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Cytochrome P450 enzymes in drug metabolism: Regulation of gene expression, enzyme activities, and impact of genetic variation

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ABSTRACT

Cytochromes P450 (CYP) are a major source of variability in drug pharmacokinetics and response. Of 57 putatively functional human CYPs only about a dozen enzymes, belonging to the CYP1, 2, and 3 families, are responsible for the biotransformation of most foreign substances including 70–80% of all drugs in clinical use. The highest expressed forms in liver are CYPs 3A4, 2C9, 2C8, 2E1, and 1A2, while 2A6, 2D6, 2B6, 2C19 and 3A5 are less abundant and CYPs 2J2, 1A1, and 1B1 are mainly expressed extrahepatically. Expression of each CYP is influenced by a unique combination of mechanisms and factors including genetic polymorphisms, induction by xenobiotics, regulation by cytokines, hormones and during disease states, as well as sex, age, and others. Multiallelic genetic polymorphisms, which strongly depend on ethnicity, play a major role for the function of CYPs 2D6, 2C19, 2C9, 2B6, 3A5 and 2A6, and lead to distinct pharmacogenetic phenotypes termed as poor, intermediate, extensive, and ultrarapid metabolizers. For these CYPs, the evidence for clinical significance regarding adverse drug reactions (ADRs), drug efficacy and dose requirement is rapidly growing. Polymorphisms in CYPs 1A1, 1A2, 2C8, 2E1, 2J2, and 3A4 are generally less predictive, but new data on CYP3A4 show that predictive variants exist and that additional variants in regulatory genes or in NADPH: cytochrome P450 oxidoreductase (POR) can have an influence. Here we review the recent progress on drug metabolism activity profiles, interindividual variability and regulation of expression, and the functional and clinical impact of genetic variation in drug metabolizing P450s.

Contents

Abbreviations: ADME, absorption, distribution, metabolism, excretion; ADR, adverse drug reaction; AhR, aromatic hydrocarbon receptor; CNV, copy number variant; CYP, cytochrome P450; DDI, drug-drug interaction; EM, extensive metabolizer; ERα, estrogen receptor alpha; FXR, farnesoid X receptor; GR, glucocorticoid receptor; GWAS, genome-wide association study; IM, intermediate metabolizer; LD, linkage disequilibrium; LXR, liver X receptor; MAF, minor allele frequency; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NNRTI, non-nucleoside reverse transcriptase inhibitor; PBREM, phenobarbital-responsive enhancer module; PCR, polymerase chain reaction; PM, poor metabolizer; POR, NADPH:cytochrome P450 oxidoreductase; PPAR, peroxisome proliferator-activated receptor; SERM, selective estrogen receptor modulator; SLCO1B1, organic anion transporting polypeptide 1B1; UM, ultrarapid metabolizer; VDR, vitamin D receptor; XREM, xenobiotics-responsive enhancer module.

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1. Introduction

Predicting the fate of a drug in a particular patient and his or her subsequent response is still a vision and far away from application in routine clinical practice. Recognizing the sources and understanding the factors that contribute to the extraordinary pharmacokinetic and pharmacodynamic variability within and between individuals remains a challenge of particular importance for drugs with narrow therapeutic index (Lin, 2007). The cytochromes P450 (CYPs) constitute the major enzyme family capable of catalyzing the oxidative biotransformation of most drugs and other lipophilic xenobiotics and are therefore of particular relevance for clinical pharmacology (Nelson, 2004; Guengerich, 2008; Zanger et al., 2008). In humans 57 putatively functional genes and 58 pseudogenes are encoded by various gene clusters distributed over most autosomal chromosomes, in comparison to 108 functional and 88 pseudogenes in the mouse (Nelson et al., 2004). Most of the human genes, which are grouped according to their sequence similarity into 18 families and 44 subfamilies (http://drnelson.uthsc.edu/human.P450.table.html), have specific endogenous functions including the biosynthesis of steroid hormones, prostaglandins, bile acids, and others (Nebert & Russell, 2002). Only about a dozen enzymes belonging to the 1, 2, and 3 CYP-families are responsible for the metabolism of the majority of drugs and other xenobiotics. Despite the broad and overlapping substrate specificities of these enzymes, many drugs are metabolized at clinically relevant concentrations by one or few enzymes only, which limits the important redundancy of the phase I drug oxidation system. Knowledge of the intrinsic and extrinsic factors that influence expression and function of the responsible enzymes is thus a prerequisite for predicting variable pharmacokinetics and drug response. While monogenic polymorphisms explain a major part of the variability for only few enzymes (in particular CYP2D6), most enzymes are multifactorially controlled including additional polymorphisms in regulatory trans-genes and nongenetic host factors including sex, age, disease, hormonal and diurnal influences and other factors (Fig. 1). In this review we cover the CYPs of families 1 to 3 which have been shown to be of major importance for the biotransformation of drugs. We review the recent progress on drug metabolism activity profiles, interindividual variability and regulation of expression, and the functional and clinical impact of genetic variation in drug metabolizing P450s, whereas epidemiological studies were only mentioned occasionally. Our intention was to provide basic knowledge for each CYP on all these aspects but to focus for the literature survey on the past ten years. In view of the enormous body of literature we could not cite all studies and we are aware that it is difficult to provide an entirely objective overview. In this sense, we would like to apologize to all authors of studies not mentioned in this review.

