environment require toxicity testing with animals and extrapolations of findings to other species in assessments of risk (Nicholson, 1981). However, wide differences in metabolic or physiological capabilities often exist among species that are classified phylogenetically as closely related, and this is especially so in the biotransformation and disposition of xenobiotics. Extrapolations of biotransformation data among species are prone to grave errors (Caldwell, 1981) unless based on knowledge of the metabolic capabilities and physiological characteristics of the species involved (Rall, 1979; Andersen, 1981). Predictability of
xenobiotic metabolism among species has been questioned repeatedly (Williams, 1947, 1967, 1974; Davis et al., 1973; Caldwell, 1980, 1981; Pacifici et al., 1981) and the need for definitive data regarding humans and livestock, as well as the species used as models, has been emphasized (Caldwell, 1980, 1981; Oser, 1981; Braun and Waechter, 1983; Friess, 1983; Rumsey, 1983).

This report provides comparative data on hepatic capabilities for phase I (oxidative, reductive, hydrolative) and II (conjugative) biotransformations of xenobiotics for cattle, sheep, swine and rats. Findings are discussed in relation to a companion study (Gregus et al., 1983) that reported comparable data, obtained simultaneously under almost identical conditions, for quail, trout and six species of laboratory animals commonly used in toxicity testing.

Methods and Materials

Animals. Western crossbred ewes with predominantly Rambouillet breeding and ranging in age from 4 to 5 yr were brought from New Mexico State University to the University of Kansas Medical Center (UKMC) for the study. Histories of diet, management, reproduction and records of hematology, serum clinical profiles as well as appraisals by experienced herdsman and animal scientists assured that these animals were representative of normal, healthy sheep. Cattle and swine were selected randomly from animals slaughtered commercially in the Kansas City area. The cattle were mature females of Hereford and Hereford x Angus breeding. The swine were crossbred or grade gilts weighing about 80 to 90 kg. All sheep, cattle and swine were inspected pre-slaughter and judged to be healthy, and their carcasses passed examinations by licensed meat inspectors. Young adult male Sprague-Dawley rats were housed in the UKMC Animal Care Center with a 12-h light-dark cycle and fed Purina Laboratory Rodent chow for about 2 wk before they were killed.

Female cattle, sheep and swine were used because of availability and convenience, and because differences in oxidative and conjugative activities of livers between sexes have not been observed in animals other than rats (Davis et al., 1973; Plaa, 1980). Male rats were used to facilitate comparison of data with values for male rats examined similarly in a companion study (Gregus et al., 1983).

Preparation of Livers. Livers were removed immediately after exsanguination of stunned sheep, cattle and swine, and after decapitation of unanaesthetized rats. Samples from the medial lobe were placed in chilled 1.15% KCl buffer until homogenized, which usually occurred within 1 h after specimen collection. Portions of livers were weighed and homogenized at 0 to 5 C in a Potter-Elvehjem glass homogenizer with teflon pestle. Homogenates were subsequently used to prepare three preparations, as follows: (1) Ten percent homogenate in .25 M sucrose containing 5 mM Tris-HCl, pH 7.4, was used for determination of UDP-glucuronosyltransferase activities. (2) Thirty-three percent homogenate in 1.15% KCl was centrifuged at 10,000 x g for 20 min and the supernatant was subsequently centrifuged at 105,000 x g for 60 min. The resulting pellet was resuspended in .1 M potassium phosphate buffer, pH 7.4, and used for determination of cytochrome P-450 concentration and of microsomal mixed-function oxidase activities. The supernatant (cytosolic fraction) was used for glutathionyl- and acetyltransferase assays. (3) Twelve and one-half percent homogenate in .25 M sucrose containing 10 mM Tris-HCl and 3 mM 2-mercaptoethanol, pH 7.4, was centrifuged at 105,000 x g for 60 min and the supernatant was used for sulfotransferase assays.

Protein and Cytochrome P-450 Assays. Protein in liver homogenates and microsomal and cytosolic preparations was measured by the method of Lowry et al. (1951). Cytochrome P-450 was measured according to Omura and Sato (1964), as described by Mazel (1971).

