Drug Metabolism

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Lecture Outline

• What it is about – some history & background
• Liver Microsomal System
  – Cytochrome P 450 families
  – Examples
  – Mechanism
• Non-Cyp biotransformations
• Practical example - acetaminophen metabolism
Evolution of Drug Metabolism As a Science

Post WWII Pioneers

• Richard Tecwyn Williams – Great Britain

  – 1942, worked on the metabolism on TNT with regard to toxicity in munitions workers; due to the war he assembled teams to work on metabolism of sulfonamides, benzene, aniline, acetanilide, phenacetin, and stilbesterol

  – Developed concept of Phase 1 & Phase 2 Reactions.
    • Biotransformation involves metabolic oxygenation, reduction, or hydrolysis; result in changes in biological activity (increased or decreased)
    • Second phase, conjugation, in almost all cases resulted in detoxification.
Evolution of Drug Metabolism As a Science

Post WWII Pioneers

• **Bernard B. Brodie**, U.S.
  
  - NYU and Laboratory of Industrial Hygiene, NYC 1949 – Metabolic fate of acetanilide and phenacetin in man (with Julius Axelrod as pre-doc; later an NIMH Nobel laureate)
  - 1950s, NIH – pioneering studies on all aspects of drug metabolism; esp. reserpine, serotonin; hexobarbital tolerance
  - 1952 – R.T. Williams spent 6 months at NIH; subsequently many students went between both labs (Richard Adamson, James Gillette, and Sidney Udenfriend)
  - 1950s, Brodie lab developed the spectrophotofluorimeter (Robert Bowman)
Metabolism vs Drug Action

Greater lipid solubility  

Drug  

Transport  

Cytochromes P450 (Oxidation)  

OH  

Transferases (Conjugation)  

O-SG  

Inactive drug  

Excretion through kidney or bile  

Drug receptor  

Biological response  

Increased water solubility

biotransformations
Drug Metabolism

**Extrahepatic microsomal enzymes**
(oxidation, conjugation)

**Hepatic microsomal enzymes**
(oxidation, conjugation)

**Hepatic non-microsomal enzymes**
(acetylation, sulfation, GSH, alcohol/aldehyde dehydrogenase, hydrolysis, ox/red)
Liver Microsomal System

- Oxidative Reactions: Cytochrome P450 mediated
  - Formation of an inactive polar metabolite
    - Phenobarbital

![Chemical structures]

- Phenobarbital (low water solubility) → p-hydroxyphenobarbital (Phase 1) → p-hydroxyphenobarbital glucuronide (Phase 2) (high water solubility)
Liver Microsomal System

- Oxidative Reactions: Cytochrome P450 mediated
  - Formation of a toxic metabolite
    - Acetaminophen – NAPQI

\[ \text{Acetaminophen} \rightarrow \text{NAPQI} \rightarrow \text{Toxic Events} \]
Liver Microsomal System

- Formation of an active metabolite
  - By Design: Purine & pyrimidine chemotherapy
  - Inadvertent: terfenadine – fexofenadine

\[ \text{5-FU} \quad \rightarrow \quad \text{5-FUMP} \]

- Terfenadine (Seldane)
- Fexofenadine (Allegra)
Sites of drug metabolism – Cytochromes P450 (CYPs)

Liver enriched
Endoplasmic reticulum

Certain transferases also localized to the ER

F.G. Gonzalez, 2009
ROH (Drug metabolite) → CYP-Fe$^{+3}$ → CYP-FeOH$^{+3}$ → CYP-FeOH$^{+3}$ → CYP-FeOH$^{+3}$ → CYP-Fe$^{+3}$ → RH (Drug) → CYP-Fe$^{+3}$ → CYP-Fe$^{+3}$ → NADPH-P450-Reductase → CYP-Fe$^{+2}$ → CYP-Fe$^{+2}$ → O$_2$ → CYP-Fe$^{+2}$ → CYP-Fe$^{+2}$ → O$_2$ → CYP-Fe$^{+2}$ → CYP-Fe$^{+2}$ → OOH → CYP-Fe$^{+2}$ → OOH → H$_2$O → H$^+$
Cytochrome P450 Isoforms (CYPs) - An Overview

