Hormonal Effects on Drug Metabolism Through the CYP System: Perspectives on Their Potential Significance in the Era of Pharmacogenomics

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Abstract: Cytochrome P450 (CYP) is a group of enzymes that metabolize drugs to a more water-soluble form, rendering them available for renal excretion. The major site of CYP expression is the liver. Nearly 50% of all medications currently on the market are metabolized by the enzyme CYP3A4, while metabolism of another 35-40% occurs through enzymes CYP1A2, CYP2C19, CYP2D6, CYP3A5 CYP3A6, and CYP3A7. Here, we summarize the current knowledge of the effects of hormones on the CYP family. The term "hormone" is used in its broad sense and includes products of the major endocrine glands (i.e., thyroid, adrenals, gonads, pancreas) and compounds that are not classically considered hormones, such as neurogenic amines, cytokines, interleukins, and eicosanoids. In addition, we comment on the effects on CYP expression of states associated with profound hormonal changes, such as pregnancy, malnutrition, obesity, diabetes mellitus, systemic inflammation, and conditions of altered extracellular fluid volume or osmolality. Available data are limited and are derived primarily from *in vitro* and animal studies. Moreover, the picture is obscured by conflicting results among studies and the complexity of the regulation of the expression and activity of elements of the CYP system. While the clinical significance of hormonal effects on the CYP system remains to be determined, we anticipate that such effects will be most pertinent to drugs with a narrow therapeutic range. Further research is needed to determine the scope and significance of these effects in view of rapid advances in the field of pharmacogenomics and the ever-increasing number of drugs available for therapeutic use.

Key Words: Cytochrome, drug metabolism, endocrine, thyroid, glucocorticoid, pregnancy, diabetes, obesity, inflammation.

I. INTRODUCTION

The spectrum of physiologic and clinical responses of human subjects to a specific drug is called pharmacodynamics. These responses show considerable variation, depending on many factors, the bases of which are: a) non-genetic (age, tobacco use status, concomitant illnesses, nutrition, coadministered drugs, and exposure to environmental pollutants and other xenobiotics in general), b) genetic (gender and the expression and activity of enzymes, drug transporters, and drug targets), and c) mixed (weight, body fat percentage, and liver/kidney/cardiovascular/respiratory function of the individual). A complex interplay among the above factors, the drug itself, and the host effector systems responsible for the action of the drug will ultimately determine the response to the drug in *individual* subjects [1]. This is in contradistinction to the study of pharmacodynamics in patient *populations*, in which more predictable data can emerge about the actions of specific drugs, mainly due to the phenomenon of statistical averaging. Therefore, although the knowledge basis of using drugs for disease treatment (pharmacology) is based on population-derived studies, the significance of our exact knowledge (or at least predictive ability) of the effect of any drug on an individual patient in clinical practice cannot be overemphasized.

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Drug metabolism is carried out in two phases: *Phase I* involves the oxidation, reduction, hydrolysis, or other transformation of a given drug molecule; these chemical reactions occur mainly through the action of enzymes belonging to the cytochrome p450 (CYP) family. In *phase II*, the solubility of the drug is increased by glycuronidation, sulfation, acetylation, or methylation, thus, enhancing its elimination.

In this review, we summarize the existing data on the complex association between hormones and the CYP system. We shall use the term "hormones" broadly, including mediator molecules secreted by immune/inflammatory cells (i.e. cytokines and interleukins) and moieties that are not classically or universally considered as part of the endocrine/hormonal system but still exert systemic actions (e.g., prostaglandins, histamine, serotonin, and adrenergic agonists). Most studies are based on *in vitro* experiments or tissue- or whole animal-based experiments. Human studies in this field are scarce and generally involve a small number of patients. As a rule, modulation of the CYP system is selective for each enzyme class or subclass (as described in section III). Consequently, results have not been consistent among the existing studies. This is a novel and emerging field of study that currently contains large swaths of unexplored territory. We believe that our contribution is timely, as further study of the effect of changes in the activity of endocrine systems on CYP enzymes may explain—at least in part—unexpected, idiosyncratic, diminished, or exaggerated drug actions observed in a variety of disease states. Classification of these

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"outlier" reactions may lead to selective dose modifications or selective use (as opposed to avoidance) of specific therapeutic compounds, depending upon the presence or absence of a defined endocrine milieu in individual patients. The latter classification will undoubtedly be aided by the rapidly advancing field of pharmacogenomics and may lead (along with other advances) to the nowadays highly desirable goal of individually tailored drug therapy.

II. OVERVIEW OF THE CYTOCHROME P450 (CYP) SYSTEM

The CYP system is a constellation of enzymes responsible for most of the phase I reactions in drug metabolism. These enzymes are expressed mainly in the liver; however, they can be found in other tissues, including the kidneys, skin, intestine, lung, and brain [2]. By definition, all proteins that contain CYP domains are enzymes. Despite the tremendous diversity exhibited by the CYP system, the general structure of CYP enzymes shows distinct features; these are summarized in Fig. **1**, and define the *superfamily* of CYP proteins (presented at Internet site: http://www.icgeb.org/~p450srv/P450domains.html; last accessed on July 7, 2004).

