Special Articles/บทความพิเศษ

Cytochrome P450s

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Cytochrome P450s or CYPs are heme proteins found in several organs but in high amount in both mammalian and human livers. The heme iron binds oxygen in the CYP active site, where oxidation of xenobiotics and endogenous compounds occurs. Electrons are supplied by the enzyme NADPH-cytochrome P450 oxidoreductase and its cofactor, NADPH. Metabolism of a substrate by a CYP consumes one molecule of O_2 and produces on oxidized substrate and a molecule of water (Fig. 1). Depending on the nature of the substrate, the reaction for some CYPs is partially "uncoupled," consuming more O_2 than substrate metabolized and producing "activated oxygen" or O_2 which is usually converted to water by the enzyme superoxide dismutase (SOD).

Among the diverse reactions carried out by mammalian CYPs are N-dealkylation, O-dealkylation, aromatic hydroxylation, N-oxidation, S-oxidation, deamination and dehalogenation (Table 1). In fact, CYPs are involved in the metabolism of dietary and xenobiotic agents, as well as the synthesis of endogenous compounds that are derived from cholesterol (e.g., steroid hormones and bile acids).

The CYPs that carry out xenobiotic metabolism have the capacity to metabolize a large number of structurally diverse chemicals. This is due both to multiple forms of CYPs and to the capacity of a single CYP to metabolize structurally dissimilar chemicals. A single compound can be metabolized by multiple CYPS and CYPs can metabolize a single compound at multiple positions. In general, eukarytic CYPs metabolize substrates at a fraction of the rate of more typical enzymes involved in intermediary metabolism and mitochondrial electron transfer. As a result, drugs generally have half-lives in the range of 3-30 hours, while endogenous compounds have half-lives of seconds or minutes.

The broad substrate specificity of CYPs is one of the underlying reasons for the high frequency of drug interactions. When two coadministered drugs are both metabolized by a single CYP, they compete for binding to the enzyme's active site. This can result in the inhibition of metabolism of one or both of the drugs, leading to elevated plasma levels. For drugs with a narrow therapeutic index such as phenytoin, the elevated serum levels may elicit unwanted toxicities. Drug-drug interactions are among the leading causes of adverse drug reactions

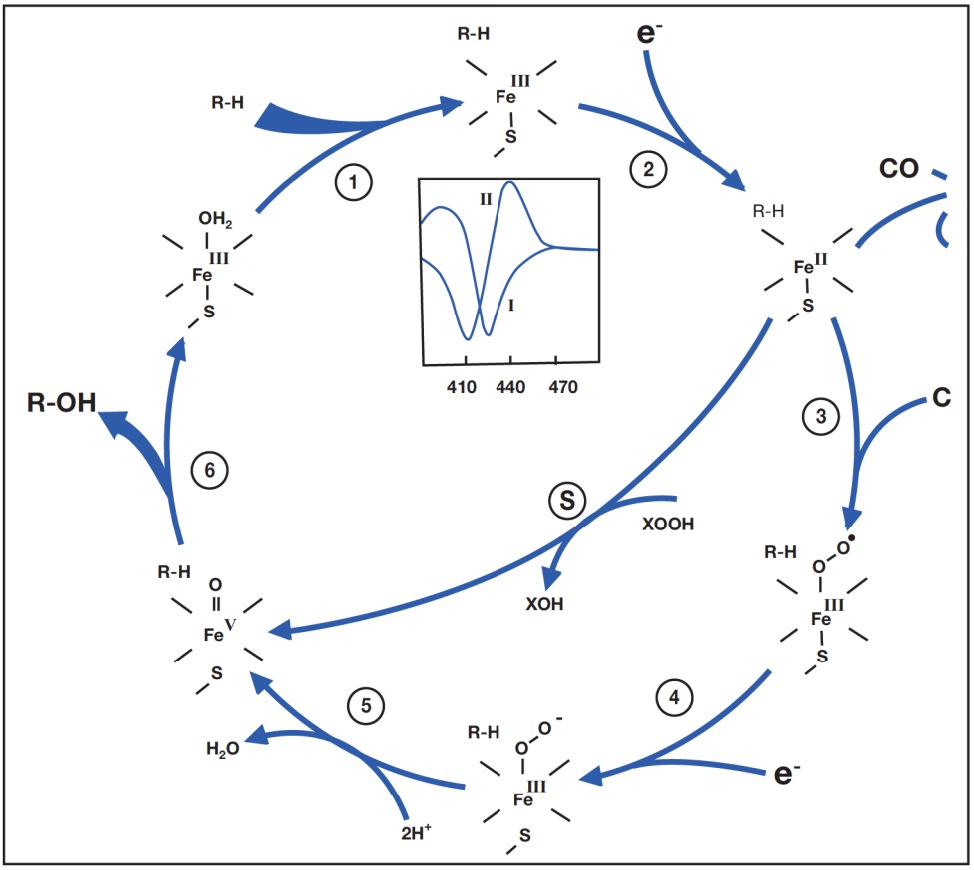
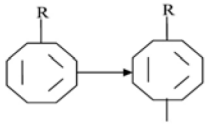
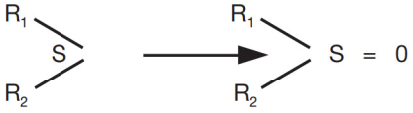