- NADPH + H⁺ + O₂ + Drug → NADP⁺ + H₂O + Oxidized Drug
- Carbon monoxide binds to the reduced Fe(II) heme and absorbs at 450 nm (origin of enzyme family name)
- CYP monooxygenase enzyme family is major catalyst of drug and endogenous compound oxidations in liver, kidney, G.I. tract, skin, lungs
- Oxidative reactions require the CYP heme protein, the reductase, NADPH, phosphatidylcholine and molecular oxygen
- CYPs are in smooth endoplasmic reticulum in close association with NADPH-CYP reductase
- The reductase serves as the electron source for the oxidative reaction cycle
CYP Families

• Multiple CYP gene families have been identified in humans, and the categories are based upon protein sequence homology.
• Most of the drug metabolizing enzymes are in CYP 1, 2, & 3 families.
• CYPs have molecular weights of 45-60 kDa.
• Frequently, two or more enzymes can catalyze the same type of oxidation, indicating redundant and broad substrate specificity.
• CYP3A4 is very common to the metabolism of many drugs; its presence in the GI tract is responsible for poor oral availability of many drugs.
ROLE OF CYP ENZYMES IN HEPATIC DRUG METABOLISM

RELATIVE HEPATIC CONTENT OF CYP ENZYMES

% DRUGS METABOLIZED BY CYP ENZYMES

A. Atkinson, 2005
# Human Liver Drug CYPs

<table>
<thead>
<tr>
<th>CYP enzyme</th>
<th>Level (% total)</th>
<th>Extent of variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A2</td>
<td>~ 13</td>
<td>~40-fold</td>
</tr>
<tr>
<td>1B1</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>2A6</td>
<td>~4</td>
<td>~30 - 100-fold</td>
</tr>
<tr>
<td>2B6</td>
<td>&lt;1</td>
<td>~50-fold</td>
</tr>
<tr>
<td>2C</td>
<td>~18</td>
<td>25-100-fold</td>
</tr>
<tr>
<td>2D6</td>
<td>Up to 2.5</td>
<td>&gt;1000-fold</td>
</tr>
<tr>
<td>2E1</td>
<td>Up to 7</td>
<td>~20-fold</td>
</tr>
<tr>
<td>2F1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2J2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3A4</td>
<td>Up to 28</td>
<td>~20-fold</td>
</tr>
<tr>
<td></td>
<td>30-60*</td>
<td>90-fold*</td>
</tr>
<tr>
<td>4A, 4B</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

S. Rendic & F.J. DiCarlo, Drug Metab Rev 29:413-80, 1997
*L. Wojnowski, Ther Drug Monit 26: 192-199, 2004
## Participation of the CYP Enzymes in Metabolism of Some Clinically Important Drugs

<table>
<thead>
<tr>
<th>CYP Enzyme</th>
<th>Examples of substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A1</td>
<td>Caffeine, Testosterone, R-Warfarin</td>
</tr>
<tr>
<td>1A2</td>
<td>Acetaminophen, Caffeine, Phenacetin, R-Warfarin</td>
</tr>
<tr>
<td>2A6</td>
<td>17β-Estradiol, Testosterone</td>
</tr>
<tr>
<td>2B6</td>
<td>Cyclophosphamide, Erythromycin, Testosterone</td>
</tr>
<tr>
<td>2C-family</td>
<td>Acetaminophen, Tolbutamide (2C9); Hexobarbital, S-Warfarin (2C9,19); Phenytoin, Testosterone, R-Warfarin, Zidovudine (2C8,9,19);</td>
</tr>
<tr>
<td>2E1</td>
<td>Acetaminophen, Caffeine, Chlorzoxazone, Halothane</td>
</tr>
<tr>
<td>2D6</td>
<td>Acetaminophen, Codeine, Debrisoquine</td>
</tr>
<tr>
<td>3A4</td>
<td>Acetaminophen, Caffeine, Carbamazepine, Codeine, Cortisol, Erythromycin, Cyclophosphamide, S- and R-Warfarin, Phenytoin, Testosterone, Halothane, Zidovudine</td>
</tr>
</tbody>
</table>

Adapted from: *S. Rendic Drug Metab Rev 34: 83-448, 2002*

*Also D.F.V. Lewis, Current Medicinal Chemistry, 2003, 10, 1955-1972*
Drug Metabolism Studies

