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SUBSTRATE-SELECTIVE INDUCTION OF RABBIT HEPATIC UDP-GLUCURONYLTRANSFERASES BY ETHANOL AND OTHER XENOBIOTICS

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Abstract—Male New Zeland white rabbits were treated with various inducers of hepatic metabolism enzymes to characterize the induction of UDP-glucuronyltransferase (UDP-GT) enzymes. Rabbits were pretreated with phenobarbital, 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT), 3-methylcholanthrene, β-naphthoflavone, Aroclor 1254, ethanol, *trans*-stilbene oxide, pregnenolone-16α-carbonitrile, or clofibric acid. Hepatic microsomes from treated and control animals were incubated with the GT_1-type substrates, *p*-nitrophenol and 1-naphthol; the GT_2-type substrate, morphine; and the steroid substrate, estrone. Compared to the rat, the rabbit was particularly resistant to UDP-GT induction. Ethanol was the most potent inducer for both GT_1 and GT_2 activities, but it failed to induce steroid (estrone, estradiol, and testosterone) UDP-GT activities. Ethanol pretreatment increased oxazepam-GT but it decreased bilirubin-GT activity. 3-Methylcholanthrene (3MC) and β-naphthoflavone (BNF) are the prototypic GT_1 inducers in the rat, but 3MC caused no induction of GT_1 activity and BNF caused induction of both GT_1 and GT_2 activities in the rabbit. None of the xenobiotic pretreatments increased the hepatic microsomal glucuronidation of estrone. These results demonstrate that the induction of UDP-GT activities, and the use of this phenomenon to classify UDP-GT forms, is somewhat species-specific and cannot necessarily be extrapolated from rats to other species. In addition, the substrate selectivity of ethanol-induced microsomal UDP-GT was established.

Substrate conjugation with glucuronic acid, catalyzed by microsomal UDP-glucuronyltransferase (UDP-GT)† (EC 2.4.1.17), is quantitatively the most important phase II metabolic transformation [1]. UDP-GT activity has profound effects on the disposition, metabolism and excretion of many xenobiotics and of several potentially toxic endogenous compounds such as steroids and bilirubin. Considerable evidence suggests the existence of several UDP-GT isozymes with differing substrate specificities. Indirect indicators of multiple UDP-GT forms include developmental studies [2] and substrate-specific induction of UDP-GT activities by drugs or hormones [3, 4].

Extensive studies, involving differential induction of rat and mouse UDP-GT activities, have yielded a tentative classification of at least two functionally distinct enzyme forms. One form, GT_1, is induced by pretreatment with 3-methylcholanthrene (3MC) and preferentially conjugates GT_1 substrates such as *p*-nitrophenol and 1-naphthol. Another form, GT_2, is induced by phenobarbital (PB) and conjugates GT_2 acceptors such as morphine and chloramphenicol [3]. Additional studies indicate the existence of other enzyme forms specific for estrogens [5] and bilirubin [6].

Recently, definitive evidence for UDP-GT polymorphism has appeared with the physical separation and purification of substrate-specific enzyme forms from rat, mouse, and rabbit hepatic microsomes. Ion-exchange and affinity chromatography have been used to isolate GT_1, GT_2, and estrone-GT activities from solubilized rat and rabbit hepatic microsomes [7–9]. Pretreatment of rats with 3MC produces increased levels of purified GT_1 (1-naphthol) activity [10]. Thus, changes in physical and chemical characteristics of UDP-GT forms after induction may now be assessed with purified isozymes.

Rabbit hepatic microsomes have been used frequently for separation and purification of UDP-GT isozymes since rabbit microsomes generally possess increased stability and higher activities than other sources [8]. However, the functional heterogeneity of rabbit hepatic UDP-GT has not been as fully characterized as that of rats and mice. Surprisingly, 3MC, the prototypic GT_1 inducer in rats and mice, does not induce GT_1 activities in rabbits [11]. In light of the significant use of rabbit liver as a source for studies on purified UDP-GT isozymes, and the paucity of literature concerning the functional heterogeneity of UDP-GT in rabbit hepatic microsomes, we investigated substrate induction patterns in rabbits after treating them with eight xenobiotics known to differentially stimulate UDP-GT activities in rats. Ethanol was also utilized as an inducer as it was shown previously to strongly induce GT_1 activity