Enzyme Assays. Microsomal N-demethylation of ethylmorphine (6.7 mM) and benzphetamine (1.0 mM) was measured by colorimetric determination of formaldehyde (Nash, 1953) as described by Lu et al. (1972). Benzopyrene (80 jg) hydroxylation and ethoxyresorufin (.50 jg) deethylation were measured fluorimetrically by methods of Nebert and Gelboin (1968) as modified by Lu et al. (1972) and by Burke and Mayer (1974), respectively. Epoxide hydrolase activity toward [3H] styrene oxide (1.5 mM) was determined as described by Oesch et al. (1971).

UDP-Glucuronosyltransferase activities were assayed using acceptors, concentrations and methods as follows: .5 mM 1-naphthol and 1.5
mM morphine (Bock et al., 1978); .5 mM p-nitrophenol (Bock et al., 1973); 1.5 mM chloramphenicol (Young and Lietman, 1978); .1 mM bilirubin (Van Roy and Heirwegh, 1968); .1 mM testosterone and .1 mM estrone (Rao et al., 1976); .5 mM valproic acid (Watkins and Klaassen, 1982); .15 mM phenolphthalein (Winsnes, 1969) and .1 mM diethylstilbestrol (Watkins et al., 1982). All assays were performed in .1 M Tris-HCl, pH 7.4, with 5 mM MgCl2 and 30 mM UDP-glucuronic acid in the presence of .05% Brij 58 for enzyme activation.

Glutathione S-transferase activities were measured by the spectrophotometric method of Habig et al. (1974) using 1-chloro-2, 4-dinitrobenzene (1 mM); 1, 2-dichloro-4-nitrobenzene (1 mM); sulfobromophthalein (.12 mM); ethacrynic acid (.4 mM); trans-4-phenyl-3-buten-2-one (.05 mM) and 1,2-epoxy-3-(p-nitrophenyl) propane (.5 mM).

Acetyltransferase activity toward isoniazid (1 mM) was assayed spectrophotometrically (Weber, 1971; Hearse and Weber, 1973), and toward 2-aminofluorene (.125 mM) and β-naphthylamine (.125 mM) was measured radiometrically (Glowinski et al., 1978). Determination of N-acetyltransferases toward p-aminobenzoic acid (.04 mM) and sulfamethazine (.04 mM) was by the colorimetric method of Hearse and Weber (1973).

Sulfotransferase activity toward estrone (.05 mM) was assayed by the method of Adams and Poulos (1967) with extraction of estrone sulfate according to Rozhin et al. (1974). Bile acid sulfotransferase was measured by the method of Chen et al. (1977) using tauroliothocholate (.1 mM) and separation of tauroliothocholate sulfate by thin layer chromatography and Adsorbosil®-5 plates. Aryl sulfotransferase activity toward 2-naphthol (.25 mM) was measured colorimetrically (Nose and Lipmann, 1958) as described by Sekura and Jacoby (1979).

Chemicals. The sources and purities of chemicals used as substrates and reagents were the same as used in our previous study with eight species of laboratory animals (Gregus et al., 1983). All were the highest quality available.

Enzymatic Reactions. All enzymatic reactions were conducted at 37°C under conditions of initial velocity with appropriate blanks. Linearity with time and with protein concentrations was verified using specimens of livers from each species. All assays were performed using protein preparations from freshly collected livers. Thus, nine experienced investigators and technicians were involved in the simultaneous performance of the 31 assays reported herein, most of which were initiated within 2 or 3 h after the preparation of homogenates.

Radioactivity of Substrates, Reagents and Products. [3H]acetyl coenzyme A (2.7 Ci/mmoll); [dichloroacetyl-1,2-14C] chloramphenicol (43.2 mCi/mmol); [1-14C]-1-naphthol (4.3 mCi/mmol); [N-methyl-3H] morphine (60 Ci/mmol); [35S]-3'-phosphoadenosine-5'-phosphosulfate (3.1 Ci/mmol) and [1α,2α-3H] testosterone (57.8 Ci/mmol) were obtained from New England Nuclear, [Monoethyl-3H] diethylstilbestrol (116 Ci/mmol) and [1-14C] valproic acid (4.67 mCi/mmol) were purchased from Amersham-Searle and [3H] styrene oxide (4.9 mCi/g) was supplied by Dr. R. P. Hanzlik.