By convention, CYP enzymes sharing more than 40% *global* sequence homology are classified as belonging to the same *family*, whereas members of the same family sharing more than 55% global homology with each other constitute a *subfamily* [3,4]. Currently, there are 18 families and 42 subfamilies in mammals with a total of 57 genes and 33 pseudogenes [3]. It is important to note that although there can be minimal *global* sequence conservation among CYP enzymes belonging in different families (as low as 10%), when the comparison is limited to their *CYP* domains, the degree of similarity is usually >50% (sequence alignments presented at Internet sites: http://www.icgeb.org/~p450srv/p450apub192.html and http://www.icgeb.org/~p450srv/

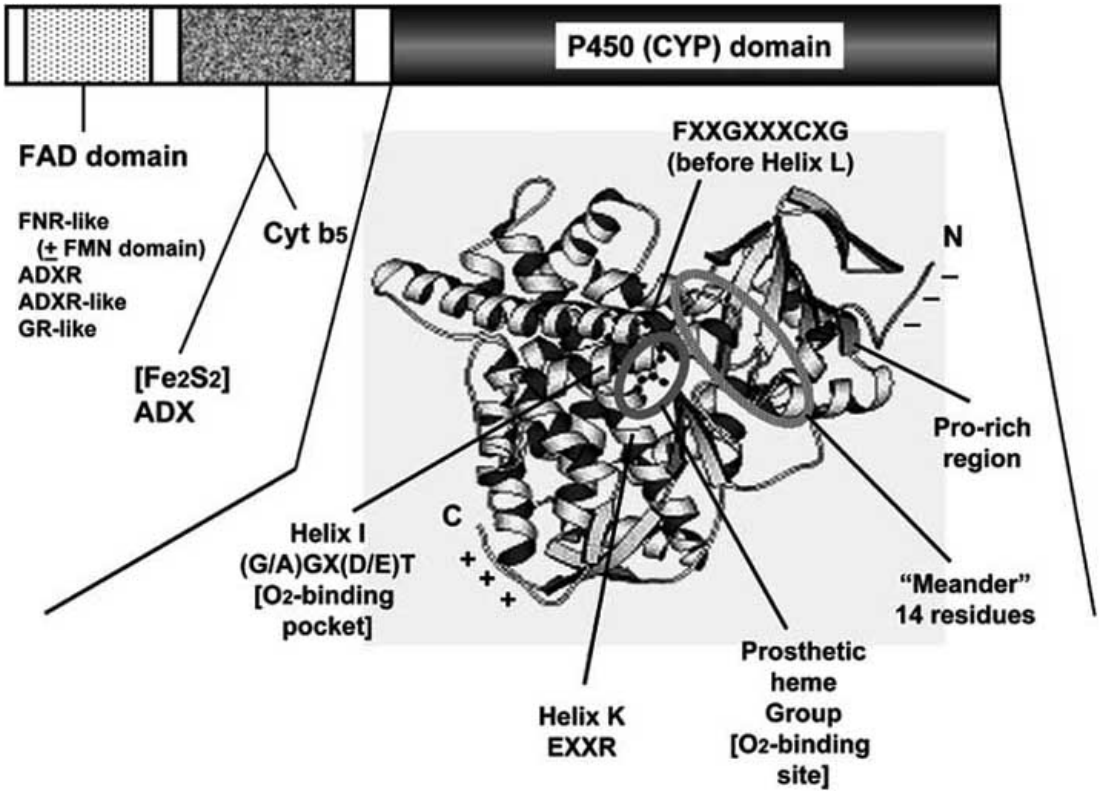

Fig. (1). General structure of CYP-containing enzymes. The N-terminus starts with a FAD domain, which in most microsomally located enzymes is "upstream" from a flavodoxin/FMN domain, followed by either an iron-sulfur protein [Fe_2S_2], such as adrenodoxin [ADX], or a cytochrome b5 domain (Cyt b_5). The majority of the protein consists of a modestly-to-highly conserved P450/CYP domain. The latter contains acidic residues in its N-terminus and basic residues in its C-terminus. Highly conserved regions include an N-terminal proline-rich stretch, Helix I, containing a (G/A)GX(D/E)T sequence, Helix K, containing a EXXR sequence, a "meander" of loops -spanning 14 residues-, and a decapeptide loop (FXXGXXXCXG) just before Helix L. The three-dimensional topography of the CYP domain reveals several substrate-binding sites (not shown for reasons of simplicity) that are in intimate proximity to a pocket containing a heme moiety, which in turn is associated with molecular oxygen (O_2). This unique structure approximates the oxygen to substrate, in the context of oxidative metabolism, which is the central function of the whole CYP superfamily (modified from [107,108]).

Abbreviations: ADX: adrenodoxin; ADXR: adrenodoxin reductase; Cyt b_5: cytochrome b_5; FAD: flavin adenine dinucleotide; [Fe_2S_2]: iron-sulfur protein; FMN: flavin adenine mononucleotide (including flavodoxin); FNR: ferredoxin:$NADP^+$ reductase; GR: glutathione reductase.

p450bpub237.html; last accessed on July 7, 2004). Moreover, the three-dimensional topography of CYP domains from even highly divergent CYP enzymes is remarkably conserved (Fig. **1**), reflecting the structural basis for crucial common functional features that are shared by all superfamily members, namely: a). embedding within (endoplasmic reticulum or mitochondrial) membranes, b). binding of small molecular substrates, and c.) association with molecular oxygen (O_2) through a heme moiety, needed for oxidative metabolism of their substrates [3].