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† Abbreviations: UDP-GT, UDP-glucuronyltransferase; ARO, Aroclor 1254; DDT, 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane; UDPGA, uridine-5-diphosphoglucuronic acid; CLOF, clofibric acid; TSO, *trans*-stilbene oxide; BNF, β-naphthoflavone; 3MC, 3-methylcholanthrene; PB, sodium phenobarbital; UNI, uninduced; ETOH, ethanol; and PCN, pregnenolone-16α-carbonitrile.

in the rabbit [12]. Substrate activities were chosen from each of the substrate groups (GT_1, GT_2, and steroids). Microsomes from ethanol-treated animals were assayed with several additional substrates to further delineate the specificity of ethanol induction. The results indicate that the presently accepted substrate/inducer patterns for hepatic UDP-GT may well be a species-specific phenomenon.

MATERIALS AND METHODS

Chemicals. 1-[1-^{14}C]Naphthol (24 mCi/mmole) and [N-*methyl*-^{14}C]morphine hydrochloride (24 mCi/mmole) were obtained from Amersham, Arlington Heights, IL. [4-^{14}C]Estrone (57 mCi/mmole), [4-^{14}C]β-estradiol (57 mCi/mmole) and [4-^{14}C]testosterone (52 mCi/mmole) were purchased from New England Nuclear, Boston, MA. Aroclor 1254 (ARO) and DDT were purchased from Analabs, Inc., North Haven, CT. UDPGA, Lubrol PX, 1-naphthol, *p*-nitrophenol, estrone, testosterone, β-estradiol, bilirubin, clofibric acid (CLOF), *trans*-stilbene oxide (TSO), β-naphthoflavone (BNF), 3-methylcholanthrene (3MC) and a plasma ethanol diagnostic kit were purchased from the Sigma Chemical Co., St. Louis, MO. Tris buffer, $MgCl_2 \cdot 6H_2O$ and ethanol were purchased from Baker Chemicals, Phillipsburg, NJ. Sodium phenobarbital (PB) was purchased from Merck, Rahway, NJ. Liquid diets were purchased from Bio-Serv, Inc., Frenchtown, NJ. Pregnenolone-16α-carbonitrile (PCN) was a gift from Dr. Paul W. O'Connell of the Upjohn Co., Kalamazoo, MI. Oxazepam was a gift from Dr. Hans W. Ruelius of Wyeth Laboratories, Inc., Philadelphia, PA. Emulgen 911 was a gift from KAO-Atlas Ltd., Tokyo.

Animal pretreatment and microsomal preparation. Male New Zealand white rabbits (2.5 to 3.5 kg) were fed compressed food pellets produced by the feed plant of Washington State University, unless otherwise indicated. Inducing agents were dissolved in olive oil and given once i.p., unless otherwise specified, at the following doses: BNF (100 mg/kg); DDT (160 mg/kg); ARO (500 mg/kg); 3MC (50 mg/kg); TSO (350 mg/kg once daily for 4 days); CLOF, sodium salt (300 mg/kg, dissolved in saline, s.c. daily in the neck area for 7 days); PCN (75 mg/kg in a 2% Tween 80 in saline solution, daily for 4 days); PB (50 mg/kg in saline, daily for 4 days); and ethanol (given as 10% of the drinking water for 14 days). Ethanol was also administered in a liquid diet, as described by DeCarli and Lieber [13] for 6 weeks. The control diet contained protein (18% of total calories), fat (35% of total calories), dextrin-maltose as carbohydrates (47% of total calories), vitamins, and trace elements. The alcohol diet was identical except that a portion of the carbohydrates was replaced isocalorically by ethanol (36% of total calories). Blood alcohol levels were determined with a Sigma plasma ethanol diagnostic kit on ear vein blood samples from ethanol-treated animals.

Male Sprague–Dawley rats (200–250 g) were pretreated i.p. with 3MC and PB according to the dosing regimens described for rabbits.

Microsomes were prepared as previously described [12]. Microsomal preparations were diluted to 10 mg protein/ml with 50 mM Tris–acetate (pH 7.4), which contained 1.0 mM EDTA and 20% (v/v) glycerol and stored at −20° for up to 8 weeks. No decrease of UDP-GT activities was observed during this time. Protein concentrations were determined with a Bio-Rad (Richmond, CA) protein assay kit that uses a Coomassie blue reagent.

