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SHORT COMMUNICATIONS

Effect of dietary phenobarbital, 3,4-benzo(α)pyrene and 3-methylcholanthrene on hepatic, intestinal and renal glutathione *S*-transferase activities in the rat*

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The glutathione *S*-transferases are cytosolic enzymes which function intracellularly in drug and carcinogen detoxification [1] and organic anion transport [2–5] in the liver, small intestine and kidney of the rat. The transferases catalyze the interaction of nucleophilic glutathione with many exogenous electrophilic substrates, including epoxides formed from the oxidation of polycyclic aromatic hydrocarbons by microsomal mixed-function oxidases [6–9]. This catalytic activity is important in that it provides one mechanism by which potential carcinogenic intermediates may be detoxified and subsequently excreted. Furthermore, in the small intestine the glutathione *S*-transferases may be the principal route of epoxide biodegradation, since the levels of epoxide hydrase, a microsomal detoxifying enzyme, are extremely low in that organ [10, 11].

Many routinely ingested environmental chemicals affect microsomal enzyme levels and thus alter drug and carcinogen metabolism [12]. For example, the intestinal metabolism of phenacetin in rat and man is greatly increased in response to a charcoal-broiled beef diet [13, 14]. Ingestion of cruciferous plants leads to induction of arylhydrocarbon hydroxylase in the small intestine of the rat [15]. Glutathione *S*-transferase activities in the liver, small intestine and kidney previously have been induced by i.p. administration of polycyclic aromatic hydrocarbons and phenobarbital [10, 16–18]. However, since the intestine is a major portal of entry for drugs and carcinogens, it was of interest to determine the influence of inducing agents in the diet on the hepatic, renal and small intestinal glutathione *S*-transferases in the rat. This report demonstrates important differences in the effects of xenobiotics on the glutathione *S*-transferases, based on the route of administration, with respect to the enzyme activities induced and the organ distribution of these effects.

A synthetic liquid diet was prepared from the following (wt/l. of diet): vitamin-free casein, 50 g; glucose, 50 g; $CaCO_3$, 2.5 g; $CaHPO_4$, 10 g; $FeNH_4(SO_4)_2 \cdot 12\,H_2O$, 1.0 g; $MnSO_4 \cdot H_2O$, 75 mg; $ZnSO_4 \cdot 7\,H_2O$, 25 mg; $CuSO_4 \cdot 5\,H_2O$, 12.5 mg; $MgSO_4 \cdot 7\,H_2O$, 1.0 g; KCl, 7.5 g; NaCl, 5.0 g; α-tocopherol, 50 mg; thiamine, 12.5 mg; riboflavin, 12.5 mg; pyridoxine, 12.5 mg; vitamin K, 12.5 mg; niacin, 12.5 mg; Ca pantothenate, 1.25 g; biotin, 1.25 mg; folic acid, 1.25 mg; inositol, 2.5 mg, *p*-aminobenzoic acid, 25 mg; choline, 25 mg; cysteine, 25 mg; Drisdol (Winthrop Laboratories, New York, NY, U.S.A.), 0.8 ml; Multivitamin Solution (G & W Laboratories, Port Reading, NJ, U.S.A.), 0.3 ml; Mazola oil, 125 ml; and distilled water, 875 ml. This diet was blended in a high-speed Waring blender for 3–4 min and then adjusted to pH 7 with concentrated NH_4OH.

Male Sprague–Dawley rats (120–140 g) were placed in individual metabolic cages and stabilized for 7 days on this synthetic diet. The animals were given this liquid diet, 50 ml/animal daily, so that the diet would be consumed completely by each animal. Unlimited distilled water was provided. Groups of rats (N = 7) were given either phenobarbital (Sigma Chemical Co., St. Louis, MO, U.S.A.), 3,4-benzo(α)pyrene (Sigma Chemical Co.) or 3-methylcholanthrene (CalBiochem, San Diego, CA, U.S.A.) (40 mg/kg/day) in the diet. Sodium phenobarbital was dissolved in water prior to blending; 3-methylcholanthrene and 3,4-benzo(α)pyrene were dissolved in corn oil. The treatment was continued for 14 days. Controls also received the synthetic diet for the 14-day treatment interval. The animals were killed and 100,000 *g* supernatant fractions were prepared from liver, kidney, and proximal, middle and distal segments of the small intestine, as previously reported [10, 16, 17]. Samples were stored at −15° until assayed for enzyme activity.