CYP3A4 is the predominant constitutive CYP system in the human liver [5]. Substrates for the enzymes are both endogenous (e.g. steroids, fatty acids, eicosanoids, and retinoids) and exogenous (e.g. drugs, chemicals, and plant products). The CYP1, CYP2, and CYP3 families, particularly their members CYP1A2, CYP2C8, CYP2C18, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, CYP3A6, and CYP3A7 are responsible for the metabolism of more than 80% of the most commonly prescribed drugs. This is summarized in Table **1** [1,3].

All hepatic CYP enzymes are polymorphic, with the most important polymorphisms seen with CYP2C9, CYP2C19, and CYP2D6 [7]. Mutations in CYP genes lead to CYP protein products with reduced, abolished, or increased enzymatic activity, with resulting altered metabolism of the drugs metabolized by a specific enzyme and the potential for adverse drug reactions in the host. Similar results can occur when the expression of CYP enzymes is altered as a consequence of disease, including endocrinopathies. Adverse drug reactions are a major burden nowadays, and it is estimated that they cost more than $100 billion annually and may be at least in part responsible for as many as 100,000 deaths per year in the United States [7].

III. ENDOCRINE DYSREGULATION AND ITS EFFECTS ON THE CYP SYSTEM

III. 1. General Aspects

Theoretically, assorted endocrine or inflammatory conditions resulting in the oversecretion or under-secretion of a particular hormone/neuropeptide/cytokine could have potent effects on drug metabolism. Heretofore, such effects have been attributed to hormonal influences on: a) gastrointestinal drug absorption rates, b) drug binding protein systems, c) drug distribution volume, d) blood flow dynamics in drug target organs, e) renal or hepatic drug excretion systems, or f) drug effector systems *per se* (e.g., the expression of receptor systems in which a drug interferes with ligand binding) [8]**.** The effects of endocrine or inflammatory conditions on pharmacokinetics are significant and complex, yet they remain rather poorly studied. One of the hindrances in research in this important area has been the inadequate characterization of drug metabolism systems. Recent advances in our understanding of these systems, and more specifically the biology of the CYP enzymes, has already yielded intriguing preliminary data in this arena.

The complexity of the interactions we are discussing here is exemplified by the presence of a zoned expression pattern of CYP enzymes in the mature mammalian liver. Indeed, these enzymes are expressed—or induced—mainly in the hepatocytes downstream from the perivenular region of each hexagonal hepatic lobule [9]. The factors that determine this graded expression pattern ("zonation") remain unclear, but it has been shown that signals mediated by growth hormone (GH) and thyroid hormones (THs) participate in this specific zonation by decreasing the expression of CYP genes in the hepatocytes that are upstream (i.e. closer to the venule of the lobular structure) [9]. Furthermore, studies in rat liver *in vivo*

Table 1. Common Substrates of Drug-Metabolizing Enzymes of Select p450 (CYP) Family Members

CYP1A2	Acetaminophen, caffeine, clomipramine, clopidogrel, clozapine, cyclobenzaprine, desipramine, flutamide, imipramine, methadone, mexiletine, mirtazapine, naproxen, nortriptyline, olanzapine, ondansetron, propafenone, propranolol, R-warfarin, tacrine, tamoxifen, theophylline, verapamil, zileuton, zolpidem
CYP2C19	Amitriptyline, clomipramine, cyclophosphamide, desmethyldiazepam, diazepam, divalproex, lansoprazole, mephenytoin, omeprazole, pantoprazole, phenobarbital, phenytoin, progesterone, proguanil, propranolol, ritonavir, valproic acid
CYP2D6	Amitriptyline, bisoprolol, carvedilol, chlorpromazine, chlorimipramine, clozapine, codeine, cyclobenzaprine, debrisoquin, desipramine, dextromethorphan, diazepam, dolasetron, donezepil, flecainide, fluoxetine, fluphenazine, haloperidol, imipramine, labetalol, loratadine, metoprolol, mexiletine, mirtazapine, morphine, nortriptyline, ondansetron, oxycodone, paroxetine, perphenazine, propafenone, propranolol, risperidone, selegeline, sertraline, S-metoprolol, thioridazine, timolol, tolterodine, tramadol, trimipramine, tropisetron, venlafaxine, zolpidem, tamoxifen
CYP3A4-7	Acetaminophen, adriamycin, aldosterone, atorvastatin, alfentanil, alprazolam, amiodarone, amitriptyline, amlodipine, bisoprolol, bromocriptine, carbamazepine, buspirone, chlorpheniramine, chlorpromazine, clarithromycin, clofibrate, cocaine, codeine, cortisol, cyclobenzaprine, cyclophosphamide, cyclosporine, dapsone, dextromethorphan, diazepam, digoxin, diltiazem, docetaxel, dolasetron, donezepil, erythromycin, etoposide, ethinyl estradiol, felodipine, flutamide, gemfibrozil, granisetron, haloperidol, hydrocortisone, ifosfamide, imipramine, indinavir, lansoprazole, lidocaine, loperamide, loratadine, losartan, lovastatin, methadone, miconazole, midazolam, mifepristone, mirtazapine, morphine, nefazodone, nisoldipine, nitrendipine, nifedipine, nelfinavir, nevirapine, nicardipine, ondansetron, paclitaxel, pimozide, phenytoin, progesterone, propafenone, quetiapine, quinidine, quinine, rifampin, ritonavir, R-warfarin, salmeterol, saquinavir, sertraline, sibutramine, sildenafil, simvastatin, sufentanil, tacrolimus, tamoxifen, terfenadine, testosterone, tiagabine, tolterodine, trazodone, triazolam, troleandomycin, venlafaxine, verapamil, vinblastine, vincristine, yohimbine, zidovudine, zileuton, zolpidem

and in rat hepatocyte cultures have shown that a variety of hormones and inflammatory conditions (through cytokine production) influence the expression and/or induction of CYP enzymes [10,11]. In the subsequent sections, we shall expand upon current knowledge of this subject, classifying presented groups of data under subheadings relevant to specific systems of hormones and other mediators that may affect CYP enzyme expression or activity.