UDP-glucuronyltransferase assays. Microsomes were shaken at 37° with substrate, UDPGA, $MgCl_2$ and 50 mM Tris–acetate buffer. Reaction rates were linear with respect to time and protein concentration. Rates were maximized for the particular detergent activator used in each assay. Enzyme activities towards the aglycones were assayed using the following conditions and substrate concentrations by methods already described (unless otherwise specified): 1 mM oxazepam [14], 1 mM *p*-nitrophenol [12]; 2 mM estrone, 2 mM estradiol, and 2 mM testosterone in the presence of 0.05% (v/v) Emulgen 911 according to the procedure of Dutton [1] for estradiol; 0.34 mM bilirubin in the presence of 0.05% Emulgen 911 [15]. 1-Naphthol activity: 0.75 mM 1-naphthol dissolved in 0.05% (v/v) dimethyl sulfoxide, 0.03 μCi [^{14}C]1-naphthol, 4 mM UDPGA, 5 mM $MgCl_2$, 0.05% (w/v) Lubrol PX and 600 μg microsomal protein in a total volume of 1 ml. The reaction was terminated after 1 min with the addition of 1 ml 0.6 M glycine/0.4 M trichloroacetic acid (TCA). The aqueous mixture was extracted with 15 ml $CHCl_3$ to remove unreacted naphthol. After centrifugation, 500 μl of the aqueous phase was removed, added to 10 ml scintillant, and counted by liquid scintillation. Morphine activity: 1.5 mM morphine sulfate, 0.10 μCi [^{14}C]morphine hydrochloride, 2 mM UDPGA, 0.07% (w/v) Lubrol PX and 3 mg microsomal protein in a total volume of 2 ml. This reaction was terminated after 5 min with 1 ml of cold TCA. After centrifugation, 1 ml of supernatant fraction was added to a test tube containing 0.2 ml of 1 M NaOH, 0.3 ml H_2O, 2 ml 40% (w/v) K_2HPO_4 and 0.5 ml morphine sulfate (0.05%, w/v). This mixture was extracted twice for 30 sec with 15 ml ethylene dichloride/amyl alcohol (7:3), and 500 μl of the aqueous phase was removed and counted. In some cases, the activating detergent was replaced by Tris buffer to assess the activities of unactivated microsomes.

Statistics. Differences in activities between control and induced microsomes were evaluated for statistical significance by means of the two-tailed Student's *t*-test.

RESULTS

Rat microsomal UDP-GT activities. In agreement with previous studies of substrate-selective induction of rat UDP-GT activities [3, 5], 3MC pretreatment effectively increased *p*-nitrophenol-GT activity (314%) while failing to stimulate morphine-GT activity (Table 1). Conversely, PB pretreatment produced a large increase in morphine-GT activity (448%) while causing a smaller but significant increase (55%) in *p*-nitrophenol-GT activity.

Rabbit microsomal GT_1 activities. Ethanol pretreatment provided the greatest increases in rabbit microsomal *p*-nitrophenol- and 1-naphthol-GT

Table 1. Effects of phenobarbital or 3-methylcholanthrene administration on rat liver microsomal UDP-glucuronyltransferase activities

Substrate	Activity (nmoles·min^{-1}·mg^{-1})		
	Control	Phenobarbital	3-Methylcholanthrene
p-Nitrophenol	52.4 ± 13.6	81.0 ± 9.2* (1.6)	217.2 ± 17.7* (4.1)
Morphine	6.1 ± 1.2	33.6 ± 3.3* (5.5)	6.4 ± 1.2 (1.0)

Values are the mean ± S.D. of three determinations from each of three animals. Numbers in parentheses represent the fold change over control values.
* Significantly increased over controls ($P < 0.01$).