Glutathione *S*-transferase activity for the following substrates was measured using cytosol as the source of the enzyme and glutathione as the co-substrate: 3,4-dichloronitrobenzene, 1-chloro-2,4-dinitrobenzene, *p*-nitrobenzyl chloride, 1,2-epoxy-3-(*p*-nitrophenoxy)propane, and ethacrynic acid [6, 10, 16, 17].

Protein was measured by the method of Lowry *et al.* [19]. Enzyme activities are expressed per mg of cytosolic protein. Comparison of the levels of enzyme activities in the various treatment groups vs controls was made with the unpaired *t*-test [20].

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Table 1. Effect of oral phenobarbital, 3,4-benzo(α)pyrene and 3-methylcholanthrene on hepatic, intestinal and renal glutathione *S*-transferase activities in the rat

		Enzyme activity*,†			
		Control	Pheno-barbital	3,4-Benzo-(α)pyrene	3-Methyl-cholanthrene
Liver	3,4-Dichloronitrobenzene	80.8 ± 4.1‡	164 ± 8 P < 0.001§	113 ± 6 P < 0.001	115 ± 4 P < 0.0025
	1-Chloro-2,4-dinitrobenzene	481 ± 35	1177 ± 52 P < 0.001	564 ± 20 NS‖	758 ± 37 P < 0.001
	p-Nitrobenzyl chloride	120 ± 5	253 ± 18 P < 0.001	189 ± 11 P < 0.001	198 ± 5 P < 0.001
	1,2-Epoxy-3-(*p*-nitrophenoxy)propane	7.42 ± 0.13	9.78 ± 0.52 P < 0.025	11.8 ± 0.7 P < 0.001	7.35 ± 0.37 NS
	Ethacrynic acid	31.0 ± 2.7	46.8 ± 1.8 P < 0.001	40.3 ± 0.8 P < 0.025	46.0 ± 0.5 P < 0.001
Proximal small intestine	3,4-Dichloronitrobenzene	8.69 ± 1.64	12.5 ± 1.2 P < 0.05	9.92 ± 0.92 NS	5.92 ± 0.61 NS
	1-Chloro-2,4-dinitrobenzene	135 ± 16	201 ± 20 P < 0.01	128 ± 12 NS	178 ± 10 P < 0.05
	p-Nitrobenzyl chloride	12.2 ± 1.8	19.5 ± 1.0 P < 0.005	13.8 ± 0.7 NS	9.34 ± 0.78 NS
	1,2-Epoxy-3-(*p*-nitrophenoxy)propane	4.47 ± 1.16	4.11 ± 1.16 NS	7.15 ± 0.98 P < 0.05	4.93 ± 0.73 NS
	Ethacrynic acid	33.6 ± 2.6	36.2 ± 2.6 NS	49.1 ± 2.6 P < 0.001	38.8 ± 2.6 NS
Middle small intestine	3,4-Dichloronitrobenzene	3.68 ± 0.61	6.24 ± 0.61 P < 0.005	4.70 ± 0.61 NS	3.78 ± 0.41 NS
	1-Chloro-2,4-dinitrobenzene	128 ± 16	132 ± 15 NS	93.2 ± 14.3 NS	170 ± 17 P < 0.05
	p-Nitrobenzyl chloride	8.05 ± 0.52	10.4 ± 1.0 P < 0.05	9.09 ± 1.04 NS	8.57 ± 0.52 NS
	1,2-Epoxy-3-(*p*-nitrophenoxy)propane	2.77 ± 0.63	3.81 ± 0.69 NS	1.97 ± 0.71 NS	2.14 ± 0.63 NS
	Ethacrynic acid	28.4 ± 2.6	28.4 ± 1.3 NS	36.1 ± 3.9 P < 0.05	25.8 ± 1.3 NS
Distal small intestine	3,4-Dichloronitrobenzene	5.93 ± 1.53	8.90 ± 0.61 P < 0.05	3.99 ± 0.51 NS	3.99 ± 0.41 NS
	1-Chloro-2,4-dinitrobenzene	55.3 ± 5.1	60.4 ± 6.1 NS	51.2 ± 7.2 NS	59.4 ± 9.2 NS
	p-Nitrobenzyl chloride	7.27 ± 0.78	9.61 ± 0.52 P < 0.05	6.23 ± 0.78 NS	5.71 ± 0.26 NS
	1,2-Epoxy-3-(*p*-nitrophenoxy)propane	2.06 ± 0.63	2.60 ± 0.81 NS	1.16 ± 0.27 NS	2.96 ± 0.63 NS
	Ethacrynic acid	20.7 ± 1.3	21.8 ± 1.1 NS	27.2 ± 2.6 P < 0.05	20.7 ± 2.6 NS
Kidney	3,4-Dichloronitrobenzene	3.35 ± 0.36	2.70 ± 0.09 NS	2.98 ± 0.36 NS	4.35 ± 0.49 NS
	1-Chloro-2,4-dinitrobenzene	22.3 ± 3.9	19.0 ± 2.0 NS	16.4 ± 1.3 NS	42.0 ± 3.9 P < 0.001
	p-Nitrobenzyl chloride	8.99 ± 0.70	8.16 ± 0.71 NS	10.3 ± 0.4 NS	19.3 ± 1.0 P < 0.001
	1,2-Epoxy-3-(*p*-nitrophenoxy)propane	5.03 ± 0.41	4.27 ± 0.26	5.16 ± 0.34	5.51 ± 0.39
	Ethacrynic acid	39.3 ± 3.5	35.7 ± 1.4 NS	41.5 ± 1.0 NS	58.3 ± 2.7 P < 0.001