III. 2. Effects of Thyroid Hormone Status

The addition of triiodothyronine (T3) to primary hepatocytes significantly reduced CYP3A4 protein and mRNA [12]. Conversely, experimental hypothyroidism in rats led to CYP3A2 induction and CYP2C11 suppression [13]. Moreover, thyroidectomized rats exhibited a marked increase in CYP8B1 protein and mRNA levels, whereas treatment of normal rats with levothyroxine significantly decreased CYP8B1 enzyme activity and mRNA [14]. The addition of T3 to a hepatoma cell line (HepG2) harboring a rabbit CYP2E1 transgene increased levels of CYP2E1 protein and mRNA [15]. Treatment of the amphibian *Xenopus laevis* with T3 increased levels of CYP1A protein [16].

No human studies regarding the effects of THs on the CYP system have been reported in the literature, although it is highly likely that both hypothyroidism and hyperthyroidism alter drug metabolism through CYP-dependent mechanisms in addition to exerting complex effects on other factors responsible for drug handling. After single oral doses of propranolol in hyperthyroid patients, the clearance of the drug has been variously reported to be increased, secondary to increased hepatic enzymatic activity, or unchanged. Similarly, clearance of metoprolol has been reported to be increased in hyperthyroid patients because it undergoes extensive hepatic metabolism to propranolol; in contrast, the oral clearance of sotalol and atenolol is not altered in hyperthyroidism because both drugs undergo mainly renal excretion [17].

III. 3. Effects of Ambient Levels of Glucocorticoids

The relationship between glucocorticoids (GCs) and members of the CYP family is quite complex. On one hand, GCs are themselves partially metabolized by CYP3A enzymes; in that aspect, coadministration of CYP inhibitors, such as itraconazole, with steroids potentiates the effects of exogenous GCs, including increased suppression of the host's hypothalamo-pituitary-adrenal axis [18]. On the other hand, GCs are CYP enzyme inducers. Most studies of the interactions between GCs and CYP have been performed *in vitro* (using assorted mammalian cell lines) or *in vivo* in rodents and have focused mainly on CYP2C11, which accounts for as much as 50% of total CYP in the male rat liver [19].

Primary cultures of human hepatocytes and liver microsomes exhibited increased levels of CYP3A after incubation with dexamethasone [12,20]. In more detailed experiments using human hepatocytes, dexamethasone and prednisone, but not prednisolone or methylprednisolone, were able to induce CYP3A at the level of both mRNA transcription and translation; no changes were noted in other CYP family members, such as CYP1A2, CYP2D6, and CYP2E1 [21]. In other experimental systems, certain members of the CYP family showed a biphasic and dose-dependent modulation after exposure to GCs. For example, in rat hepatocytes, dexamethasone alone did not induce either CYP2B1 or CYP2B2; however, the combination of phenobarbital (PB) and low doses of dexamethasone substantially potentiated PB-induced CYP2B1/CYP2B2 expression. In contrast, high doses of dexamethasone abolished PB induction of CYP2B1/CYP2B2. Additionally, CYP3A1 remained inducible by PB even in the presence of high concentrations of dexamethasone [22]. In human hepatocyte cultures, the expression of both CYP2C8 and CYP2C9 was increased by dexamethasone in a dose-dependent manner [23]. In male rats, adrenalectomy selectively decreased CYP2C11 activity to 70% of the control levels, with normal activity being restored after dexamethasone administration [24].

The molecular basis of CYP induction by GCs has recently been further elucidated. The promoter region of the CYP3A23 gene has three binding sites for members of the nuclear receptor superfamily of transcription factors. Binding of GCs to their cognate glucocorticoid receptors (GRs) leads to a three-step process that results in modulation of the transcription of the target gene (CYP3A23). In the first step in this mechanism, submicromolar concentrations of GCs increase cellular levels of pregnane-X receptor (PXR) and retinoid X receptor (RXR) in a GR-mediated manner. The second step involves the binding of a PXR/RXR heterodimer to the main dexamethasone responsive region (DexRE-2) of the CYP3A23 promoter, thus initiating transcription. In the third and final step, two additional upstream promoter binding sites in the CYP3A23 promoter physically associate with chicken ovalbumin upstream promoter-transcription factor(COUP-TF) and hepatocyte nuclear factor-4(HNF-4). Indeed, both of these accessory nuclear transcription factors must be present for maximal gene inducibility by GCs [25].

In a similar manner, experiments in human hepatocytes revealed the existence of both a consensus GC-responsive element (GRE) and a constitutive androstane receptor (CAR)-responsive element in the regulatory region of the CYP2C9 gene [23,26]. Despite the presence of the GRE, GRs are believed to be involved in CYP inducibility primarily indirectly (i.e. through control of PXR, RXR, and CAR gene expression. This may explain why CYP induction usually occurs in submicromolar GC concentrations, which typically are unable to activate gene transcription maximally through liganded GR-GRE interactions through conventional GREs [27,28].

