EFFECTS OF RETINOIC ACID TREATMENT OF RATS ON HEPATIC MICROSONAL METABOLISM AND CYTOCHROMES P450

Correlation Between Retinoic Acid Receptor/Retinoid X Receptor Selectivity and Effects on Metabolic Enzymes

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ABSTRACT:
Retinoids are compounds that bind to and activate one or more retinoid receptors to elicit various physiological responses. There are two families of retinoid receptors, i.e., retinoic acid receptors (RAR) and retinoid X receptors (RXR), for which the various synthetic and naturally occurring retinoids have differing selectivities. The synthetic analogs LG100268 and LGD1069 (Targetretin) are RXR-selective, whereas ALRT1550 is highly RAR-selective. Naturally occurring all-trans-retinoic acid (Tretinoin) has a degree of selectivity for RAR, whereas ALRT1057 (9-cis-retinoic acid, Panretin) is equally active at RAR and RXR (i.e., a pan-agonist). To evaluate the effects of these compounds on metabolic enzymes, male Sprague-Dawley rats received daily oral doses for 4 days, and liver microsomes were prepared on day 5. As a class, these ligands exerted profound effects on hepatic microsomal metabolic enzyme levels. Those with RAR activity decreased hepatic cytochrome P450 (CYP or P450) levels and in vitro metabolism of the compound of pretreatment, whereas those exerting predominantly RXR activity increased these parameters. A similar relationship was observed when glucuronidation was examined. Hepatic CYP2B1/2 was unaffected and CYP3A was decreased by RAR-selective ARLT1550, whereas both were induced by ligands selective for RXR. However, both RAR- and RXR-selective ligands decreased CYP1A2, whereas they induced CYP4A4. Although the mechanisms underlying these effects are not known, these results suggest that RAR- and RXR-binding ligands exert distinct effects on hepatic metabolism, and they indicate the potential for drug-drug interactions, especially involving CYP3A. The nature of such interactions would depend on the RAR/RXR selectivity of the ligand and the P450 isozymes responsible for the metabolism of coadministered drugs.

Retinoids are compounds that bind to and activate one or more of the known nuclear retinoid receptor subtypes, to modulate gene expression. A number of compounds in this class are being investigated for use as chemopreventive and chemotherapeutic agents (Gudas et al., 1987; Smith et al., 1992) and have been used clinically to treat promyelocytic leukemia, leukoplakia, severe acne, and other skin conditions (Orfanos et al., 1987; Smith et al., 1992; Vokes et al., 1993). As research progresses in this exciting field, new biological effects and potential therapeutic uses continue to be identified.

The molecular mechanisms by which retinoids exert their effects are complex. There are two classes of retinoid receptors, RAR and RXR, within each of which three subtypes (α, β, and γ) are recognized. Numerous synthetic and endogenous retinoid receptor-binding ligands, which display varying affinities for these receptors, have been identified; the term “rexinoid” has been coined to refer to compounds that are selective for RXR, and it has been proposed that the term “retinoid” be reserved for ligands that bind RAR (Mukherjee et al., 1997). Whether bound or unbound by ligand, RXR can either form homodimers or heterodimerize with other ligand-bound nuclear receptors, such as the RAR, PPAR, vitamin D receptor, thyroid hormone receptor, or “orphan receptors” (receptors for which no endogenous ligand is known) (Chambon, 1996). This dimer formation is necessary for the activity of these receptors, making RXR a key regulator of the activity of nonsteroidal nuclear receptors, including RAR and RXR itself (Mangelsdorf and Evans, 1995). Considering this role of RXR, it is obvious that the relative activities of retinoids at RAR and RXR may have profound effects on their overall biological effects. Examples of this relationship include the correlations between the RAR and RXR selectivity of ligands and their lipid-modulating (Standeven et al., 1996; Vu-Dac et al., 1996), cell-differentiating (Boylan et al., 1995), apoptotic (Boehm et al., 1995), anti-proliferative (Zhang et al., 1996), and insulin-sensitizing (Mukherjee et al., 1997) effects.