activities, enhancing conjugation rates by 49 and 34% respectively (Figs 1 and 2). The inductive effect of ethanol was more pronounced when animals were pair-fed isocaloric liquid diets; treatment with the ethanol diet produced a *p*-nitrophenol-GT activity of 309 nmoles·mg^{-1}·min^{-1} compared with 138 nmoles·mg^{-1}·min^{-1} after the control diet, a 123% increase. The rabbits that received ethanol in the drinking water consumed 25–35 ml ethanol per day and had a blood alcohol level (BAL) of 0.03 ± 0.01% (g/100 ml), whereas rabbits fed the ethanol liquid diet daily consumed 40–45 ml ethanol and had a BAL of 0.04 ± 0.02%. The isocaloric diets were developed [13] to avoid the unequal caloric intake that occurs when ethanol is added to drinking water. In the liquid diets, a portion of the carbohydrate in the alcohol diet is replaced isocalorically by ethanol. However, a study [16] involving manipulation of dietary caloric intake in rats showed that the low carbohydrate content of the ethanol liquid diet contributes to ethanol induction of the microsomal ethanol-oxidizing system. This results in exaggerated differences between enzyme activities from control and ethanol diets. This same study showed that a hypercaloric diet has no effect on microsomal enzyme activities. Since the daily average ethanol

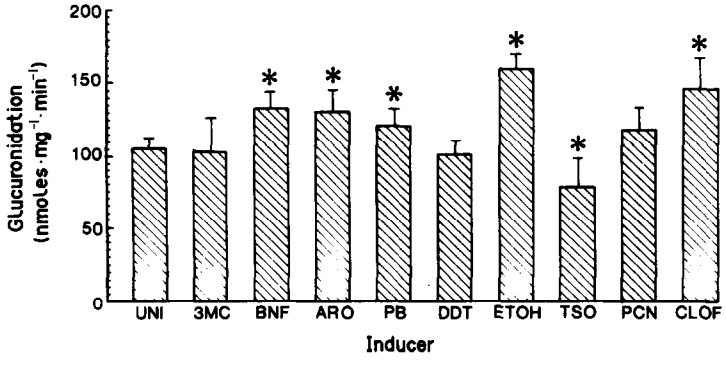

Fig. 1. Effect of inducer pretreatment on *p*-nitrophenol-GT activity. Values are the mean ± S.D. for at least three determinations from each of at least three animals. Asterisks indicate values significantly different from uninduced (UNI) ($P < 0.05$).

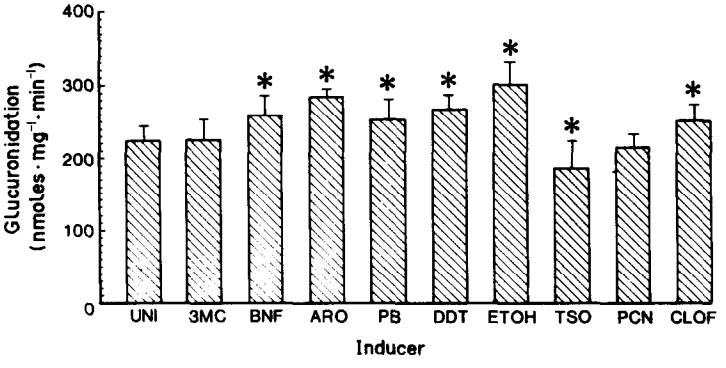

Fig. 2. Effect of inducer pretreatment on 1-naphthol-GT activity. Values are the mean ± S.D. for at least three determinations from each of at least three animals. Asterisks indicate values significantly different from UNI ($P < 0.05$).

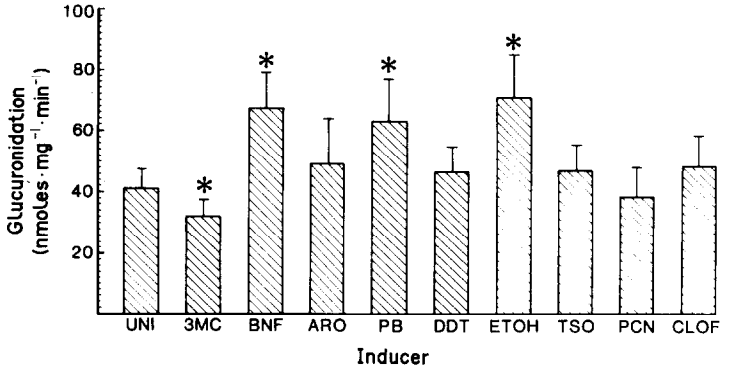

Fig. 3. Effect of inducer pretreatment on morphine-GT activity. Values are the mean ± S.D. for at least three determinations from each of at least three animals. Asterisks indicate values significantly different from UNI ($P < 0.05$).

