Peroxisome proliferation is a pathophysiological condition characterized by an increased number and size of hepatic peroxisomes (Reddy and Krishnakanta, 1975; Gibson, 1993). It occurs in rodents after treatment with any of a diverse group of chemical agents called peroxisome proliferators and is associated with increased peroxisomal β-oxidation of fatty acids with a concomitant increase in the generation of hydrogen peroxide (Arnaiz et al., 1995). The latter agent may be responsible for the increased incidence of hepatocarcinogenesis in rodents treated with peroxisome proliferators (Rao and Reddy, 1987). Included among the agents that induce peroxisome proliferation are certain hypolipidemic drugs, such as nafenopin and other fibrac acid derivatives, phthalate ester plasticizers, chlorophenoxy acid herbicides and a natural product, the C19 adrenal steroid dehydroepiandrosterone (DHEA)1. The molecular events associated with peroxisome proliferation in rodents include the induced expression of hepatic peroxisomal β-oxidation enzymes including acyl-CoA oxidase (ACO1), enoyl-CoA hydratase/3-hydroxy acyl-CoA dehydrogenase (bifunctional enzyme), and 3-ketoacyl-CoA thiolase (Reddy, 1994). The microsomal CYP4A family of lauric acid ω-hydroxylases are also induced by peroxisome proliferators (Wu et al., 1989). Activity of CYP4A is thought to lead to increased production of medium- and long-chain dicarboxylic acids, providing substrates for peroxisomal β-oxidation.

Although DHEA is a normal sterol present as a sulfate conjugate in the circulation of primates (Yamada et al., 1991; Hertz et al., 1993; Arnaiz et al., 1995), its effect on peroxisome proliferation is only seen at pharmacological doses in rodents. However, DHEA feeding is associated with a number of beneficial effects that may be distinct from peroxisome proliferation, including antiobesity/antidiabetic effects in mice (Coleman et al., 1982), protection from chemically-induced and spontaneous cancer in mice (Schwartz, 1979; Inano et al., 1995), hypolipidemic and antiobesity effects in human (Nesler et al., 1988; Nesler et al., 1991) and enhanced immune response in mice (Loria et al., 1988; Ben-Nathan et al., 1992). Because of DHEA’s cancer chemoprotective properties, it may exert regulatory effects that are distinct from foreign compound peroxisome proliferators including a possible change in the inventory of drug metabolizing enzymes in liver (Wu et al., 1989).

The inductive effect of peroxisome proliferators is mediated at the level of transcription by a member of the steroid/thyroid hormone receptor superfamily termed the peroxisome proliferator activated receptor (PPAR) (Iseemann and Green, 1990). Since its initial discovery in mouse, several isoforms of PPAR have been found in rodents,
human, and Xenopus, which show differences in tissue specificity and responsiveness to peroxisome proliferators (Dreyer et al., 1992). PPARα is highly expressed in liver and was shown by targeted gene disruption to be required for the peroxisome proliferative response in mice, including the response to DHEA (Lee et al., 1995; Peters et al., 1996). Several hypolipidemic drugs, fatty acids and eicosanoids are reported to bind PPARα, but to date, DHEA or its derivatives have not been shown to be direct acting ligands (Devchand et al., 1996; Forman et al., 1997; Kliwer et al., 1997). PPARα binds to cis-acting peroxisome proliferator responsive elements (PPREs) in the 5’ region of genes as part of a heterodimeric complex with retinoid X receptor (RXR), another member of the nuclear hormone receptor family (Gearing et al., 1993; Issemann et al., 1993). RXR is a common heterodimerization partner with several nuclear hormone receptors including the retinoic acid receptor (RAR), vitamin D₃ receptor, the thyroid hormone receptor (TR), and the newly identified pregnane X receptor (PXR) (Sonenberg, 1993; Kliwer et al., 1998). Some investigators have hypothesized that competitive binding among nuclear receptors for RXR or other receptors can modulate responses to various agents (Chu et al., 1995; Miyamoto et al., 1997).