• Determine the nature of metabolites
  Stable metabolites → good
  Electrophiles → bad
  Bind to cellular nucleophile - DNA, RNA and protein
  Cause cell death or transformation – cancer

• Which P450s are involved in metabolism of the drug candidate?
  Several P450s → good
  Single P450 → bad
  CYP2D6 - polymorphism
  CYP3A4 - drug interactions
## Factors Influencing Activity and Level of CYP Enzymes

<table>
<thead>
<tr>
<th>Category</th>
<th>Enzymes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrition</td>
<td>1A1; 1A2; 1B1, 2A6, 2B6, 2C8,9,19; 2D6, 3A4,5</td>
</tr>
<tr>
<td>Smoking</td>
<td>1A1; 1A2, 2E1</td>
</tr>
<tr>
<td>Alcohol</td>
<td>2E1</td>
</tr>
<tr>
<td>Drugs</td>
<td>1A1, 1A2; 2A6; 2B6; 2C; 2D6; 3A3, 3A4,5</td>
</tr>
<tr>
<td>Environment</td>
<td>1A1, 1A2; 2A6; 1B; 2E1; 3A3, 3A4, 5</td>
</tr>
<tr>
<td>Genetic Polymorphism</td>
<td>1A; 2A6; 2C9,19; 2D6; 2E1</td>
</tr>
</tbody>
</table>

*Red* indicates enzymes important in drug metabolism

Adapted from: *S. Rendic Drug Metab Rev 34: 83-448, 2002*
Non-nitrogenous Substances that Affect Drug Metabolism

• **Grapefruit juice** - CYP 3A4 inhibitor; highly variable effects; fucocoumarins

• **St John’s wort, other herbal products**

• **Isosafrole, safrole**
  – CYP1A1, CYP1A2 inhibitor; found in root beer, perfume
Overheard Conversation

• At a B&B breakfast table, after grapefruit juice was served, someone remarked “A friend read the package insert with her prescription and the fine print warned against drinking grapefruit juice…is this true? Should it be avoided with all medications? How about grapefruit itself? How about orange juice?”
Effect of Grapefruit Juice on Felodipine Plasma Concentration

Grapefruit Juice Facts

• GJ or G, lime, or Sun Drop Citrus soda, Seville OJ (not most OJ) elevates plasma peak drug concentration, not elimination $t_{1/2}$
• GJ reduced metabolite/parent drug AUC ratio
• GJ caused 62% reduction in small bowel enterocyte 3A4 and 3A5 protein; liver not as markedly affected (i.v. pharmacokinetics unchanged)
• GJ effects last ~4 h, require new enzyme synthesis
• Effect cumulative (up to 5x $C_{\text{max}}$) and highly variable among individuals depending upon 3A4 small bowel basal levels
First-Pass Metabolism after Oral Administration of a Drug, as Exemplified by Felodipine and Its Interaction with Grapefruit Juice

### Limited Expression of Human Drug Metabolizing CYPs in Extrahepatic Tissues

<table>
<thead>
<tr>
<th>CYP Enzyme</th>
<th>Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A1</td>
<td>Lung, kidney, GI tract, skin, placenta, others</td>
</tr>
<tr>
<td>1B1</td>
<td>Skin, kidney, prostate, mammary, others</td>
</tr>
<tr>
<td>2A6</td>
<td>Lung, nasal membrane, others</td>
</tr>
<tr>
<td>2B6</td>
<td>GI tract, lung</td>
</tr>
<tr>
<td>2C</td>
<td>GI tract (small intestine mucosa) larynx, lung</td>
</tr>
<tr>
<td>2D6</td>
<td>GI tract</td>
</tr>
<tr>
<td>2E1</td>
<td>Lung, placenta, others</td>
</tr>
<tr>
<td>2F1</td>
<td>Lung, placenta</td>
</tr>
<tr>
<td>2J2</td>
<td>Heart</td>
</tr>
<tr>
<td>3A4</td>
<td>GI tract, lung, placenta, fetus, uterus, kidney</td>
</tr>
<tr>
<td>4B1</td>
<td>Lung, placenta</td>
</tr>
<tr>
<td>4A11</td>
<td>Kidney</td>
</tr>
</tbody>
</table>

_S. Rendic & F.J. DiCarlo, Drug Metab Rev 29:413-80, 1997_
Unified View of CYP Catalyzed Reactions