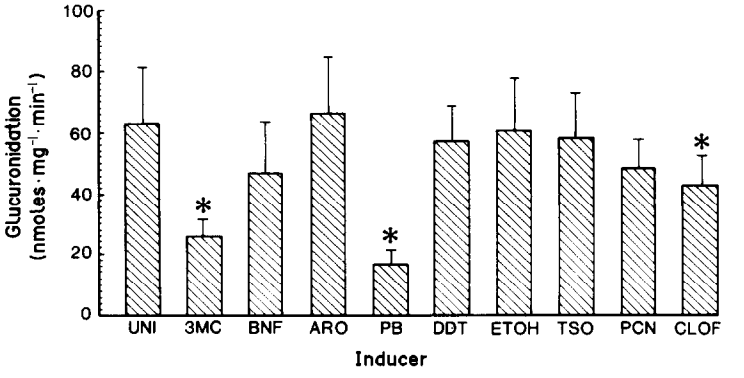

Fig. 4. Effect of inducer pretreatment on estrone-GT activity. Values are the mean ± S.D. for at least three determinations from each of at least three animals. Asterisks indicate values significantly different from UNI ($P < 0.05$).

intake and BALs produced by the two different ethanol treatments were similar, we used a protocol of ethanol in the drinking water as the ethanol treatment, due to its simplicity.

Aroclor 1254, CLOF, PB and BNF were less potent inducers of the two GT_1 substrates than was ethanol. DDT caused a 19% increase in 1-naphthol-GT activity without affecting *p*-nitrophenol conjugation rates, while TSO produced significant decreases in both activities. Surprisingly, 3MC, the prototypic GT_1 inducer for rats and mice, produced no enhancement of either activity, even when the administered dose was increased from 50 to 200 mg/kg. PCN, an inducer of bilirubin-GT in rats [3], had no effect on GT_1 activities.

Rabbit microsomal GT_2 activity. Ethanol pretreatment again produced the largest increase in activity, raising the rate of morphine conjugation 72% over values from untreated animals (Fig. 3). PB, the prototypic GT_2 inducer in rats and mice, also increased morphine-GT activity (54%), as did BNF (65%), a compound normally associated with GT_1 induction in other species. DDT has been classified as a GT_2 inducer in rats [5], but had no effect on morphine-GT activity in this study. 3MC decreased conjugation rates slightly, whereas the remaining inducers did not influence morphine-GT activity.

Rabbit microsomal estrone-GT activity. While no inducer raised estrone-GT activity above the control value (Fig. 4), PB, 3MC, and CLOF decreased activity, with PB causing the largest (74%) decrease in conjugation rate.

Substrate selectivity of ethanol induction. In addition to the substrates described above, microsomes from untreated and ethanol-treated rabbits were assayed for UDP-GT activities with bilirubin, estradiol, testosterone, and oxazepam (Table 2). Estradiol and testosterone activities were unaffected by ethanol treatment, whereas oxazepam-GT activity was increased by 47% and bilirubin-GT activity was lowered by 37%. When activities were measured in the native state, ethanol-induced changes in UDP-GT activities followed the pattern observed in the activated state. The only difference caused by detergent activation was that, in the native state, ethanol pretreatment showed a 144% increase in morphine-GT activity, while in the activated state only a 72% increase was observed.

DISCUSSION

The results of this study indicate that rabbit hepatic UDP-GT does not respond quantitatively to xenobiotic pretreatment in the fashion typically observed

Table 2. Effect of ethanol treatment on rabbit hepatic microsomal UDP-GT activities measured in the native and activated state