In addition to being metabolized by rat hepatic P450 enzymes (Genchi et al., 1996) and GT (Genchi et al., 1996; Sass et al., 1994), retinoids can affect P450 levels (Li et al., 1995; Tsambaos et al., 1994; Goerz et al., 1994; Westin et al., 1993) and hepatic GT activity (Rozman et al., 1987). Moreover, retinoids have been shown to modulate the activity of genes involved in oxidative metabolism.
and, specifically, to affect transcription of the gene for CYP1A1 (Vecchini et al., 1994). However, the detailed nature of these effects, and especially the relative importance of RAR and RXR activity in their expression, is not known. The present study was undertaken to assess, in rats, the effects of treatment with a number of ligands, with a range of RAR/RXR selectivities, on total P450 levels and P450 isozyme profiles. In addition, the effects of treatment with these compounds on their own rate of metabolism by P450, as well as GT, in hepatic microsomes were evaluated.

Five ligands were examined for their effects on drug-metabolizing enzymes. Of the five, two are considered rexinoids; LG100268 has the greatest selectivity for RXR ($K_i$ for RXR $>333$-fold lower than that for RAR), whereas the RXR selectivity of LGD1069 (Targetrin) is somewhat less ($K_i$ for RXR $>35$-fold lower than that for RAR) (Boehm et al., 1995). ALRT1057 (9-cis-retinoic acid, Panretin) is equally active at RAR and RXR (i.e. a pan-agonist), whereas ATRA (Tretinoin) has a degree of selectivity for RAR ($K_i$ for RAR about 30-fold lower than that for RXR) and ALRT1550 is highly RAR-selective ($K_i$ for RAR about 300-fold lower than that for RXR) (Zhang et al., 1996). The in vivo receptor selectivity of LG100268 (Standeven et al., 1996) and LGD1069 (Gottardis et al., 1996) has been demonstrated at the dose ranges used in the current study; the higher dose of LGD1069 was used because the potency of LGD1069 at RXR is 5–8-fold lower than that of LG100268 (Boehm et al., 1995). Based on literature data (Collins et al., 1994), ATRA administered to rats at 30 mg/kg/day should produce plasma concentrations that preferentially activate RAR ($K_i = 17–19$ nM) over RXR ($K_i = 290–880$ nM) (Zhang et al., 1996). Finally, an oral dose of 0.05 mg/kg/day of ALRT1550 has been shown to exert significant RXR-mediated effects in rats (Ligand Pharmaceuticals, Inc., data on file), and the peak plasma concentration projected to result from such a dose ($\sim 20$ nM) should not stimulate RXR ($K_i = 223–560$ nM) (Boehm et al., 1995).

Materials and Methods

Photolabile Retinoids. For the photolabile retinoids used in this study (ALRT1550, ATRA, and ALRT1057), all procedures were conducted under subdued ambient light, to minimize isomerization.

Chemicals. ATRA, PEG 400, CMC, Tris-HCl, KCl, sucrose, potassium phosphate, EDTA, protein standards, NADP, UDP-glucuronic acid, MgCl$_2$, ammonium acetate, glucose-6-phosphate dehydrogenase, glucose-6-phosphate, $\beta$-glucuronidase, D-saccharic acid-1,4-lactone, Brij 58, and fetal BSA were purchased from Sigma Chemical Co. (St. Louis, MO). ALRT1550 [2(E,4E,6E)-7-(3,5-di-tert-butylphenyl)-3-methylcta-2,4,6-trienoic acid], ALRT1057 (9-cis-retinoic acid), LGD1069 [4-[1-[3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl]ethyl]benzoic acid], and LG100268 [6-[1-[3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl]cyclopropyl]nicotinic acid] (fig. 1) were provided by the Departments of Retinoid Chemistry Research or Chemical Development, Ligand Pharmaceuticals, Inc. (San Diego, CA). Acetonitrile, glacial acetic acid, and Tween 80 were purchased from VWR Scientific Products (San Diego, CA).

Animal Treatment and Preparation of Microsomes. All drugs were formulated as aqueous microparticulate suspensions in 9:95% PEG 400/0.05% Tween 80/0.9% CMC/89.1% water (v/v/w/v). The formulation was prepared by dissolving drug in ethanol, adding PEG 400 (containing 0.5% Tween 80) and then diluting the solution with water during vortex-mixing to precipitate the drug. Ethanol and water were removed in vacuo using a Rotavapor evaporator (Buchi RE111) maintained at 30°C, leaving a microparticulate suspension in PEG 400 and Tween 80. The microparticulate suspension was added 9 volumes of 1% CMC. Dosing suspensions were prepared on the first day of the study and stored in a refrigerator at 2–5°C throughout the study.