There is a relationship between thyroid hormone and some physiological effects of peroxisome proliferators. Both DHEA and nafenopin treatment decrease circulating triiodothyronine (T₃) levels by 30 to 40% and near physiological doses of T₃ have been shown to suppress DHEA-dependent induction of the CYP4A family of enzymes in rat liver and kidney (Webb et al., 1996) This effect is more pronounced for CYP4A2 relative to CYP4A1 and CYP4A3. Chu et al. (1995) demonstrated that treating rodents with T₃ decreased the ability of peroxisome proliferators to induce some of the regulated enzymes. This modulation could result from competition between PPARα and TR for their common dimerization partner RXR. T₃ may promote TR-RXR formation, thus decreasing availability of RXR for interaction with PPAR and inhibiting expression of peroxisome proliferator responsive genes. Alternatively, thyroid hormone is known to repress some genes through negative thyroid hormone response elements (nTRES) that remain poorly defined (Chatterjee et al., 1989; Carr and Wong, 1994). Also, Miyamoto et al. (1997) have demonstrated a ligand-independent mechanism in which TR competitively binds to PPREs and inhibits PPARα-mediated gene transcription. The present study was undertaken to compare the effects of DHEA and nafenopin on the expression of several genes involved in lipid and foreign compound metabolism, and to determine whether T₃ differentially modulates these effects.

Materials and Methods

Materials. Nafenopin was provided by Ciba-Geigy Co. (Ardles, NY). DHEA and T₃ were purchased from Sigma Chemical Co. (St. Louis, MO). Immature (100 g) male rats were obtained from Harlan Sprague Dawley, Inc. (Indianapolis, IN). Rat chow AIN-76A or AIN-76A chow containing 0.45% Nafenopin was provided by Ciba-Geigy Co. (Ardsley, NY).

Animal Treatments and Isolation of RNA. Sprague-Dawley rats were maintained on antioxidant free synthetic (AIN-76A) diets for several days before receiving daily i.p. injections for 4 days with corn oil vehicle or nafenopin (40 mg/kg body weight), and were killed on day 5. A second group was maintained on a diet of AIN-76A supplemented with 0.45% DHEA for 6 days with decapitation on day 7. Animals treated with T₃ were either euthyroid (sham operated) or thyroidectomized and were administered T₃ at 10 mg/100 g body weight by daily i.p. injection for 7 days. Animals were anesthetized with CO₂ before decapitation. The livers and kidneys were immediately removed after decapitation, weighed, frozen in liquid nitrogen, and stored at −70°C until they were used for RNA isolation. RNA was isolated by the procedure of Chomczynski and Sacchi (1987), washed with 4 M LiCl to remove glycogen, redissolved in denaturing solution, and reprecipitated with isopropanol. The RNA pellets were washed with 75% ethanol, dried under vacuum, dissolved in autoclaved water, and stored at −70°C.

Northern Blot Analysis. Total cellular RNA (25 µg) was incubated for 15 min at 65°C in MOPS buffer [40 mM 3-N-morpholinopropionate-sulfonic acid/10 mM sodium acetate/1 mM ethylenediamine-tetraacetic acid (EDTA)] at 17.5% deionized formaldehyde, 50% deionized formamide, and 50 µg/ml ethidium bromide. The RNA samples were separated by electrophoresis on denaturing gels containing 1% agarose, MOPS buffer, and 15% formaldehyde. Transfer was performed by capillary action onto Genescreen membranes (NEN Life Sciences Products, Boston, MA) according to manufacturer’s instructions. After overnight transfer, RNA was cross-linked to the membrane by exposure to ultraviolet radiation and drying in a vacuum oven at 80°C (Brown and Mackey, 1997). Single-stranded deoxyoligonucleotide probes were prepared by 5’ end-labeling with [γ⁻³²P]ATP. The probe for GAPDH was prepared from a rat cDNA with [α⁻³²P]CTP and a random primed DNA synthesis kit (Boehringer Mannheim Corp., Indianapolis, IN). Membranes were prehybridized for 2 h at 45°C in heat-sealed bags containing 5× standard saline phosphate-EDTA (SSPE; 50 mM NaH₂PO₄, pH 7.7, containing 0.9 NaCl and 5 mM EDTA), 1× Denhardt’s solution (0.02% Ficoll, 0.02% polyvinylpyrrolidone, 0.02% acetylated bovine serum albumin), 1% sodium dodecyl sulfate, 150 µg/ml single-stranded salmon sperm DNA, and 0% 16% formamide depending on the sequence of the oligonucleotide. For the GAPDH probe, Denhardt’s solution was increased to 5× and formamide was 50%. After prehybridization, the bags were drained and hybridization solution of the same composition excluding salmon sperm DNA and including probe at 1.5 × 10⁸ cpm/ml was added. The hybridizations were carried out overnight in a 45°C water bath. The membranes were then washed twice at room temperature for 10 min in 2× SSPE followed by a high stringency wash in 0.2× SSPE also at room temperature. For the GAPDH probe, a higher stringency (0.1× SSPE) was used. After washing, the membranes were exposed to a storage phosphor screen and scanned 24 h after a PhosphorImager (Molecular Dynamics, Sunnyvale, CA). The signals were quantified with ImageQuant software.