Whether the above observations have any clinical significance remains unclear because there have been very few studies with human subjects. Erythromycin demethylation (measured by breath $^{14}CO_2$ production) is catalyzed by CYP3A; in 5 patients given ^{14}C-labeled N-methyl erythromycin and pretreated with dexamethasone (at very high doses, ranging from 18-32 mg daily for 2-9 days), breath $^{14}CO_2$ production increased by an average of 55% from baseline levels [29]. Conversely, using triazolam as a probe for CYP3A activity, 10 healthy volunteers were randomized to receive either low-dose dexamethasone (1.5 mg) daily for 4 days or placebo. They all received a single 0.5-mg dose of

triazolam on the 5th day. The mean area under the curve for plasma triazolam was 19% smaller during the dexamethasone treatment phase than with placebo, although the difference did not reach statistical significance. Additionally, triazolam pharmacodynamics did not differ between the two groups [30].

In another study, 12 volunteers received high-dose dexamethasone (16 mg) daily for 5 days and were examined with the erythromycin demethylation breath test to assess CYP3A activity. In this study, the percentage of erythromycin metabolized per hour increased from 2.20% at baseline to 2.67% on day 5, while the mean increase in hepatic CYP3A4 activity was 26% [31]. In a nonrandomized, three-phase crossover study, 10 volunteers were studied after receiving either a single 32-mg dose of dexamethasone or 8 mg of dexamethasone daily for 10 days, using triazolam as a probe for CYP3A activity. Although the single-dose dexamethasone had no effect on triazolam pharmacokinetics, the 10-day treatment resulted in a 30% decrease in maximum serum triazolam concentration, presumed to be secondary to CYP3A induction [32].

Of note, there are no reported studies of drug metabolism through the CYP system in subjects with an endogenous excess of GC (i.e. Cushing's syndrome).

III. 4. Effects of Reproductive Hormones

Gonadal steroids are among the most widely used compounds, either as oral contraceptive pills (OCPs) or as hormone replacement therapy (HRT) agents. Studies in ovariectomized rats after the administration of lindane (which has anti-estrogenic properties in rats) showed an increase in CYP1A, CYP2B1, and CYP2B2 proteins [33]. Several human studies have shown that OCPs and HRT have a significant effect on CYP enzymes, generally inhibiting enzymatic activity. The clearance of caffeine is decreased by more than 50% with OCPs, probably secondary to CYP1A2 inhibition [34-36]. Antipyrine metabolism is decreased in women on OCPs [37,38]. Antipyrine is metabolized by several CYP family members, mainly CYP1A2, CYP2A6, and CYP3A [39]. In the treatment of Alzheimer's disease, tacrine was more efficacious in postmenopausal subjects on HRT than in estrogen-deficient patients. The basis of the effect is the inhibition of CYP1A2-induced transformation of tacrine to its inactive metabolite 1-hydroxytacrine [40]. Methylprednisone metabolism (mediated mainly by CYP3A4) was inhibited by OCPs [41]. Low-dose OCPs inhibited the metabolism of certain benzodiazepines, such as alprazolam and triazolam, whereas they enhanced the metabolism of others, such as temazepam [42]. Intake of OCPs significantly reduced CYP2C19 activity [42,43], but both HRT and OCPs decreased CYP2B6 activity [43]. Finally, gestogen, a progestin, strongly inhibited CYP3A4 activity [45].

In contrast to the above findings, Gorski *et al.* [46] found no difference in hepatic or intestinal CYP3A4 activity between menopausal women on HRT and matched control subjects. Similarly, no difference was noted in hepatic or renal CYP3A4 activity before and after OCP administration in premenopausal women [47]. Furthermore, in other studies, the kinetics of erythromycin elimination (dependent on CYP3A4) were not significantly affected by HRT [48].

Pregnancy is a condition characterized by high serum estrogen levels. Despite the generally inhibitory actions of estrogenic compounds on the CYP systems discussed above, several human studies have shown that pregnancy has minimal effects on CYP2C19 and CYP3A4 but does induce an increase in CYP2D6 levels [49-51]. CYP3A1 is the major component of the CYP system in the rat placenta [52]. Women with intrahepatic cholestasis during pregnancy exhibited significantly decreased placental P450-dependent oxygenases and P450-aromatase; these decreases might be associated with risks to the well-being of the fetus [53].

III. 5. Effects of Growth Hormone Deficiency or Excess

In the rat liver, the expression of CYP2C11 exhibits a sexual dimorphism, with high levels in males and much lower levels in females. This dimorphism is believed to be maintained by the differential secretion patterns of GH in male *vs.* female animals. In male animals after hypophysectomy, continuous GH infusion—mimicking the female pattern of GH secretion—led to significant decreases of the initially high levels of microsomal CYP2C11 to levels typically found in normal female rats [18]. The addition of GH to primary cultures of human hepatocytes increased CYP3A4 mRNA by 9.1-fold, yet no consistent change was noted in mRNA expression for CYP1A2, CYP2C9, or CYP2E1 [11]. Rasmussen *et al.* [54] studied the effects of GH and GH-dependent insulin-like growth factor-1 (IGF-1) on gene expression of the sex-dimorphic enzymes CYP2C11 and CYP2C12 in normal and hypophysectomized male rats. In the normal rats, continuous treatment with GH or IGF-1 decreased CYP2C11 mRNA by 97% and 53%, respectively, and both IGF-1 and GH led to an 8-fold increase in CYP2C12 mRNA. In the hypophysectomized rats, treatment with GH or IGF-1 caused 92% and 63% decreases in CYP2C11 mRNA, respectively, and an approximately 80% increase in CYP2C12 mRNA. Using the same animal model, Waxman *et al.* [55] showed that intermittent GH administration (male pattern) markedly enhances the expression of CYP2C11 but is not required for the expression of other CYP enzymes, such as CYP2A2 and CYP3A2.