Male Sprague-Dawley rats (250 g; Harlan Sprague-Dawley, San Diego, CA) were used after 1 week of acclimatization. The animals were allowed free access to food (Harlan Teklab LM-485 Diet 7012) and water at all times. Three rats were assigned to each drug treatment group. Each group was treated by oral gavage (5 ml/kg), for 4 consecutive days, with ALRT1550 (0.05 mg/kg/day), ATRA (30 mg/kg/day), ALRT1057 (30 mg/kg/day), LGD1069 (100 mg/kg/day), or LG100268 (30 mg/kg/day). In addition, four rats received vehicle daily. On day 5, the rats were euthanized by asphyxiation with carbon dioxide, and their livers were removed.

Microsomes were prepared by a method based on that of Guengerich (1982). Livers were homogenized in 50 mM Tris-HCl (pH 7.4) containing 150 mM KCl and 2 mM EDTA. Microsomes were prepared by ultracentrifugation (100,000g for 60 min) of the postmitochondrial supernatant (10,000g for 20 min). The first microsomal pellet was resuspended in 10 mM EDTA (pH 7.4) containing 150 mM KCl and was reisolated by ultracentrifugation. The washed microsomes were suspended in 250 mM sucrose and stored at −70°C.

Determination of Microsomal Protein and P450 Concentrations. Protein concentrations in the microsomal samples were determined using a Sigma Diagnostics kit (procedure 541; Sigma) based on the biuret reaction assay (Doumas et al., 1981). The absorbance of standards and samples was measured at 595 nm. P450 concentrations were determined from difference spectra of the reduced protein at 450 nm (Omura and Sato, 1964), obtained using an UVikon 941 spectrophotometer (Kontron Instruments, Zurich, Switzerland).

Western Blot Immunoassays. The relative levels of various P450 isoforms in the microsomes were measured by Western blot analysis conducted using Amersham Life Science ECL kits (Amersham International plc, Buckinghamshire, UK), which, except for CYP2C11, included the primary antibody. For CYP2C11, the primary antibody was obtained from Oxford Biomedical Research (Oxford, MI) or Gentest Corp (Woburn, MA) and the secondary antibody was obtained from Sigma. For each P450 isozyme, microsomes from control and treated rat livers were analyzed on the same gel, to allow evaluation of the effect of treatment without measurement of absolute concentrations. The amount of microsomal proteins loaded onto the gels was varied, based on data from preliminary experiments, from 10 to 60 µg, to maintain the responses in a linear range. Proteins were separated by 12% sodium dodecyl sulfate-polyacrylamide electrophoresis and were electrophoretically blotted onto nitrocellulose membranes. Blots were incubated first with primary anti-P450 and then with secondary antibody followed by streptavidin-horseradish peroxidase. Finally, detection reagents were added to the
Measurement of Microsomal Metabolism Rates. P450- and GT-mediated metabolism rates were determined in separate experiments. Six replicate tubes were used for each rat in each group. After the reaction had been started (in the case of P450, by addition of NADPH-generating solution; in the case of GT, by addition of UDP-glucuronic acid), the incubation was quenched immediately in three tubes and after various periods in the remaining three tubes. The rate of metabolism was measured by quantifying the metabolites formed over time, using HPLC with UV detection. For LGD1069, ALRT1057, and ATRA, these metabolites were 6/7-hydroxy-LGD1069, 4-hydroxy-ALRT1057, and 4-hydroxy-ATRA, respectively, for P450 incubations or acyl glucuronides for glucuronidation incubations. The chemical structures of the ALRT1550 and LG100268 metabolites remain unproven but are presumed to be monohydroxylated or acyl-glucuronidated as well. Assay parameters (substrate concentration and incubation time) were optimized for each substrate so that incubations were conducted under initial-rate conditions (data not shown).

For determination of P450-mediated metabolism, the assay mixtures contained the following, in a final volume of 0.5 ml: 1 mg/ml microsomal protein, 100 mM potassium phosphate buffer (pH 7.4), 1 mM EDTA, 1 mM MgCl2, 1% BSA, 5 mM glucose-6-phosphate, 1 mM NADP, and 1 unit/ml glucose-6-phosphate dehydrogenase. The final concentrations of ALRT1550, ATRA, ALRT1057, LGD1069, and LG100268 in the incubation were 40, 13, 18, 100, and 50 μM, respectively. After 30, 20, 20, 6, or 15 min, respectively, each reaction was stopped by addition of 1 ml of ice-cold ethanol.