* Activities are given in nmoles product formed/mg of protein/min.
† Spontaneous conversion of substrate is substracted to give enzymatic conversion.
‡ Mean ± standard deviation.
§ P values for treatment control group.
‖ Not significant.

The effects of administration of inducing agents in the diet on glutathione *S*-transferase substrate activities in the liver, kidney and small intestine are summarized in Table 1. Statistically significant increases in hepatic transferase activities for the following substrates were observed in phenobarbital-treated animals vs control animals: 3,4-dichloronitrobenzene (102 per cent),1-chloro-2,4-dinitrobenzene (145 per cent), *p*-nitrobenzyl chloride (111 per cent), 1,2-epoxy-3-(*p*-nitrophenoxy)propane (31 per cent) and ethacrynic acid (51 per cent). 3,4-Benzo(α)pyrene treatment resulted in significant increases in hepatic activity for the following substrates: 3,4-dichloronitrobenzene (41 per cent), *p*-nitrobenzyl chloride (58 per cent), 1,2-epoxy-3-(*p*-nitrophenoxy)propane (59 per cent) and ethacrynic acid (30 per cent). Activity for1-chloro-2,4-dinitrobenzene was not increased by 3,4-benzo(α)pyrene.

3-Methylcholanthrene gave the following significant increases: 3,4-dichloronitrobenzene (42 per cent), 1-chloro-2,4-dinitrobenzene (58 per cent), *p*-nitrobenzyl chloride (65 per cent), and ethacrynic acid (48 per cent). 3-Methylcholanthrene treatment had no effect on activity with 1,2-epoxy-3-(*p*-nitrophenoxy)propane.

In the intestine, phenobarbital treatment caused significant increase in activity for the following substrates in the proximal, middle and distal segments, respectively: 3,4-dichloronitrobenzene (44, 74 and 50 per cent), 1-chloro-2,4-dinitrobenzene (49 per cent, NS, NS),* and *p*-nitrobenzyl chloride (66, 29 and 32 per cent). Activity with 1,2-epoxy-3-(*p*-nitrophenoxy)propane and ethacrynic acid were not altered with phenobarbital treatment. Dietary 3,4-benzo(α)pyrene increased activity for ethacrynic acid in proximal (46 per cent), middle (27 per cent) and distal intestine (31 per cent). Activity with epoxide substrate was increased 60 per cent by 3,4-benzo(α)pyrene in the proximal segment, with the more distal segments being unaffected. The other intestinal activities were not affected by 3,4-benzo(α)pyrene. 3-Methylcholanthrene increased activity for 1-chloro-2,4-dinitrobenzene in the proximal (32 per cent) and middle (33 per cent) small intestine but produced no significant increases in the other substrate activities in any segment of the intestine.