Fig.1 *P450 cycle responsible for the biotransformation of xenobiotic (RH) to the hydroxylated product (R-OH).*

Table 1. Major oxidation reactions involved in drug metabolism.

• Oxidation reactions		
N - Dealkylation	$RNHCH_3$	$\rightarrow RNH_2 + CH_2O$
O - Dealkylation	$ROCH_3$	$\rightarrow ROH + CH_2O$
Aliphatic Hydroxylation	$RCH2CH_3$	$\rightarrow RCHOHCH_3$
Aromatic hydroxylation		
N - Oxidation	$RHN2$	$\rightarrow RNHOHOH$
S - Oxidation		
Deamination	$RCHCH_3$ | NH_2	$\rightarrow RCCH_3$ ‖ $O + NH_3$
Dehalogenation	CCl_4	$\rightarrow CHCl_3$

Nomenclature of CYPs

There are 57 functional CYP genes and 58 pseudogenes in humans. These genes are grouped into families and subfamilies. CYPs are named with the root "CYP" followed by a number designating family, a letter denoting the subfamily, and a second number designating the isoform. Thus, CYP3A4 is family 3, subfamily A and isoform (gene) number 4. In humans, 12 CYPs in families 1-3 (CYP1A1, 1A2, 1B1, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4 and 3A5) are primarily responsible for xenobiotic metabolism. The liver contains the greatest abundance of xenobiotic-metabolizing CYPs CYPs are also expressed throughout the GI tract, and, in lower amounts, in lung, kidney, and the central nervous system (CNS). The most important CYPs for drug metabolism are those in the CYP2C, CYP2D, and CYP3A subfamilies. CYP3A4, the most abundantly expressed, is involved in the metabolism of approximately 50% of clinically used drugs. The CYP1A, CYP1B, CYP2A, CYP2B, and CYP2E subfamilies are rarely involved in the metabolism of therapeutic drugs, but they catalyze the metabolic activation of many protoxins and procarcinogens.

There are large interindividual variations in CYP activity due to genetic polymorphism. Human CYP genes that exhibit polymorphism include CYP2A6, CYP2C9, CYP2C19 and CYP2D6.