Construction of Plasmid Reporter Genes. For production of reporter constructs, the plasmid p71.4A2 containing an EcoRI fragment of the CYP4A2 gene from −1865 to +1192 (relative to transcription start site) was provided by Dr. Frank Gonzalez (Laboratory for Molecular Carcinogenesis, National Cancer Institute, Bethesda, MD). Plasmids pA4.2-LUC [1 and 2; with an simian virus 40 (SV40) promoter and 2 with a cytomegalovirus (CMV) promoter) were created by ligating a Dral fragment from p71.4A2 into the Smal cloning site of expression vectors pGL2.promoter and pGL2.CMV, respectively. These constructs contain CYP4A2 sequence from −1865 to −25 bases upstream of transcription. Expression vector pGL2.CMV was made by removing a 206-bp HindIII-XhoI fragment containing the SV40 promoter from pGL2.promoter (Promega, Madison, WI) and replacing it with a 630-bp EcoRI-BamHI CMV promoter fragment from pCMVβ (Clontech, Palo Alto, CA) by blunt end ligation. Expression vector for rat TRβ was provided by Dr. Ronald J. Koenig (Department of Internal Medicine, University of Michigan, Ann Arbor MI). The positive control for the T₃ response, pT109GH2RLUC, contained two copies of the rat growth hormone TRE and was provided by Dr. Doug Darling (Department of Biological and Biophysical Sciences, University of Louisville, Louisville, KY).

Cell Culture and Transient Transfections. Human hepatoma (HepG2)
cells were maintained in Dulbecco’s modified eagle medium supplemented with 10% fetal bovine serum (Atlanta Biologicals, Norcross, GA) at 37°C and 5% CO2. For transfections, cells were seeded in 6-well, 35-mm culture dishes at 5 × 105 cells per well and incubated under normal growth conditions for 16 h until they reached 50 to 80% confluency. Transfections were performed with Lipofectamine plus (Life Technologies, Inc., Gaithersburg, MD) according to the manufacturer’s instructions. Transfection mixtures were incubated for 5 h at 37°C, and the medium was removed and replaced with fresh Dulbecco’s modified eagle medium containing 10% fetal bovine serum with or without T3. Each treatment was performed in duplicate. Transfected cells were harvested 48 h later with Promega’s cell lysis reagent (25 mM Tris phosphate, pH 7.8, 2 mM EDTA, 2 mM diethiothreitol, 5% glycerol, 1% Triton X-100) according to manufacturer’s instructions. As an internal control for transfection efficiency, a β-galactosidase-expressing plasmid (pCMVβ from Clontech) was cotransfected along with luciferase reporter genes and human TRβ expression vector. β-Galactosidase activity was determined based on the method described by Rosenthal (1987). Each sample was assayed twice (with undiluted and 1:5 diluted extract) to assure the absorbance readings were within the linear range of measurement. Luciferase assays were performed by mixing 20 µl of cellular extract with 100 µl of luciferase assay reagent (from Promega) followed by measurement of emitted light in a luminometer. The final value reported for each sample, in relative luciferase (light) units, was the average of duplicate assays.

Results

Messenger RNAs for cytochrome P4504A1 (CYP4A1) and ACO1 were comparably elevated in adolescent male rats treated with either DHEA or nafenopin (Fig. 1). However, whereas ACO1 and CYP4A1 show similar induction by both nafenopin and DHEA, CYP3A23 mRNA was induced 17-fold by DHEA feeding but not by the classical peroxisome proliferator nafenopin (Fig. 1). CYP3A23 has not previously been shown to be induced in processes associated with peroxisomal β-oxidation, and its induction by DHEA may occur by a mechanism independent of peroxisome proliferation and PPARα.