For determination of GT-mediated metabolism, the assay mixtures contained the following, in a final volume of 0.5 ml: 1 mg/ml microsomal protein, 200 mM Tris buffer (pH 7.4), 10 mM MgCl2, 1.25 mM D-saccharic acid-1,4-lactone, 0.05% (w/v) Brij 58, and 1% BSA. The final concentrations of ALRT1550, ATRA, ALRT1057, LGD1069, and LG100268 in the incubation were 40, 100, 100, 65, and 50 μM, respectively. Reactions were initiated by the addition of UDP-glucuronic acid. After 30, 60, 60, 20, or 15 min, respectively, the reaction was stopped by addition of 1 ml of ice-cold ethanol.

Chromatographic Analysis. After quenching with ethanol, microsomal samples were chilled at −20°C for at least 1 hr. After centrifugation, 1-ml aliquots were evaporated under a nitrogen stream or, for ALRT1550, ATRA, and ALRT1057, in vacuo using a Savant model AS290 SpeedVac concentrator (Savant Instruments, Inc., Farmingdale, NY). Samples were reconstituted in 250 μl of 40% acetonitrile in 10 mM ammonium acetate/glacial acetic acid (100:1). Reverse-phase gradient HPLC (Hewlett-Packard model 1050), with a Microsorb-MV C18 analytical column (5 μm, 4.6 × 250 mm; Rainin Instrument Co., Woburn, MA) maintained at 40°C, was used to separate the retinoids and their metabolites. For ALRT1550, LGD1069, and LG100268, the solvent gradient was ramped linearly from 20 to 80% acetonitrile/glacial acetic acid (100:1) in 10 mM ammonium acetate/glacial acetic acid (100:1) over 20 min and was then maintained for an additional 15 min at 80% acetonitrile. For ATRA and ALRT1057, the solvent gradient was ramped linearly from 65 to 100% acetonitrile/glacial acetic acid (100:1) in 10 mM ammonium acetate/glacial acetic acid (100:1) over 11 min and was then maintained for an additional 5 min at 100% acetonitrile. Peak detection for ALRT1550, ATRA, ALRT1057, LGD1069, and LG100268 metabolites was at 340, 348, 262, and 281 nm, respectively.

Data Analysis. Statistical analyses were performed using Student’s t tests; p values of <0.05 were considered statistically significant.

Results

Effect of Treatment on Microsomal Metabolism. As a class, these compounds exerted significant effects on their own P450-mediated metabolism (fig. 2). Decreases in the P450-mediated metabolism of ALRT1550 and ATRA were seen in microsomes from rats treated with these retinoids, although the effect of ATRA treatment was not statistically significant (p = 0.06). The pan-agonist ALRT1057 did not affect its own P450-mediated metabolism, whereas treatment of rats with LGD1069 or LG100268 resulted in increased rates of metabolism of these retinoids. The same pattern was seen for GT-mediated metabolism, except that ATRA caused a significant decrease in its own glucuronidation (fig. 3).

Effect of Treatment on Total P450 Concentration. Corresponding to the observed changes in metabolic rates, ligands with significant RAR activity (ALRT1550, ATRA, and ALRT1057) tended to decrease hepatic microsomal P450 levels in rats, whereas the retinoids increased P450 (fig. 4).

Effect of Treatment on P450 Isozyme Content. Mixed results were obtained regarding effects on individual P450 isozymes (fig. 5). Most of the compounds tested induced some isozymes while reducing the levels of others; the exception was ATRA, which did not induce any isozyme. Examination of the data on an isozyme-by-isozyme basis revealed that some isozymes were affected similarly by all five ligands. For example, with the exception of ATRA, all ligands caused a significant induction of microsomal CYP3A, although the magnitude of induction was greater with the retinoids (16- and 72-fold increases with LGD1069 and LG100268, respectively). Conversely, microsomal CYP1A2 was decreased by all five ligands, although the effect was not statistically significant for ATRA or ALRT1057. Other isozymes responded differently to different compounds. Two isozymes appeared to be affected according to the RAR/RXR selectivity of the ligand. Microsomal CYP2B1/2 was induced by compounds with RXR activity, including ALRT1057, but was unaffected by the RAR-selective compounds. Similarly, CYP3A levels were induced by the retinoids, but compounds without RXR selectivity did not affect CYP3A levels. However, unlike CYP2B1/2, CYP3A levels were decreased 70% by the RAR-selective ALRT1550. The effects on microsomal CYP2C11 varied without discernible patterns, and the effects on CYP2E were limited to roughly 30% reductions by ATRA and ALRT1057.