Human hepatic microsome contains about 0.5 nmol (25 μg) P450 per mg protein, as assayed spectrally, although individual variation is large. Immunoassay analysis, combined with the knowledge of the expression patterns of specific human P450 enzymes, indicates that most of the hepatic P450

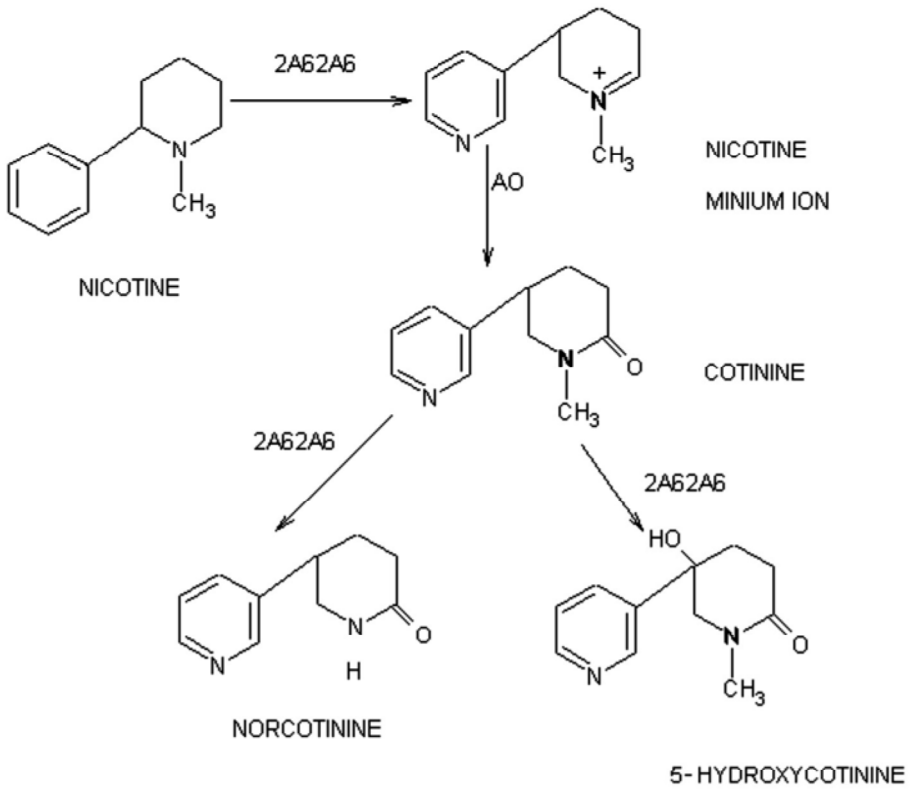


Fig. 2 *Metabolism of nicotime by CYP2A6 (Drug Metab Dispos 2001;29:91-5)*

content can be accounted for by enzymes 1A2, the 2C subfamily (2C8, 2C9, 2C18, 2C19), 2E1, and the most abundant P450 enzyme, 3A4. However, it should be borne in mind that even a P450 expressed at a low level may control the metabolism of a substance for which it has specificity. For example, P450 2A6 (CYP2A6) is not highly expressed in human liver, but it accounts for most of the nicotine detoxication activity (Fig.2).

Table 2 lists typical substrates of some human P450 enzymes of pharmacological and toxicological importance. The first known instance in which a mutation of a human P450 gene associated with an inherited disease is the human CYP1B1 gene which is the locus of the autosomal recessive disorder known as "primary congenital glaucoma" (buphthalmos or "ox-eye", because of the distended appearance of the eyes, due to increased intraocular pressure). CYP1B1 activity is believed to be required for metabolism of retinoids which control the development of ocular structures (canal of Schlemm and trabecular meshwork).

Table 2. Typical substrates of selected hepatic P450 enzymes

1A2	**2C19**	**3A4**
Aflatoxin B_1	Omeprozole	Cyclosporon
Caffeine	Mephenytoin	Dapsone
Phenacetin	**2D6**	Erythromycin
2A6	Debrisquine	Nifedipine
Coumarin	Desipramine	Quinidine
Nicotine	Dextromethorphan	Taxol
2B6	**2E1**	
Cyclophosphamide	Aniline	
Diazepam	Ethanol	
Tamoxifen	Chlorzoxazone	
2C9		
Celecoxib		
Tolbutamide		
Aminopyrine		

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