Complete scintillation cocktail 3A70 was obtained from Research Products International. Radioactivity was measured by liquid scintillation spectrophotometry in a Packard Model 3330 Tricarb, with appropriate corrections for quenching by use of automatic external standardization.

Data Processing and Evaluation. All assays were performed in duplicate or triplicate for each liver sampled. Means and standard errors (X ± s/√n) were generated for five or six individuals of each species. Data from individuals across species were subjected to one-way analysis of variance, Bartlett’s chi-square test for heterogeneity of variance, and Duncan’s new multiple range test for separation of means (Snedecor and Cochran, 1980) where F values were significant.

Results and Discussion

Liver Size and Cytochrome P-450 Content. All liver weights were within ranges regarded as normal. Gross morphology and visual appearances were also regarded as normal. Protein concentrations (mg/g) were as follows: rats, 124 ± 4; sheep, 128 ± 6; cattle, 98 ± 7 and swine, 113 ± 6. The value for cattle differs (P<.05) from values for rats and sheep, but not for swine. Cytochrome P-450 contents (table 1) varied almost twofold among species, and

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7 Boston, MA.
8 Arlington Heights, IL.
9 Univ. of Kansas, Lawrence.
10 Elk Grove, IL.
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*aValues are mean ± SE; N = 5 or 6.

*bBarlett's chi-square test show heterogeneity of variance (P<.05).

c,d,e,fMeans with the different superscripts differ (P<.05).
values for swine were lower than values for rats, sheep and cattle. All were within ranges reported for normal animals of the respective species.

**Enzyme Activities.** The mean and standard errors of activities for six enzyme systems and 29 substrates are shown in table 1. Bartlett's (chi-square) test showed heterogeneity of variance among species for 19 of the 29 enzyme assays. Differences among means for species differed by orders of magnitude in some cases, and heterogeneity of variance is expected in such cases. Duncan's multiple range test was applied routinely for separation of means; although the implications of heterogeneity of variance must be considered when comparing means. Such considerations are facilitated by the display of standard errors along with the means (table 1).

**Mixed-Function Oxidases.** Results are shown graphically in figure 1. Values for rats lie within ranges that have been reported as normal, although benzo(a)pyrene hydroxylase activity is almost twofold greater than values obtained similarly in a companion study (Gregus et al., 1983). Benzo(a)pyrene hydroxylase activities for sheep and cattle were well below levels for rats, and swine were about one-half that of cattle and sheep. Values for livestock species are in the same general range as levels for mice and quail but two-to fourfold greater than comparable data for guinea pigs, rabbits, cats, dogs and rainbow trout (Gregus et al., 1983).

The N-demethylase activities of livers from cattle and sheep toward benzphetamine (figure 1) were about equal to values for rats and about 1.5 to twofold greater than swine, and were 20 to 40% lower than rats toward ethylmorphine. Activities for swine are roughly equal to values observed for guinea pigs, dogs and quail (Gregus et al., 1983).

Ethoxyresorufin O-deethylase activities in cattle livers were 11- to 17-fold greater than in livers of rats, sheep and swine (figure 1). Likewise, levels for cattle were higher than the levels for all species evaluated by Gregus et al. (1983) except rabbits, which exhibited activities about equal to those for cattle in the present study.

Styrene oxide hydrolase activities (figure 2) for cattle and sheep were about two- or three- fold greater than values for swine, which were in the same range as values for rats (figure 2), and for guinea pigs and dogs (Gregus et al., 1983). All livestock species had activities that were three- to fivefold greater than values for mice, rabbits, cats, bobwhite quail and rainbow trout (Gregus et al., 1983).