In humans, DHEA levels decreased dramatically with age. There may also be age and gender related differences in the response to pharmacological doses of DHEA. To determine whether regulation by DHEA and nafenopin differed as a function of age and gender in rodents, gene expression was compared in mature (200–240 g) and immature (80–100 g) male or female rats treated with either DHEA or nafenopin. Figure 2B shows the mRNA levels for CYP4A1, CYP4A3, and CYP3A23 as a function of age and gender. CYP4A1 was dramatically induced by both DHEA (25- to 70-fold) and nafenopin (25- to 100-fold) in livers from mature or immature, male and female rats. In animals from both age groups, induction was somewhat higher in females (70- to 100-fold) than males (25- to 30-fold). The group of mature female rats, induction by DHEA was not statistically significant. This was due to a large S.D. created by an unusually high level of mRNA expression in a single animal (see the sixth lane of the Northern blot). The level of induction in individual mature female animals was 16-, 16.4-, and 44-fold. CYP4A3 was also induced by DHEA (4- to 13-fold) and nafenopin (4- to 23-fold) regardless of gender or age of the animal. The level of induction in immature animals was similar between males and females. However, in mature males, CYP4A3 was induced 13-fold by DHEA and 23-fold by nafenopin. Induction in females was only 4.6- and 4-fold by DHEA and nafenopin, respectively. Induction of CYP4A3 in mature females also did not reach statistical significance due to a large S.D. created by a strong signal from a single animal (lane 6, Northern blot). Individually, induction in these animals was 3-, 3.4-, and 7.4-fold. CYP3A23 was induced by DHEA, but not nafenopin, in both mature and immature, male and female animals. Induction in immature animals was more dramatic than in mature animals, and within this group CYP3A23 was induced to a greater extent in immature females than immature males. Again, induction of CYP3A23 by DHEA in livers of mature females did not attain statistical significance due to the unusually high level of mRNA expression in a single animal (sixth lane of Northern blot). Induction by DHEA in individual mature females was 2.4-, 2.6-, and 7.7-fold.

Previous studies have shown that induction of the CYP4A family of enzymes by DHEA is inhibited by treatment with thyroid hormone, T3 (Webb et al., 1996). To determine whether CYP3A23 may be regulated differently with respect to T3, rat liver RNA from euthyroid and thyroidectomized animals was examined for expression of ACO1, CYP4A2, and CYP3A23. Cotreatment of thyroidectomized animals with DHEA and T3 inhibited the induction of all three mRNAs (Fig. 3A, lane 6, and Fig. 3B). Thyroidectomy in the absence of T3 actually increased the signal for DHEA-induced CYP3A23 and ACO1 mR-
NAs, but slightly decreased the signal for CYP4A2 (Fig. 3A, compare lanes 2 and 4). Because there was no detectable level of mRNA in the controls, no quantitative assessment of fold induction can be made, although quantification of the signals (Fig. 3B) clearly shows these differences (compare solid and striped bars in Fig. 3B). To determine whether T_3 would repress basal expression of CYP4A2, we examined rat kidney, where this gene is expressed in the absence of DHEA or nafenopin treatment. ACO1 and CYP3A23 are not measurably expressed in rat kidney (Fig. 3A, lanes 7–10). CYP4A2 mRNA, however, exhibited a high constitutive (control) expression that was slightly increased by DHEA (lanes 7 and 8). In animals given daily injections of T_3, CYP4A2 expression in the kidney was reduced in both control and DHEA-treated animals (lanes 9 and 10).

In light of T_3's negative effect on constitutive expression of CYP4A2 mRNA in the kidney, and our observations that this gene is more sensitive to T_3 than CYP4A1 (Webb et al., 1996) it was possible

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**FIG. 2.** DHEA and nafenopin induce CYP4A and 3A mRNA expression in livers of immature and mature, male and female rats.