	Activity [nmoles·min^{-1}·(mg protein)$^{-1}$]			
	Control		Ethanol-induced	
Substrate	Native	Activated	Native	Activated
p-Nitrophenol	38.5 ± 4.8	107.7 ± 6.9	53.5 ± 6.2* (1.4)	160.4 ± 10.7* (1.5)
1-Naphthol	84.4 ± 8.0	227.8 ± 19.7	114.5 ± 6.6* (1.3)	305.1 ± 31.4* (1.3)
Morphine	4.8 ± 0.4	41.1 ± 6.4	11.9 ± 1.3* (2.4)	70.7 ± 14.2* (1.7)
Oxazepam	0.093 ± 0.009	0.15 ± 0.009	0.13 ± 0.010* (1.4)	0.22 ± 0.012* (1.5)
Bilirubin	0.28 ± 0.013	0.46 ± 0.020	0.22 ± 0.012 (0.8)	0.29 ± 0.011 (0.6)
Estrone	37.8 ± 5.4	63.7 ± 17.6	37.7 ± 3.5 (1.0)	60.4 ± 17.8 (1.0)
Estradiol	30.0 ± 3.7	69.4 ± 9.9	33.9 ± 5.0 (1.0)	62.5 ± 12.8 (1.0)
Testosterone	2.0 ± 0.20	2.79 ± 0.23	2.0 ± 0.43 (1.0)	2.64 ± 0.17 (1.0)

Values are the mean ± S.D. for at least three determinations from each of at least three animals. Numbers in parentheses represent fold change from control values.
* Significantly increased over controls ($P < 0.01$).

for rats. While in rats and mice, increases of 400–600% are observed in certain UDP-GT activities after treatment with appropriate inducers [5], the largest activity enhancement we observed in the rabbit was the 123% increase in *p*-nitrophenol-GT activity produced by the ethanol liquid diet pretreatment. Activity increases of less than 100% for other inducers were more typical.

The lack of a large induction response could conceivably have been the result of inadequate dosing; however, in several cases (e.g. 3MC, BNF, Aroclor), a 4-fold increase in the amount of inducer failed to produce significant increases in activities above those observed at the loser dosages. There were direct indications that, in fact, the rabbits were receiving a substantial body load of xenobiotic: 3MC pretreatment at 50 mg/kg produced the spectrally distinct cytochrome P-448 in the liver, a phenomenon normally associated with induction of specific isozymes of the cytochrome P-450 monooxygenases; PB pretreatment at 50 mg/kg caused a significant increase in liver weight and protein content (data not shown); a larger PB dose of 80 mg/kg was lethal; and ethanol pretreatment produced a significant BAL of 0.02 to 0.05%.

The literature reveals that, when rabbit hepatic UDP-GT activities are measured after xenobiotic pretreatment, little or no induction is observed. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin, a potent inducer of UDP-GT activities in the rat, failed to enhance rabbit UDP-GT activities [17], and 3MC [11] lacked inductive capabilities in the rabbit. Our work confirms and extends these reports and suggests that either rabbits are anomalous in their lack of a significant UDP-GT reduction response or the UDP-GT induction phenomenon itself may be peculiar only to certain species. In a study using human liver microsomes, patients treated with PB until the day of death exhibited maximal increases in various UDP-GT activities of 100–200% as compared to values from untreated patients [18]. Thus, relatively weak UDP-GT induction responses produced by xenobiotic treatment may be a characteristic shared by rabbit and man.

The qualitative aspects of the induction patterns also differed widely between the rat and rabbit. While PB behaved as a selective GT_2 inducer in the rabbit, as evidenced by increased induction of morphine-GT (54%) over 1-naphthol-GT (12%) and *p*-nitrophenol-GT (15%), 3MC failed to increase activity. BNF, normally considered a GT_1 inducer, produced an induction pattern similar to that of PB, selectively increasing morphine-GT (65%) more than 1-naphthol-GT (15%) or *p*-nitrophenol-GT (22%). Thus, in the rabbit, PB and BNF appeared to be selective GT_2 inducers, whereas 3MC failed to stimulate any of the activities. CLOF and ARO acted as selective GT_1 inducers in the rabbit, enhancing 1-naphthol-GT and *p*-nitrophenol-GT without affecting morphine-GT. This is a further deviation from observations in the rat, where CLOF fails to induce morphine-GT while ARO induces both GT_1 and GT_2 activities [5].

The epoxide hydrolase inducer, TSO, significantly lowered GT_1 activities without affecting other UDP-GT activities. UDP-GT activities in rats pretreated with high doses of TSO were decreased, and it was suggested that TSO or a metabolite might interfere with activity assays [5]. However, we believe that TSO is probably not present in significant amounts in the microsomal preparation and that the low conjugation rates are probably due to TSO induction of other proteins, producing a net decrease in UDP-GT activities on a per milligram of protein basis.