**Sulfotransferases.** Sheep livers were consistently more active than rats (figure 3); whereas cattle and swine were more active than rats.
all exhibited remarkably high activity (0.62 to 3.9 mmol·min⁻¹·mg protein⁻¹) toward p-aminobenzoic acid (figure 4). Conversely, all livestock species exhibited remarkably low acetyltransferase activities (<0.01 nmol·min⁻¹·mg protein⁻¹) toward sulfamethazine and isoniazid. Gregus et al. (1983) observed similarly low activities for rats, mice, guinea pigs, cats, dogs, quail and trout, but found high activity in rabbits (1.5 mmol·min⁻¹·mg protein⁻¹) toward sulfamethazine and all four other substrates. Activity of sheep liver acetyltransferase for isoniazid was barely detectable. In contrast to

toward two of the three substrates tested. Cattle had the highest and lowest activities toward 2-naphthol and tauroliothocholate, respectively; while swine had the lowest activity toward 2-naphthol. The sulfation of tauroliothocholate by sheep and swine was three- to fourfold greater than cattle and rats (figure 3). Furthermore, the values are three-to fourfold greater than rats, guinea pigs and rabbits and 20- to 30-fold greater than mice, cats, dogs, quail and trout (Gregus et al., 1983).

Acetyltransferases. Cattle, sheep and swine livers failed to exhibit any measurable activity (<0.0002 nmol·min⁻¹·mg protein⁻¹) toward β-naphthylamine or 2-aminofluorene; although
these livestock species, quail and trout were poor acetylators of p-aminobenzoic acid and sulfamethazine, but were highly effective acetylators of β-naphthylamine and 2-amino-fluorene as well as isoniazid (Gregus et al., 1983). Variations among species in the present study and the research of Gregus et al. (1983) were wider for acetyltransferase activity than any other systems studied. Acetyltransferase activity thus appears to be the least predictable of all these phase I and phase II biotransformations in terms of phylogenetic relationships. The suggestion that herbivores are generally good acetylators, and some other generalities that have been noted, (Davis et al., 1973; Caldwell, 1981) are contradicted by the present study and the data of Gregus et al. (1983).

**Glutathione S-Transferases.** Activities of liver cytosolic preparations toward six substrates are shown in figure 5. All species actively transformed 1-chloro-2, 4-dinitrobenzene, but rats and swine were about twofold more active than sheep and cattle; whereas mice, guinea pigs and rabbits were three- to fivefold more active than rats (Gregus et al., 1983). Except for rats, which transform all six substrates actively, there are few, if any, consistent patterns in the data. For example, sheep were most active of livestock species toward sulfobromophthalein and least active toward trans-4-phenyl-3-butene-2-one; whereas swine were most active toward 1-chloro-2, 4-dinitrobenzene but least active toward ethacrynic acid and 1,2-epoxy-3-(p-nitrophenoxy) propane. The 40-fold higher activity of rats than livestock species toward 1,2-dichloro-4-nitrobenzene is equalled by mice, cats and dogs (Gregus et al., 1983).

**UDP-Glucuronosyltransferases.** Activities of liver homogenate preparations toward 10 substrates are shown in figure 6. No ranking of species is afforded by the data, neither among livestock species (present study) nor in comparison with laboratory animals evaluated by Gregus et al. (1983). The results suggest caution in any attempts to predict the glucuronidation of any given substrate(s) based on data for any other substrate(s) even within species. Although there seems to be a pattern for activities toward 1-naphthol and p-nitrophenol [i.e., group I substrates in rats (Bock et al., 1973)], there is no pattern among species for the group II substrates (figure 6). Moreover, the activities in livestock species toward estrone were high in

![Figure 5](image5.png)

**Figure 5.** Glutathione-S-transferase activities of hepatic cytosolic preparations from rats, sheep, cattle and swine toward six xenobiotic substrates.