RNA was isolated from livers of mature (200–240 g) or immature (80–100 g) male or female rats fed a diet containing 0.45% DHEA or treated i.p. with nafenopin (NAF) in corn oil (40 mg/kg) or corn oil alone (cont). All procedures were performed as described under Materials and Methods. A. Total RNA was subjected to Northern analysis with ^32^P-labeled probes for the indicated mRNAs: CYP4A1, CYP4A3, CYP3A23, and GAPDH. Quantification of levels of specific mRNAs were generated with a PhosphorImager. Samples of RNA from three animals within each treatment group were analyzed separately. B. Relative expression of mRNAs were quantified with ImageQuant software and normalized for loading differences with GAPDH. Controls for each mRNA were assigned values of 1, and results of treatments are expressed relative to controls. Error bars represent the S.D. from a mean of three animals per treatment group. An asterisk (*) above the bar indicates significant difference from control (P < .01 determined with a paired Student’s t test); double asterisks (**) above the bar indicates significant difference from control (P < .001).
that a cis-acting nTRE may exist within the CYP4A2 gene. To investigate this possibility, we constructed a luciferase reporter gene containing 1840 bp of 5' flanking region from rat CYP4A2 (Fig. 4A). This region contains the rat CYP4A2 sequence extending from −1865 to −25 bp relative to the transcription start site, including a consensus nuclear receptor binding site motif (AGGTCA) implicated in known nTREs (34,35). In initial experiments, expression of p4A2-LUC1 was negatively regulated by T3 in HepG2 cells cotransfected with an

Fig. 3. Effect of thyroid hormone status on CYP4A2 and CYP4A23 mRNA expression of DHEA responsive genes.

RNA from immature male rats was subjected to Northern analysis as described under Materials and Methods. A, Lanes 1 through 6 each contained total liver RNA pooled from three animals per treatment group and lanes 7 through 10 contained total kidney RNA pooled from three animals per treatment group. RNA in each lane is as follows: lane 1, euthyroid control; lane 2, euthyroid + DHEA; lane 3, thyroidectomized; lane 4, thyroidectomized + DHEA; lane 5, thyroidectomized + T3; lane 6, thyroidectomized + T3 + DHEA; lane 7, control kidney; lane 8, DHEA kidney; lane 9, T3 kidney; lane 10, T3 + DHEA kidney. Euthyroid animals were sham operated; all DHEA treatments were p.o. 0.45%. T3 treated animals were given daily i.p. injections of T3 at 10 mg/100 g body weight. B, Quantification of the indicated rat liver RNAs levels were generated with a PhosphorImager. Relative expression of mRNAs were quantified with ImageQuant software and normalized for loading differences with GAPDH. The signals for ACO1, CYP3A23, and CYP4A2 from control animals were undetectable. Abbreviations: Eu, euthyroid; Tx, thyroidectomized; C, control untreated; D, DHEA; T3, thyroid hormone.
A. The plasmid construct (p4A2-LUC2) contains rat CYP4A2 sequence from −1865 to −25 bp relative to the transcription start site. A putative negative TRE (nTRE) binding motif (AGGTCA) is located at −93 bp. The CMV promoter (CMV), is linked to luciferase coding sequence indicated (LUC). B, Reporter gene p4A2-LUC2 (2 μg) or control gene (pT-109GH2RLUC) (2 μg) were transfected into HepG2 cells along with 1 μg of expression vectors pCMVβ and 0.5 μg of pTRβ (TR). Transfected cells were treated with vehicle or 1 × 10−6 M T3 and maintained under normal growth conditions for 2 days followed by harvesting of cell extracts. Luciferase and β-galactosidase activities were determined as described under Materials and Methods. All treatments were performed in duplicate. Luciferase activity in cellular extract was corrected for β-galactosidase activity and is expressed relative to controls set to 1. Error bars represent the range from the mean for duplicate transfections.

**FIG. 4. CYP4A2 5′ flanking sequence does not contain a functional nTRE.**

A. The expression vector for TRβ. However, the parental plasmid (pGL2.promoter) was also responsive to T3, making interpretation of these data impossible (data not shown). Subsequently, the SV40 promoter of pGL2 was replaced with a CMV promoter fragment to create pGL2.CMV. This vector did not respond to T3 (data not shown). When the CYP4A2 5′-flanking sequence was cloned into this vector, the resulting construct (p4A2-LUC2) was unresponsive to T3 in transfected HepG2 cells (Fig. 4B). Expression of a control luciferase construct containing the rat growth hormone TRE was induced by T3. These data do not support a model involving a negative TRE in the CYP4A2 gene, at least not within the region of the gene contained in the CYP4A2 construct (−25 to −1865).