Estrone glucuronidation activity proved resistant to induction by the compounds tested (Fig. 4), paralleling previous observations for rats in which estrone, and steroid glucuronidation in general, did not respond to a series of inducing agents [5, 19]. In fact, PB, 3MC, and CLOF all produced large decreases in estrone-GT activity. These activity decreases may be due to either a loss in catalytic viability of existing estrone-GT or a decrease in enzyme content. The absence of estrone-GT inducibility and the unique sensitivity of this isozyme to activity loss suggest that estrone-GT is less susceptible to xenobiotic inducers that produce enhanced levels of other UDP-GT enzyme forms.

The inductive effects of ethanol consumption on rabbit hepatic cytochrome P-450 monooxygenase levels are well documented [20], but little is known of the influence of ethanol on UDP-GT activities in rabbits. Chronic consumption of ethanol in male Wistar rats does not increase significantly *p*-nitrophenol-GT microsomal activities [21]. In the present study, however, ethanol pretreatment in rabbits produced the largest increases in 1-naphthol-, *p*-nitrophenol-, and morphine-GT activities. In addition, oxazepam-GT activity was increased 47% over control values while bilirubin-GT activity was decreased by 37% (Table 1). Oxazepam has been classified as a GT_2 substrate in studies performed with rat and rabbit liver microsomes [14, 22]. Therefore, in the rabbit, ethanol consumption selectively induces GT_1 and GT_2 activities, does not affect steroid conjugation, and lowers bilirubin-GT activity. These observations correlate well with the results of one of the few reports concerning the effects of ethanol intake on human hepatic UDP-GT [23]. In that study, hepatic biopsies from chronic alcoholics exhibited a 57% increase in *p*-nitrophenol-GT activity over samples from untreated patients, whereas the bilirubin-GT activities were decreased 33%. The lack of inductive effects by ethanol on any of the steroid-GT activities agrees with the concept of the resistance of these enzyme forms to inducers in general.

The consequences of ethanol interaction with the UDP-GT system appear to be similar to those observed with the cytochrome P-450 monooxygenase system. The physical presence of ethanol inhibits both systems, yet prolonged ethanol intake can produce increased microsomal activities. In the cytochrome P-450 system, ethanol induces a unique, isolatable cytochrome P-450 isozyme [20]. Ethanol may also induce a unique UDP-GT isozyme, and this possibility is currently under investigation in our laboratory.

UDP-GT operates in a latent, constrained state *in vivo*. There are many factors that may alter the degree of latency, including microsomal preparation and xenobiotic treatment. Our UDP-GT activities were measured in a maximally activated, non-latent state to produce a more reliable and consistent evaluation of enzyme activity. Ethanol consumption affects the phospholipid composition of biological membranes [24]. For this reason, the activities in Table 1 were measured in both the activated and latent states (with and without optimal detergent concentration), to observe changes in membrane effects caused by ethanol. Ethanol induction of GT_1 and GT_2 activities was apparent in the latent state, and therefore the increased conjugation rates are probably operable *in vivo*. In most cases, detergent activation produced similar increases in UDP-GT activities for control and ethanol-induced microsomes, indicating the lack of any change in latency. However, ethanol induction of morphine-GT was more pronounced in the unactivated than the activated state, and therefore ethanol treatment may decrease morphine-GT latency.

In conclusion, GT_1 and GT_2 enzyme forms most likely exist independently in the rabbit, since these activities have been individually isolated from rabbit hepatic microsomes. However, these isozymes do not appear to respond to xenobiotic inducers in the pattern established for rodent species. Studies performed with rats and mice have provided valuable information concerning many aspects of UDP-GT function. However, the present study suggests that the readily accepted substrate/inducer patterns that have been constructed from rat and mouse data may well be species-dependent. It is worth noting that rabbit hepatic UDP-GT induction corresponds well with existing reports of induction of human hepatic UDP-GT activities [18]. The continued exposure of man to UDP-GT inducers, and the possible substrate-selective UDP-GT induction that occurs upon exposure to prescribed drugs or other xenobiotics [18], may warrant further investigation of the rabbit and other nonrodent species as predictive models for the human UDP-GT induction response.

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