Discussion

The existence of interactions between retinoids and P450 and GT systems is well established; retinoids both affect and are metabolized...
by these systems. The potential for the metabolism of retinoids to be affected by alterations in P450 and GT enzyme levels (caused by pretreatment with either themselves or other drugs) is demonstrated by the induction of the P450-mediated metabolism of ATRA by dexamethasone and phenobarbital (Martini and Murray, 1994) and the induction of the glucuronidation of ATRA by 3-methylcholanthrene and clofibrate (Genchi et al., 1996; Sass et al., 1994). In addition, P450 inhibitors have been shown to prolong the in vivo half-life of ATRA in rats (Van Wauwe et al., 1988, 1990) and mice (Achkar et al., 1994). Therefore, the potential for drug-drug interactions, as well as alterations in their own metabolism after repeated administration, is clearly evident for the retinoids. However, very little is known about either the nature of the effects of retinoids on these metabolic enzyme systems or the relationship between RAR/RXR selectivity and these effects. Considering the very different actions of RAR agonists and RXR agonists in other biological systems, it might be anticipated that retinoids with differing activities at RAR and RXR would have distinct effects on the P450 and GT systems. In the present work, five retinoid receptor ligands with activities ranging from highly RAR-selective to highly RXR-selective were evaluated for their effects on their own phase I and phase II metabolism and on hepatic P450 isozyme profiles. The results clearly demonstrate that, as a class, retinoid receptor ligands affect their own phase I and phase II metab-

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**FIG. 3.** Initial rates of GT-mediated metabolism of retinoids in hepatic microsomes from rats treated with the same retinoid.

Rats received daily oral doses of ALRT1550 (0.05 mg/kg), ATRA (30 mg/kg), ALRT1057 (30 mg/kg), LGD1069 (100 mg/kg), LG100268 (30 mg/kg), or vehicle for 4 days. Liver microsomes were prepared on day 5. Microsomes were incubated with the retinoid of pretreatment, and the rates of metabolite formation were measured as described in Materials and Methods. Results are the mean ± SD of the rate of metabolite formation expressed as a percentage of the rate of metabolite formation in microsomes from vehicle-treated rats (N = 3 or 4). The rates of metabolite formation in microsomes from vehicle-treated rats were as follows: ALRT1550, 10.5 ± 0.5 pmol/mg/min; ATRA, 50.2 ± 1.9 pmol/mg/min; ALRT1057, 83.8 ± 6.2 pmol/mg/min; LGD1069, 241 ± 30.0 pmol/mg/min; LG100268, 217 ± 11.2 pmol/mg/min. Asterisks, significantly different from vehicle-treated control (p < 0.05).

**FIG. 4.** Total hepatic microsomal P450 concentration in rats treated with various retinoids.

Rats received daily oral doses of ALRT1550 (0.05 mg/kg), ATRA (30 mg/kg), ALRT1057 (30 mg/kg), LGD1069 (100 mg/kg), LG100268 (30 mg/kg), or vehicle for 4 days. Liver microsomes were prepared on day 5. Total microsomal P450 was measured as described in Materials and Methods. Results are the mean ± SD of the concentration expressed as a percentage of the concentration in microsomes from vehicle-treated rats (598 ± 56.4 pmol/mg microsomal protein, N = 3 or 4). Asterisks, significantly different from vehicle-treated control (p < 0.05).

**FIG. 5.** Relative hepatic content of microsomal P450 isozymes in rats treated with various retinoids.

Rats received daily oral doses of ALRT1550 (0.05 mg/kg), ATRA (30 mg/kg), ALRT1057 (30 mg/kg), LGD1069 (100 mg/kg), LG100268 (30 mg/kg), or vehicle for 4 days. Liver microsomes were prepared on day 5. Microsomal P450 isozymes were quantified as described in Materials and Methods. Results are the mean ± SD of the isozyme content expressed as a percentage of the isozyme content in microsomes from vehicle-treated rats (N = 3 or 4); values on the bars represent the means. Asterisks, significantly different from vehicle-treated control (p < 0.05).
olism and exert profound effects on hepatic P450 isoforms profiles. Because properties other than their RAR/RXR selectivities, or even their actions at retinoid receptors, might have led to the effects observed, these data do not prove that RAR activity is associated with certain effects on these enzymes whereas RXR activity is associated with other effects. In addition, the magnitude of the effects induced by the various retinoids depends on their relative potencies at the retinoid receptors and the drug concentrations achieved at the receptors, which are functions of the administered doses and the pharmacokinetic characteristics of the compounds. Much more extensive studies would be required to evaluate the relative potencies of the different ligands to produce the observed effects. Qualitatively, however, the actions of these ligands on these enzymes are evident.