![Figure 6](image6.png)

**Figure 6.** UDP-glucuronosyl transferase activity of hepatic homogenate preparations from rats, sheep, cattle and swine toward varied substrates.
Discussion

Comparative species studies of hepatic phase I (oxidative, reductive, hydrolytic) and phase II (conjugative) biotransformations have provided a sizeable body of data regarding species' activities toward specific substrates. Most reports involve few species and few enzyme systems (Grover and Sims, 1964; Castro and Gillette, 1967; Wit, 1968; Davies et al., 1969; Davis et al., 1973; Chasseaud, 1974; Oesch, 1974; Litterst et al., 1975; 1976; Kulkarni et al., 1976; Walker, 1978; Walker et al., 1978; Kato, 1979; Lu and West, 1980). Only sporadic data (limited enzyme systems and limited substrates) have been reported for livestock species. The present report provides a broad spectrum of data, involving six enzyme systems and 29 substrates, and should become an important baseline for comparisons of cattle, sheep and swine with other species. The data are directly comparable with results from a companion study (Gregus et al., 1983), and together they provide important descriptive and quantitative relationships among livestock and laboratory species commonly used in toxicity testing. These results suggest a basis for selection of small animal models for livestock in regard to hepatic phase I and phase II enzymes, based on interpolations of data among species rather than extrapolations based on phylogenetic classifications.

There are few, if any, broad generalizations that can be drawn from the present data; rather, they contradict some generalizations already drawn in previous experimentation. For example, the notion that herbivores have greatest capacity for conjugations and carnivores the least (Davis et al., 1973) is strictly contradicted by results of our companion research showing that UDP-glucuronosyltransferase activity toward a variety of substrates was highest in dogs over seven other species including the herbivores, guinea pigs and rabbits (Gregus et al., 1983). Likewise, the present study shows that swine livers exceeded cattle and(or) sheep livers in sulfo- (two of three substrates), acetyl- (one of three substrates), glutathionyl- (three of six substrates) and UDP-glucuronosyl- (seven of 10 substrates) transferases. Sheep were generally, but not consistently, more active in glucuronosyl transfer than cattle or swine. Both cattle and sheep had higher mixed-function oxidase activity than swine, but no consistent patterns existed among livestock species in relation to the laboratory animals of Gregus et al. (1983).

The present results, together with those of Gregus et al. (1983), confirm the conclusion of Davis et al. (1973; p. 731): "the results...illustrate the futility of attempting to extrapolate information derived from one species of animal to another species." However, they suggest it may become possible to utilize one species as a model for another, based on interpolations of data for each species, rather than on extrapolations. It is likely that such interpolations (based on comparative studies of enzyme system capabilities) will bear faint resemblance to phylogenetic matching as currently practiced in the selection of model species for humans and livestock in toxicity testing. Furthermore, it is certain that such modeling of species must give consideration to inducible as well as inherent biotransformation capabilities (Thompson et al., 1982; Watkins et al., 1982). Efforts in this direction have been ranked among the critical issues of the 1980s, with particular reference to management of risks to the human food supply (Hart, 1981; Friess, 1983).

The role of hepatic biotransformations in the disposition of xenobiotics is widely recognized, and appropriate data of the type reported herein are accumulating, which will facilitate development of public policies to accommodate the management of risks from xenobiotics in the environment and the food chain. What is less widely recognized is the importance of biotransformations by tissues and microflora of the gastrointestinal tract (Hartiala, 1973). In ruminants, especially, the (inducible) activities of microbial populations often exceed in toxicological importance the biotransformations of liver. For example, the recent observation of significant dehalogenation of halobenzoates by a stable methanogenic consortium enriched from lake sediment and sewage sludge, suggesting ecologically important removal of chlorinated xenobiotics from the environment (Suflita et al., 1982), suggests the possibility that adapted populations of rumen microorganisms may likewise biotransform significant quantities of haloaromatic contaminants in the diet. The same may be true for some types of biotransformations by gastrointestinal tissues, notably rumen papillae;
but the evidence is sparse. Studies of biotransformation capacities in gastrointestinal tissues of livestock and poultry species are required, along with renal and hepatic capabilities of the type reported herein, to support sound policies for management of xenobiotics in agriculturally important species.

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