In the kidney, 3-methylcholanthrene caused increases in transferase activity for the following substrates: 3,4-dichloronitrobenzene (30 per cent), 1-chloro-2,4-dinitrobenzene (88 per cent), *p*-nitrobenzyl chloride (115 per cent) and ethacrynic acid (37 per cent). 3-Methylcholanthrene did not increase activity for 1,2-epoxy-3-(*p*-nitrophenoxy)propane in the kidney. Dietary phenobarbital and 3,4-benzo(α)pyrene had no inductive effects in the kidney.

The recent literature contains a number of reports concerning the influence of dietary and nutritional factors on drug metabolism [12, 13, 15, 21, 22]. Benzpyrene hydroxylase activity is affected by diet and starvation [23, 24], and glutathione *S*-transferase activity is reduced upon fasting [10]. Induction of microsomal oxidases by cruciferous plants, charcoal-broiled food and carcinogens in the diet has been described [13–15]; however, the glutathione *S*-transferases have not been evaluated from the viewpoint of dietary xenobiotic induction. Previous work has demonstrated induction of the transferases only with parenteral xenobiotics.

In this study, we have demonstrated the induction of hepatic, intestinal and renal glutathione *S*-transferase activities in rats which were given orally either 3,4-benzo(α)pyrene, 3-methylcholanthrene or phenobarbital in a controlled manner. In the liver, all five substrate activities were induced by dietary phenobarbital, whereas only one of these activities was not induced by either of the dietary polycyclic hydrocarbons. Interestingly, in the case of 3,4-benzo(α)pyrene this activity was with 1-chloro-2,4-dinitrobenzene, and in the case of 3-methylcholanthrene the unaffected hepatic activity was for the epoxide substrate. It is also noteworthy that with phenobarbital treatment the increase in enzyme activities with 3,4-dichloronitrobenzene, 1-chloro-2,4-dinitrobenzene and *p*-nitrobenzyl chloride was significantly greater than the increase in activities with epoxide and ethacrynic acid. Similar increases in enzyme activity were seen for all substrates in response to polycyclic hydrocarbons. We previously observed the same phenomenon with the administration of parenteral polycyclic aromatic hydrocarbons [16].

In the small intestine, dietary phenobarbital treatment resulted in induction of the activities with 3,4-dichloronitrobenzene, 1-chloro-2,4-dinitrobenzene, and *p*-nitrobenzyl chloride exclusively. In contrast, we previously showed that parenteral phenobarbital at twice the dose had no effect on two of these activities, having selectively induced activity only for *p*-nitrobenzyl chloride in the more distal intestine [10]. In the intestine, dietary 3,4-benzo(α)pyrene induced activity for ethacrynic acid in all three segments and induced activity for epoxide only in the proximal segment. 3-Methylcholanthrene in the diet induced activity only for 1-chloro-2,4-dinitrobenzene (proximal and middle) but did not alter the levels of the other activities in the three segments of the small intestine. Previous work with parenteral administration of these two polycyclic aromatic hydrocarbons at about half the dose demonstrated induction of activities of *p*-nitrobenzyl chloride and ethacrynic acid in the more distal intestine.

In the kidney, dietary phenobarbital and 3,4-benzo(α)pyrene were without effect on the transferases, whereas 3-methylcholanthrene significantly induced activity for 1-chloro-2,4-dinitrobenzene, *p*-nitrobenzyl chloride and ethacrynic acid. In contrast, previous work with parenteral administration of xenobiotics showed phenobarbital induction of activity for *p*-nitrobenzyl chloride and 3-methylcholanthrene, and 3,4-benzo(α)pyrene induction of activity for 3,4-dichloronitrobenzene and *p*-nitrobenzyl chloride in the kidney [17].

In summary, glutathione *S*-transferase activity for several substrates is induced in the liver, small intestine and kidney by orally administered phenobarbital, 3-methylcholanthrene and 3,4-benzo(α)pyrene. In contrast to parenteral administration, phenobarbital in the diet has a greater influence on the transferases in the small intestine. The phenobarbital induction in the liver and small intestine is significantly greater for activity with 3,4-dichloronitrobenzene, 1-chloro-2,4-dinitrobenzene and *p*-nitrobenzyl chloride, as opposed to activity with epoxide or ethacrynic acid. This difference in degree of induction is not seen with polycyclic aromatic hydrocarbons and suggests a greater induction of certain transferases by phenobarbital. In each of the organs there are differences in the inductive effects of dietary 3,4-benzo(α)pyrene and 3-methylcholanthrene. In addition, in no organ is the inductive spectrum of these two dietary carcinogens the same for the oral the parenteral route of administration. The explanation for these differences awaits further study but could be related either to fundamental differences in the mechanism of action of the two hydrocarbons or to differences in absorption, metabolism or bioavailability of ingested polycyclic hydrocarbons. Thus, this study demonstrates that the route of entry of a given xenobiotic plays an important role in the induction of the glutathione *S*-transferases in various organs.