<table>
<thead>
<tr>
<th>Category</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon Hydroxylation</td>
<td>1. H atom abstraction</td>
</tr>
<tr>
<td></td>
<td>2. Oxygen rebound</td>
</tr>
<tr>
<td>Heteroatom Release</td>
<td>1. Nonbonded electron abstraction</td>
</tr>
<tr>
<td></td>
<td>2. H atom abstraction</td>
</tr>
<tr>
<td></td>
<td>3. Oxygen rebound</td>
</tr>
<tr>
<td></td>
<td>4. Non-enzymatic rearrangement</td>
</tr>
<tr>
<td>Heteroatom Oxygenation</td>
<td>1. 1&lt;sup&gt;st&lt;/sup&gt; Nonbonded electron abstraction</td>
</tr>
<tr>
<td></td>
<td>2. 2&lt;sup&gt;nd&lt;/sup&gt; nonbonded electron abstraction</td>
</tr>
<tr>
<td></td>
<td>3. Oxygen rebound</td>
</tr>
<tr>
<td>Epoxidation, and Group Migration, and</td>
<td>Stepwise processes involving discrete radical and/or</td>
</tr>
<tr>
<td>Olefinic Suicide Inactivation</td>
<td>cationic substrate intermediates (not epoxide intermediates).</td>
</tr>
</tbody>
</table>
1. Carbon Hydroxylation

\[
\{\text{FeO}\}^{3+} + \text{HC} \rightarrow \{\text{Fe-OH}\}^{3+} \text{C} \rightarrow \{\text{Fe}\}^{3+} + \text{HO-C}^{-}
\]

2. Heteroatom Release (Dealkylation)

\[
\{\text{FeO}\}^{3+} + \text{N=CHR} \rightarrow \{\text{FeO}\}^{2+} + \text{NH} + \text{O=CHR}
\]

(Also for O, S, P, Halo, etc)
3. Heteroatom Oxygenation

\[
\{\text{Fe}=\text{O}\}^{3+} \text{ } \overset{\text{X}}{\longrightarrow} \{\text{Fe}=\text{O}\}^{2+} \text{ } \overset{\text{X}}{\longrightarrow} \{\text{Fe}\}^{3+} \text{ } \overset{\text{O}}{\longrightarrow} \text{X}^{-}
\]

4. Epoxidation, Group Migration, and Olefinic Suicide Inactivation

\[
\{\text{Fe}=\text{O}\}^{3+} \overset{\text{Fe}^{2+}-\text{N-pyrrole complex}}{\longrightarrow} \overset{\text{N-porphyrin-heme adduct}}{\longrightarrow} \]

\[
\begin{array}{c}
\text{R}_1 \text{R}_2 \\
\text{R}_3 \text{R}_4 \\
\text{O} \\
\end{array}
\overset{\text{R}_1 \text{R}_2}{\longrightarrow} \overset{\text{R}_3 \text{R}_4}{\longrightarrow} \overset{\text{R}_1 \text{R}_2}{\longrightarrow} \overset{\text{R}_3 \text{R}_4}{\longrightarrow}
\]

\[
\begin{array}{c}
\text{R}_1 \text{R}_2 \\
\text{R}_3 \text{R}_4 \\
\text{O} \\
\end{array}
\]
Phenytoin is metabolized by CYP enzymes to form an arene oxide, which is then hydrolyzed by epoxide hydrolase to form the 3,4-dihydroxy derivative. This intermediate is then oxidized by an oxidase to form an ortho-quinone intermediate. The question is whether this ortho-quinone intermediate can form a protein adduct.
Amodiaquine N-Dealkylation – CYP2C8

\[ \text{Amodiaquine} \xrightarrow{\text{CYP2C8}} \text{N-des-ethyl amodiaquine} + \text{acetaldehyde} \]
Human liver microsomes

Microsomes minus NADPH

CYP2B8
CYP1A1
CYP1B1

AQ
DEAQ

M2
CYP Biotransformations - Summary

- Chemically diverse small molecules are converted, generally to more polar compounds
- Common biotransformations include:
  - Aromatic hydroxylation
  - Dealkylation (N-, O-, S-)
  - Benzylic carbon hydroxylation
  - Deamination
  - Dehalogenation
Non-CYP Drug Biotransformations (1)