2. Factors that influence cytochromes P450 expression and function

2.1. Genetic polymorphism

Heritable genetic variation in drug metabolizing enzyme genes has been studied for over 60 years and many intriguing examples of the genetic influence on drug biotransformation have been investigated at great detail and for some of them clinical relevance has been studied (Meyer, 2004). Interestingly, loss-of-function polymorphisms in *CYP* genes surprisingly often affect splicing and expression, rather than transcription or protein structure (Sadee et al., 2011). Gain-of-function variants include copy number variants (CNV) with an increased number of functional gene copies in *CYP2D6* and *CYP2A6* (Johansson & Ingelman-Sundberg, 2008), as well as promoter variants (e.g. in *CYP2B6*, *CYP2C19*) and amino acid variants with increased substrate turnover (e.g. in *CYP2B6*, *CYP2C8*). Surprisingly few polymorphisms affect clearly the substrate selectivity or the inducibility of drug metabolic pathways. Important polymorphisms of drug metabolizing CYPs with functional and clinical correlates are summarized in Table 1.

The CYP-specific drug oxidation phenotype can be determined in vivo using selective model substrates (Walsky & Obach, 2004; Fuhr et

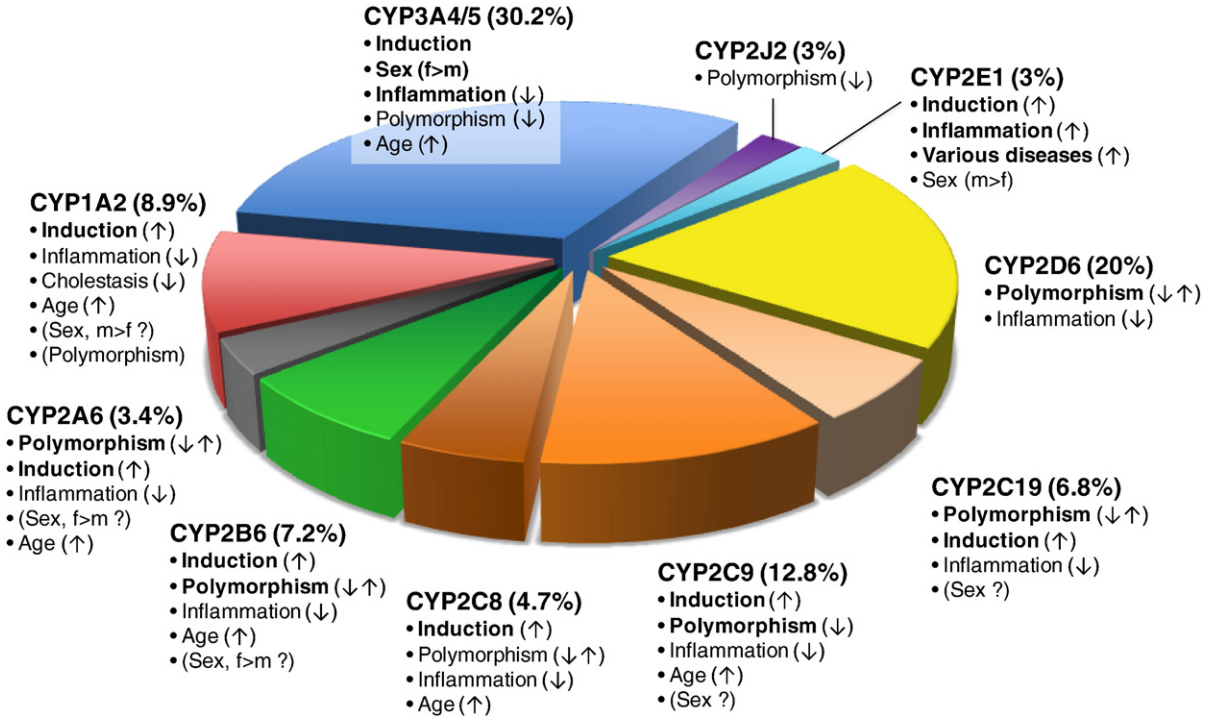

Fig. 1. Fraction of clinically used drugs metabolized by P450 isoforms and factors influencing variability. A total of 248 drug metabolism pathways with known CYP involvement (Table 3; chemicals and endogenous substrates excluded) were analyzed. Each metabolic pathway was only counted once for the major contributing CYP isoform. Important variability factors are indicated by bold type with possible directions of influence indicated (↑, increased activity; ↓, decreased activity; ↑↓, increased and decreased activity). Factors of controversial significance are shown in parentheses.