As is the case with other hormones and their effect on CYP enzymes, human studies with GH are few in number and small in size and offer conflicting data, thus preventing the drawing of firm conclusions. In 6 GH-deficient children, N-demethylation of caffeine (through CYP1A2) decreased 1 month after GH treatment initiation [56]. In another study, antipyrine clearance (APC) (dependent on CYP1A2, CYP2A6, and CYP3A [38]) was studied in 11 GH-deficient adults. In all subjects, APC was low before GH initiation. Subjects were randomized to receive GH or placebo for 6 months. Subjects on GH showed higher APC than those on placebo, thus demonstrating that GH induces the activity of hepatic CYP enzymes (probably through its mediator, IGF-1 [57]). This was further confirmed when all subjects started receiving GH treatment after the end of randomization [58]. A randomized, placebo-controlled trial of 30 healthy elderly (average age, 75 years) men showed that GH induced

CYP1A2 activity and inhibited CYP2C19 but had no effect on either CYP2D6 or CYP3A4 [59]. Finally, a study of codeine metabolism (mediated primarily through CYP2D6 and CYP3A) in 11 GH-deficient adults showed an 83% increase in CYP3A activity 3 months after GH initiation *vs.* baseline values at the time of study entry but no change in CYP2D6 activity [60].

III. 6. Effects of Diabetes Mellitus

Primary cultured rat hepatocytes provide an ideal model for studying the effects of insulin on CYP enzymes because *in vivo* studies can be confounded by the profound metabolic and hormonal changes occurring in diabetic patients. Additionally, hepatocytes are the primary metabolic target of both insulin and the hormones that counteract its actions [57].

In more detail, in rat hepatocytes cultured in the presence of insulin, its removal from the culture medium led to an 80% decrease in PB induction of CYP2B mRNA and protein expression, a 50% decrease in PB induction of CYP3A4 mRNA, and a 30% decrease in clofibrate induction of CYP4A mRNA. In contrast, in the absence of insulin, xenobiotic-induced CYP2E1 expression was enhanced, denoting that insulin has complex effects on transcriptional regulation of the CYP gene family, depending on the particular target gene and experimental conditions [61]. Of note, CYP2C11 mRNA expression decreased by 80% in cultures of rat hepatocytes after the addition of glucagon [62].

Corroborating this *in vitro* data, animal models of experimental diabetes mellitus (DM) also reveal alterations in the expression of liver CYP enzymes, mainly manifesting as decreased CYP2C11 expression in the diabetic state. Responses of CYP enzymes to streptozotocin-induced DM vary for different members of the CYP family. Hence, patterns of no change, rapid decline with the onset of the DM, and acute restoration after insulin treatment initiation, as well as rapid increase with the onset of DM and reduction of expression back to baseline levels by insulin, have all been observed in diabetic rats [63]. Induction of CYP3 and CYP4 proteins through an increase in their mRNA levels has been observed in rats with experimentally induced and spontaneously occurring DM; these changes were abolished after treatment with insulin [64,65]. In contrast, in male rats, treatment with streptozotocin for 14 days resulted in a 24% decrease in CYP2C11 mRNA levels compared with controls; the mechanism was partially GH-dependent [66]. In hepatic microsomes of diabetic rats, the levels of CYP2A1, CYP2C6, CYP2C7, CYP2E1, CYP3A2, and CYP4A3 were higher than in normoglycemic control animals, and the level of CYP2C11 was lower; all changes were reversed by insulin [67] Furthermore, it has been proposed that the presence or absence of high ambient glucose levels modulates CYP activity by changing the lipid environment of the hepatocyte rather than changing the CYP amounts directly [68]. Human studies are sparse and very small in size. In 15 patients with type 1 DM, APC was 72% higher than in control subjects (showing increased activity of mainly CYP1A2), whereas no changes were observed in the 16 patients with type 2 DM [69]. A much larger Finnish study with 298 diabetic patients made an effort to characterize the effects of type 1 and 2 DM on CYP enzymes after stratification for age, sex, disease duration, and degree of liver fatty infiltration [70]. Newly diagnosed, treatment-naive type 1 diabetics had higher APC than controls, but it was normalized after the initiation of insulin. Patients with long-standing type 1 DM and insufficient control by insulin metabolized antipyrine faster than controls up to the age of 59 years, but after age 60, there was no difference. In contrast, the APC rate did not differ between newly diagnosed type 2 diabetics and controls, and a short course of sulphonylurea treatment did not affect this. Patients with long-standing type 2 DM metabolized antipyrine at a slower rate than controls, but in subjects older than 60 years, the APC was the same between diabetics and controls. Regarding the effect of sex, men with type 1 DM metabolized antipyrine much faster than women, but there was no sex difference in APC among type 2 diabetics.

All the above studies clearly show that DM influences the CYP enzymes in a most convoluted way. This is potentially quite important for diabetic patients who have additional comorbidities and who also are typically on multiple medications. Because age, sex, and duration of disease are the main determining factors of interactions between the diabetic state and CYP expression and activity, it seems logical that not all diabetics respond the same to any given medication, and dose adjustments will be necessary for maximum efficacy of a given drug and avoidance of its toxicities. Clearly, further and larger studies are needed, given the increasing incidence of both types of DM in the general population and the associated polypharmacy in diabetics [71].