**Discussion**

DHEA at pharmacological doses behaves like other peroxisome proliferators in inducing the general phenomenon of peroxisomal proliferation and the expression of related genes such as ACO1 and the CYP4A family in rodents. The enzyme products of these genes are generally involved in lipid metabolism and peroxisome function and are known to be induced 10- to 30-fold by peroxisome proliferators (Reddy, 1994). ACO1 is the first and rate-limiting step of peroxisomal fatty acid β-oxidation, whereas cytochrome P4504As contribute to the formation of dicarboxylic fatty acids that may be preferentially metabolized in peroxisomes as opposed to mitochondria (Reddy, 1994). Peroxisome proliferation is thought to represent a physiological response to perturbation of lipid homeostasis leading to lipid overload; it can also be initiated by vitamin E deficiency, high fat diets and certain long-chain carboxylic acids. Lee et al. (1995) and Peters et al. (1996) have shown that mice lacking a functional PPARα gene do not demonstrate peroxisome proliferation or induction of ACO1 and CYP4A genes in response to DHEA or foreign compound peroxisome proliferators. Therefore, the similar regulation of CYP4A1 and ACO1 mRNAs by DHEA and nafenopin shown in Fig. 1 likely reflects a common mechanism of induction involving PPARα. In this report, CYP3A23 was shown to be induced by DHEA in vivo, but not by nafenopin, suggesting an activity of DHEA in rodents that is regulated independent of peroxisome proliferation; i.e., not involving PPARα. This may be explained by the recent identification of an orphan nuclear receptor, the PXR, which binds to hormone response elements in CYP3A genes and is activated by naturally occurring and synthetic pregnane-derived steroids (Kliewer et al., 1998). CYP3A23 is involved in the metabolism of drugs, environmental chemicals, and...
steroids. In fact, the 3α family is considered the major form of cytochrome P450 expressed in human liver for metabolism of xenobiotic compounds (Shimada et al., 1994). Changes in the inventory of drug metabolizing enzymes in rodent liver, such as induction of CYP3A23, may contribute to cancer chemoprotection resulting from DHEA treatment.

In earlier studies examining various steroids for chemoprotective ability, one of the most potent agents was pregnenolone 16α-carbonitrile (Seyle, 1971). This compound was later found to transcriptionally activate the CYP3A23 gene in rat liver (Elshourbagy and Guzeian, 1980). The synthetic glucocorticoid dexamethasone also stimulates expression of CYP3A23 mRNA, in a fashion that has been termed a nonclassical glucocorticoid response (Simmons et al., 1987; Quattrochi et al., 1995). The response is seen with glucocorticoid receptor agonists and antagonists, such as pregnenolone 16α-carbonitrile and RU486, and also may be mediated by the recently identified PXR (Kliewer et al., 1998). DHEA demonstrates some antiglucocorticoid effects, including enhancement of immune response in mice (Loria et al., 1988; Ben-Nathan et al., 1992). It is possible that DHEA or its metabolites could stimulate the nonclassical glucocorticoid response by activating the PXR.

Both CYP4A1 and 4A3 were induced by DHEA and nafenopin independent of age or gender, although there were quantitative differences in levels of induction. In mature animals females were generally less responsive than males (Fig. 2). In immature animals, CYP4A1 induction was also less in females than males, but CYP4A3 was induced equally. The reasons for these quantitative differences are unclear, but may affect the capacity to form dicarboxylic fatty acid substrates for peroxisomal metabolism. In striking comparison, CYP3A23 was induced by DHEA but not nafenopin in both male and female rats. Induction was much more dramatic in immature than mature animals, and among the immature animals, female rats were more responsive than males. However, regardless of the age or gender of the animals this gene was induced by DHEA, and not the peroxi-

In summary, these data show that DHEA exerted regulatory effects not only on peroxisome proliferation associated genes, but also on the CYP3A23 gene, which encodes an enzyme involved in foreign compound metabolism and was not affected by the peroxisome proliferator nafenopin. This suggests an inductive process that may be independent of PPARs and perhaps associated with chemoprotection by DHEA. This effect differs quantitatively with respect to age and gender. Because we have shown that the effect of T₃ is common for DHEA and nafenopin induction of CYP4A2 (Webb et al., 1996) and DHEA induction of CYP3A23, thyroid hormone receptor apparently represses the functions of both PPARs and PXR, perhaps by competing for their heterodimerization partner RXR. Future studies should focus on mechanisms of gene regulation by DHEA, its possible interaction with PXR and how T₃ signaling pathways influence DHEA activity.

References