- **Conjugation (Phase 2 Rxs)** –
  - Major Conjugation Reactions
    - **Glucuronidation** (high capacity) – greatly enhances water solubility
    - **Sulfation** (low capacity) - greatly enhances water solubility
    - **Acetylation** (variable capacity)
      - Examples: Procainamide, Isoniazid
  - Other Conjugation Reactions: O-Methylation, S-Methylation, Amino Acid Conjugation (glycine, taurine, glutathione)
  - Many conjugation enzymes exhibit polymorphism
Conjugation Reactions
Glucuronidation

Liver has several soluble UDP-Gluc-transferases
Glucuronic acid conjugation to phenols, 3°-amines, aromatic amines

Arrows indicate site of glucuronide attachment
Conjugation Reactions
Sulfation

Examples: ethanol, p-hydroxyacetanilide, 3-hydroxycoumarin
Conjugation Reactions
Acetylation

Examples: Procainamide, isoniazid, sulfanilimide, histamine
• *N*-acetyl transferase (NAT) enzyme is found in many tissues, including liver
• Acetylation may not enhance water vs. lipid solubility
Procainamide

Unchanged in Urine, 59%

H₂N-\(\begin{array}{c} \text{O} \\ \text{N} \end{array}\)\text{H}

24% Fast
17% Slow
↑ 3%

Unchanged in Urine, 85%

NAPA

Unchanged in Urine, 85%

Unchanged in Urine, 85%

0.3%

1%
Procainamide

H₂N-\begin{array}{c}
\text{trace metabolite} \\
\text{non-enzymatic} \\
\text{Lupus?}
\end{array}

\text{NH}

\text{HO-N-}

\text{O=N-}

\text{NH}

\text{NH}

\text{O=N-}
Non-CYP Biotransformations
Oxidations (1)

- **Monoamine Oxidase (MAO), Diamine Oxidase (DAO)** - MAO (mitochondrial) oxidatively deaminates endogenous substrates including neurotransmitters (dopamine, serotonin, norepinephrine, epinephrine); drugs designed to inhibit MAO used to affect balance of CNS neurotransmitters (L-DOPA); MPTP converted to toxin MPP+ through MAO-B. DAO substrates include histamine and polyamines.

- **Alcohol & Aldehyde Dehydrogenase** - non-specific enzymes found in soluble fraction of liver; ethanol metabolism

- **Xanthine Oxidase** - converts hypoxanthine to xanthine, and then to uric acid. Drug substrates include theophylline, 6-mercaptopurine. Allopurinol is substrate and inhibitor of xanthine oxidase; delays metabolism of other substrates; effective for treatment of gout.
• **Flavin Monooxygenases**
  – Family of enzymes that catalyze oxygenation of nitrogen, phosphorus, sulfur – particularly facile formation of N-oxides
  – Different FMO isoforms have been isolated from liver, lung (S.K. Krueger, D.E. Williams 2005, Pharmacol Ther 106:357-87)
  – Require molecular oxygen, NADPH, flavin adenosine dinucleotide (FAD)
  – Single point (loose) enzyme-substrate contact with reactive hydroperoxyflavin monooxygenating agent
  – FMOs are heat labile and metal-free, unlike CYPs
  – Factors affecting FMOs (diet, drugs, sex) not as highly studied as CYPs
Non-CYP Biotransformations
Oxidations - FMO vs. CYP + Conjugations

nicotine
10%
$N^\prime$-glucuronide
3–5%

FMO3

$N^\prime$-1'-oxide
3–7%

cotinine
9–15%
$N^\prime$-glucuronide
12–20%

3-hydroxycotinine
34–42%
$O$-glucuronide
7–23%

cotinine -$N$-1'-oxide
1–4%

Data from review by Tricker, 2003, Toxicology, 183, 151-73
Non-CYP Biotransformations
Hydrolysis – Ester or Amide

• Procaine – ester, rapidly hydrolyzed

• Procainamide - amide, more slowly hydrolyzed; valuable anti-arrhythmic

• N-acetylprocainamide (NAPA); metabolite with anti-arrhythmic activity, 2.5 x longer elimination half-life (Atkinson et al., 1988, Angiology, 39, 655-67)
Additional Effects on Drug Metabolism

• Species Differences
  – Major differences in different species have been recognized for many years (R.T. Williams).
    • Phenylbutazone half-life is 3 h in rabbit, ~6 h in rat, guinea pig, and dog and 3 days in humans.