III. 7. Effects of Obesity

Obesity has reached epidemic proportions in the Western world and is a leading preventable cause of morbidity and mortality [72]. Obesity has been linked to hypertension, hyperlipidemia, gout, DM, osteoarthritis of the hip and knee, coronary artery disease, cardiac diastolic dysfunction, urolithiasis, gallbladder disease, nonalcoholic steatohepatitis, microalbuminuria, depression, and certain cancers [73]. Furthermore, obese people use a large amount of medications [74]; therefore, any effect of obesity on drug metabolism is an important public health issue.

Rats rendered obese after feeding on an energy-rich diet exhibited induction of CYP2E1 [75]. Obese Zucker rats showed decreased activity of CYP2C11, which could not be reversed by PB [76]. However, a similar study in overfed, obese rats failed to detect any alterations in CYP2C11 or CYP3A or any lack of induction of these enzymes after PB administration [77]. Obese *ob/ob* mice showed decreased CYP1A2 activity regardless of sex, whereas female *ob/ob* mice showed increased CYP2E1 activity [78]. These mice had higher total CYP levels, higher CYP2B1 and CYP2A activity, and lower CYP2E1 activity than controls [79]. Leptin administration in *ob/ob* mice decreased the elevated baseline levels of CYP2B1 and CYP2A but further increased the levels of CYP2E1 [79]. It is not clear if these changes were due to leptin *per se* or secondary to changes in GH, cortisol, insulin, or other factors affected by leptin administration.

Human studies of the relationship between obesity and CYP enzymes (excellently reviewed in [80]) have not been consistent. It seems that obesity causes a decrease in CYP3A4 activity and an increase in CYP2E1 activity, whereas the data on the direction of changes in CYP1A2, CYP2C9, CYP2C19, and CYP2D6 remain inconclusive.

III. 8. Effects of Malnutrition or Vitamin Deficiency/ Excess States

Dietary factors modulate the expression of CYP enzymes, although the mechanisms underlying this process remain unclear. Caloric restriction of rats for 20 months resulted in increased liver CYP2E1 expression [81]. Similar results were obtained with much less protracted periods of food restriction, such as 1-3 days [82,83], or even 8 hours [84]. In humans, decreased food intake is often associated with increased ethanol consumption, so the expression of CYP2E1 was studied during ethanol treatment and starvation. In this series of experiments, short-term, high-intensity ethanol consumption resulted in a 20-fold increase in the levels of CYP2E1 apoprotein and a 16-fold increase in the enzyme's catalytic activity in both fed and starved animals. In contrast, the amount of CYP2E1 mRNA increased only in starved animals [85]. Ethanol has also been found to induce renal CYP2E1 expression in male rats [86].

Vitamin A deficiency in rats reduced total microsomal CYP content to levels less than 72% of controls, decreased CYP-mediated oxidation, and reduced CYP2C11 protein and mRNA levels. All the changes were reversed with the inclusion of all-*trans*-retinoic acid in the diet [87]. Using a similar model of vitamin A deficiency, other investigators reported decreases in microsomal CYP4A and CYP2C11 protein expression by 64% and 68%, respectively, compared with controls, whereas no change was observed in CYP3A levels [88].

III. 9. Effects of Calciotropic Hormones

Only one study in the literature has reported on the effects of cholecalciferol on the CYP enzymes. Yamazaki *et al*. [89] reported that cholecalciferol inhibits CYP1A1, CYP2C8, and CYP2C19 activity on recombinant enzyme systems. The effects of changes in the concentration of minerals, intact parathyroid hormone or parathyroid hormone fragments, or vitamin D metabolites other than cholecalciferol, either acutely or chronically, remain unknown.

III. 10. Effects of Alterations in the Activity of the Sympathoadrenal-Renin System

One study showed that liver hilar denervation, with subsequent deprivation of sympathetic impulses to the hepatocytes, had no effect on total CYP expression [90]. The effects of an excess or deficiency of epinephrine, norepinephrine, renin, and aldosterone on CYP expression has not been studied to date.

III. 11. Effects of Alterations in Fluid Volume and Osmolality Regulation Systems/Salt Homeostasis

Manipulation of the expression of renal CYP isoforms could theoretically have profound effects on renal physiology, given the distribution and significant activity of CYP enzymes in the kidney. Indeed, alterations in renal expression or activity of CYP enzymes have been implicated in the pathogenesis of hypertension [91]. Arachidonic acid metabolism, a process much more closely dependent on renal than hepatic CYP enzymes, results in the production of a variety of compounds: epoxyeicosatrienoic acids *via* epoxygenase (of the CYP2C family), and 20-hydroxyeicosatetraenoic acid *via* ω-hydroxylase (of the CYP4A family) [92]. These compounds have diverse biological actions, such as activity on vascular smooth muscle, renal blood flow dynamics, modulation of ion channels, and mitogenicity [91]. Experiments in rats showed that treatment with NaCl resulted in increased cortical and medullary epoxygenase (CYP2C-dependent) activity, and decreased cortical ω-hydroxylase (CYP4A-dependent) activity [93,94].