Based on the effects of repeated treatment on P450, GT, and the metabolism of the compound used for treatment, it appears that RAR activation leads to decreased microsomal metabolism, mediated by decreases in enzyme concentrations, whereas RXR activation enhances microsomal metabolism by increasing these enzymes. The case of ATRA is of special interest, because it has been found that, in the treatment of cancer, continuous administration of ATRA results in a loss of effectiveness ("retinoid resistance") resulting from progressive decreases in plasma concentrations (Muindi et al., 1994). Although ATRA metabolism is mediated in part by P450, the present data indicate that, as measured as the total enzyme level, isoform levels, and activity for the metabolism of ATRA, P450 is not induced by ATRA, at least in rats. Lipid hydroperoxides and cellular retinoic acid-binding protein are cellular components that both accelerate the metabolism of ATRA and are inducible (Muindi and Young, 1993; Fiorella and Napoli, 1994; Cornier et al., 1992). Among other possibilities, it may be that alterations in these substances, and not induction of P450, are responsible for clinical retinoid resistance.

Generally, the trends for total P450 were reflected in overall isoform levels and were probably driven by the observed changes in CYP2C11 and CYP3A, because these isoforms constitute approximately 50% of total P450 in the livers of mature male rats (Waxman et al., 1985). The effects on CYP2B1/2 and CYP3A were clearly correlated with RAR/RXR selectivity; these isoforms were unaffected (CYP2B1/2) or decreased (CYP3A) by RAR-selective compounds but induced by retinoids. The effects on CYP3A were particularly dramatic, ranging from a 70% decrease after treatment with RXR-selective ALRT1550 to a 5–9-fold induction after retinoid treatment. CYP3A is also involved in the metabolism of LGD1069 in rats (Hein et al., 1996), so that autoinduction of this isoform likely leads to the decreased drug concentrations seen after repeated administration of LGD1069 to rats (Ligand Pharmaceuticals, Inc., data on file). CYP3A4, as the major constitutive isoform present in adult human liver and the isoform responsible for the metabolism of a wide range of xenobiotics (Wrighton and Stevens, 1992), is a common mediator of drug-drug interactions. Therefore, if retinoid receptor-binding ligands cause changes in P450s in humans similar or analogous to those they cause in rats, they could alter the metabolism of themselves or coadministered drugs; the nature of these changes would depend on the RAR/RXR selectivity of the ligand and the P450 isoforms responsible for the metabolism of coadministered drugs.

The mechanisms underlying the effects of these compounds on P450 levels await further study. The correlation between RAR/RXR selectivities and effects on microsomal metabolism and P450, GT, CYP2B1/2, and CYP3A3 levels indicates that RXR activation may modulate drug-metabolizing enzymes. Whether effects of RXR activation on drug-metabolizing enzymes might be mediated through enhanced RXR homodimer formation, enhanced heterodimer formation with unknown partners, or sequestration of RXR in homodimer form (Pahl and Chytil, 1996) is not known. The situation is complicated by the observation that, for several isoforms, there is no apparent correlation between RAR/RXR selectivity and the effect of treatment, indicating that factors other than RAR and RXR selectivity are involved in these effects. The correlation between RXR activity and induction of CYP3A4 is not surprising, because peroxisome proliferators are known to induce this isoform (Gibson, 1989) and the RXR-PPAR heterodimer activates this signaling pathway (Schoonjans et al., 1996; Aldridge et al., 1995); in addition, RXR ligands alone can activate the heterodimer (Kurokawa et al., 1993). The effect of the RAR-selective ARLT1550 to induce CYP4A4 is not as easily understood, because RAR is not known to form heterodimers with PPAR; this finding invites further study.

In summary, retinoid receptor-binding ligands have profound and mixed effects on rat liver drug-metabolizing enzymes and on their own metabolism. RXR activity appears to enhance, and RAR activity appears to decrease, microsomal phase I and II metabolism of these compounds, and the levels of some isoforms. Regardless of the mechanisms involved, the complex effects on P450 isoform profiles indicate that compounds in this class have the potential to interact with the metabolism of coadministered drugs that are metabolized by P450.
antagonizes basal as well as coal tar- and glucocorticoid-induced cytochrome P4501A1 expression in human skin. Carcinogenesis (Lond) 16:519–524.