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* NS = not significant.

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Lysolecithin is a selective reversible inhibitor of mitochondrial monoamine oxidase

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It is now well established that in rat liver and many other tissues there are two forms of mitochondrial monoamine oxidase, which differ in their substrate specificity for amines [1]. These have been called the A-enzyme and the B-enzyme, a designation originally based on their differential sensitivity to the irreversible inhibitor clorgyline® (*N*-methyl-*N*-propargyl-3-(2,4-dichlorophenoxy) propylamine) as shown by Johnston [2]. These two enzyme species appear to have immunologically identical active sites, the differences in inhibitor sensitivity and substrate specificity observed in the membrane bound state presumably arising from lipid modification of a single protein species [3–5]. This report demonstrates that lysolecithins show a selective reversible inhibition of the A and B forms of mitochondrial monoamine oxidase. Rat liver mitochondrial outer membranes were purified as described previously, except that the final dialysis was against 10 mM K phosphate buffer, pH 7.2 [6]. Pure preparations of synthetic myristoyl lysolecithin (C14) and palmitoyl lysolecithin (C16) were isolated as products of the action of cabbage phospholipase A_2 on pure dimyristoyl lecithin and dipalmitoyl lecithin respectively as described in detail [7].

The activity of the B-enzyme was followed spectrophotometrically using benzylamine HCl as the substrate and the activity of the A-enzyme using a radio-assay for [^{3}H]-5-hydroxyindole acetaldehyde production using [^{3}H]-5-hydroxytryptamine as substrate [6, 8]. All assays were carried out in 50 mM K phosphate buffer, pH 7.2, as Tris buffers have been found to inhibit the A and B enzymes selectively [9]. Assays were carried out at 30° under air saturating conditions. Time courses were linear under all conditions, and initial rates of reaction were measured. All chemicals were of A.R. purity.

The oxidative deamination of both benzylamine and 5-hydroxytryptamine was inhibited in a fully reversible fashion by both of the lysolecithins, and exhibited no time dependence. The reversibility could be demonstrated by dilution, or by centrifuging the membranes (100,000 for 1 hr) and resuspending them in fresh 10 mM K phosphate buffer, pH 7.2. The recovered activity was > 95 per cent, and was all in the pellet. Double reciprocal plots of the steady state kinetic data for palmitoyl lysolecithin inhibition of benzylamine (B-enzyme) and 5-hydroxytryptamine (A-enzyme) oxidations are shown in Fig. 1. The inhibition is mixed in form, altering both the apparent V_{max} and K_m for substrate (yielding two K_i values), a similar result being obtained for myristoyl lysolecithin. Dixon replots, slope and intercept replots of this data were linear in all cases, and the various inhibition constants (K_i) demonstrating affinity of the lysolecithins for the two enzyme species are listed in Table 1.

That the inhibition was freely reversible, instantaneous and subject to steady state kinetic analysis with no anomalies, suggests that the lysolecithins interact freely with a site on the enzyme's surface exposed to the aqueous environment, rather than with one buried in the bilayer. This is not too surprising, as experiments have indicated extensive hydrophobic areas in the area of the active site of monoamine oxidase [10, 11]. Both the palmitoyl and myristoyl lysolecithins appear to be equally efficacious as inhibitors of the two enzyme species, however there appears to be a distinct preference for their interaction with the B enzyme (benzylamine as substrate). This is demonstrated by a 4–8 fold lower value for the K_i (slope) and 6–7 fold lower value for the K_i (intercept) shown towards the B-enzyme.

This report demonstrates that lipids can selectively modulate the activity of mitochondrial monoamine oxidase, albeit in a reversible fashion. This selective modulation may function *in vivo*, for the normal concentration of lysolecithin in rat liver has been estimated as 1.5 mg/ml (approx. 2.9 mM) considering a uniform distribution