Because CYP enzymes are also expressed in the intestinal mucosal cells, dietary salt can modulate their expression in gut epithelia. In rats fed high-sodium diets, plasma peak concentrations of orally administered quinidine (a CYP3A substrate) were significantly lower than those in animals exposed to normal or low-sodium diets. No differences between the two groups were found when the NaCl was administered intravenously in equiosmolar amounts [95].

III. 12. Effects of Cytokines, Interleukins, and Other Inflammatory Mediators

The effects of inflammation and infection on the hepatic CYP system in animal models has been recently and exhaustively summarized by Morgan [10]. In general, most CYP enzymes are suppressed during inflammation, although there are notable exceptions. This suppression of CYP levels is mainly a transcriptional effect, although modulation of mRNA stability and protein turnover also plays a role [10].

Administration of interleukin-1, interleukin-6, or tumor necrosis factor led to decreased enzymatic activity of CYP1A1, CYP2C11, CYP2C12, CYP2E1, and CYP3A2 [10]. Experimentally induced fever in the rat (*via* interleukin-1β administration) resulted in impaired hepatic drug-metabolizing activity. This effect was only partially resolved after the hyperthermia subsided with the use of aspirin [96]. *Schistosoma mansoni*-infected male mice showed a 97% reduction in CYP1A1 activity and a 96% reduction in CYP2B1/2 activity 45 days after infection [97].

Leukotrienes and prostaglandins are mediators of inflammation. In the rat, the CYP4F family is responsible for metabolizing these compounds; thus, changes in the expression of CYP4F can modulate inflammation [91]. In rat hepatocytes, the addition of the bacterial endotoxin lipopolysaccharide (LPS) decreased the expression of CYP4F4 and CYP4F5 expression by 50% and 40%, respectively [98]. In animal models of traumatic brain injury, concentrations of leukotrienes and prostaglandins are elevated immediately after the injury because of decreased metabolism of these compounds secondary to decreased CYP4F expression in the brain [98]. LPS inhibited PB-induced CYP2B1/2 expression in rat livers, at both the mRNA and protein levels [99]. Similar inhibitory effects of LPS have been observed in mice after 24 hours of LPS treatment, but not after 6 or 12 hours [100]. Interestingly, in rats, inflammatory processes strictly localized to the brain

resulted in decreased CYP2B, CYP2E, and CYP2D expression, not only in brain tissue, but also in the liver [101]. The signal leading to the modulation of these enzymes in the liver could be hormonal, given the profound effects of intracerebroventricular cytokine administration on multiple hypothalamo-pituitary axes (reviewed recently by McCann *et al.* [102]). Moreover, several cytokines play a major role in the pathogenesis of the "euthyroid sick syndrome", a condition associated with non-thyroidal systemic illness in humans that results in profound changes in TH production and tissue effects (reviewed recently by Papanicolaou [103]). Additionally, cytokines influence—at several levels—the functional activity of the hypothalamo-pituitary-adrenal [104] and hypothalamo-pituitary-gonadal axes [105]. Hence, immune mediators could also affect CYP expression indirectly through their aforementioned actions on thyroid, adrenal, and gonadal hormonal systems. Finally, experimental administration of bacterial endotoxin in healthy women resulted in decreased clearance of antipyrine, hexobarbitone, and theophylline [106].

From the above, it is clear that infectious and inflammatory processes and tissue injury have a profound effect on CYP enzymes (at both local and distant sites) with potentially important clinical and toxicological consequences.

IV. CONCLUSIONS

CYP isoforms catalyze degradation (or occasionally activation) of the vast majority of currently used drugs and are involved in elimination of xenobiotics and endogenous metabolically active compounds. It is becoming progressively clearer that the major classes of CYP genes are selectively regulated by hormones and substances with hormone-like action, thus creating tightly controlled networks. We have presented current knowledge on the actions of thyroid, adrenal, and reproductive hormones, growth hormone, and immune mediators on CYP expression. In addition, we commented on the effects of glycemic dysregulation (diabetes) and obesity/malnutrition on these enzymatic systems. Of note, the relationship between CYP and a broad variety of hormonal physiologic systems (and their constituents), including the systems responsible for sympathoadrenal-renin axis activity, fluid volume and osmolality regulation, and calcium/mineral homeostasis, are completely unknown and, hence, are candidates for further study. More stringent studies, using multiple concentration gradients and time kinetics of exposure to hormonal mediators in *in vitro* experiments, strictly controlled and designed experimental animal protocols, and clinical correlative studies are needed to further clarify these issues. We hope these studies will produce a wealth of new data that would be useful for targeting established therapies and intelligent development of new ones, especially considering the rapidly evolving field of pharmacogenetics/pharmacogenomics and the fact that endocrine and hormonal responses—which influence the CYP system—also have for the most part a genetic/genomic basis.

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ABBREVIATIONS

APC	=	Antipyrine clearance
CAR	=	Constitutive androstane receptor
CYP	=	Cytochrome P450
DexRE-2	=	Dexamethasone responsive region-2
DM	=	Diabetes mellitus
GC	=	Glucocorticoid
GR	=	Glucocorticoid receptor
GRE	=	Glucocorticoid-responsive element
GH	=	Growth hormone
HRT	=	Hormone replacement therapy
IGF-1	=	Insulin-like growth factor-1
IFN	=	Interferon
IL	=	Interleukin
LPS	=	Lipopolysaccharide
OCPs	=	Oral contraceptive pills
PB	=	Phenobarbital
PXR	=	Pregnane X receptor
RXR	=	Retinoid X receptor
T3	=	Triiodothyronine
TH	=	Thyroid hormone

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