• Induction
  – Two major categories of CYP inducers
    • Phenobarbital is prototype of one group - enhances metabolism of wide variety of substrates by causing proliferation of SER and CYP in liver cells.
    • Polycyclic aromatic hydrocarbons are second type of inducer (ex: benzo[a]pyrene).
  – Induction appears to be environmental adaptive response of organism
  – Orphan Nuclear Receptors (PXR, CAR) are regulators of drug metabolizing gene expression
PXR and CAR Protect Against Xenobiotics

xenobiotics

co-activator

PBP

CAR

PXR

target genes

cytoplasm

nucleus

xenoprotection

S.A. Kliewer
Distinct and overlapping actions of PXR and CAR

Mechanism of Induction of CYP3A4-Mediated Metabolism of Drug Substrates (Panel A) and the Resulting Reduced Plasma Drug Concentration (Panel B)

Acetaminophen (APAP)

Over-the-counter drug:
relieving pain,
reducing fever,
relieving the symptoms of
allergies, cold, cough, and flu.

Co-administration:
Sedative
Antihistamine
Vasoconstrictants
Expectorants
Antitussive
Analgesics

Tylenol
(Top seller, controlling 35% of the pain
killer market in North America)
Acetaminophen (Paracetamol)

- Acetanilide – 1886 – accidentally discovered antipyretic; excessively toxic (methemoglobinemia); para-aminophenol and derivatives were tested.
- Phenacetin introduced in 1887, and extensively used in analgesic mixtures until implicated in analgesic abuse nephropathy
- Acetaminophen recognized as metabolite in 1899
- 1948-49 Brodie and Axelrod recognized methemoglobinemia due to acetanilide and analgesia to acetaminophen
- 1955 acetaminophen introduced in US
Acetaminophen and p-Aminophenols

**Acetanilide, 1886**  
(accidental discovery of antipyretic activity; high toxicity)

**Phenacetin or acetophenetidin, 1887**  
(nephrotoxic, methemoglobinemia)

**Acetaminophen, 1893**  
(Metabolic pathway quantified; (Brodie & Axelrod, 1948) popular in US since 1955)

70-90%  
75-80%

49
Acetaminophen Toxicity

• Acetaminophen overdose results in more calls to poison control centers in the United States than overdose with any other pharmacologic substance.

• The American Liver Foundation reports that 35% of cases of severe liver failure are caused by acetaminophen poisoning which may require organ transplantation.

• N-acetyl cysteine is an effective antidote, especially if administered within 10 h of ingestion [NEJM 319:1557-1562, 1988]

Acetaminophen Metabolism

~60%

~35%

CYP2E1*
CYP1A2
CYP3A11

*NAPQI

Protein adducts,
Oxidative stress
Toxicity

N-acetyl-p-benzoquinone imine

*induced by ethanol, isoniazid
Acetaminophen Protein Adducts

Acetaminophen toxicity mechanism

- N-acetyl cysteine is an effective agent to block GSH depletion and rescue from liver damaging toxicity
  - CAR-null mice are resistant to acetaminophen toxicity
    - hepatic GSH lowered in wild type (but not in KO) after acetaminophen
    - CAR-humanized mice demonstrate same toxicity response
- Activation of PXR induces CYP3A11 and markedly enhances acetaminophen toxicity in wild type mice
- CAR transcription co-activator KO blocks toxicity (2005)
NAPQI toxicity linked to PXR activation

[Diagram of molecular structures and pathways involving CAR, PXR, CYP2E1*, CYP3A11, and SH groups suggesting oxidative stress mechanism]
Drug Metabolism - Web Information Resources

• http://en.wikipedia.org/wiki/Cytochrome_P450_oxidase
  – General web site regarding all aspects of chemical structure (sequence and 3D) of P450 proteins from multiple species; links to related sites including leading researchers on P450

• http://www.fda.gov/cder/guidance/

• http://www.sigmaaldrich.com/Area_of_Interest/Biochemicals/Enzyme_Explorer.html
  – Site has many commercially available drug metabolizing enzymes and useful links to multiple drug metabolism resources