Available online at www.sciencedirect.com

SCIENCE DIRECT

Toxicology and Applied Pharmacology 207 (2005) S57 – S61

Toxicology and Applied Pharmacology

www.elsevier.com/locate/ytaap

Review

Novel extrahepatic cytochrome P450s

Maria Karlgren*, Shin-ichi Miura, Magnus Ingelman-Sundberg

Division of Molecular Toxicology, Institute of Environmental Medicine, Karolinska Institutet, SE-171 77 Stockholm, Sweden

Received 15 July 2004; revised 9 December 2004; accepted 9 December 2004
Available online 28 June 2005

Abstract

The cytochrome P450 enzymes are highly expressed in the liver and are involved in the metabolism of xenobiotics. Because of the initiatives associated with the Human Genome Project, a great progress has recently been seen in the identification and characterization of novel extrahepatic P450s, including CYP2S1, CYP2R1, CYP2U1 and CYP2W1. Like the hepatic enzymes, these P450s may play a role in the tissue-specific metabolism of foreign compounds, but they may also have important endogenous functions. CYP2S1 has been shown to metabolize all-*trans* retinoic acid and CYP2R1 is a major vitamin D 25-hydroxylase. Regarding their metabolism of xenobiotics, much remains to be established, but CYP2S1 metabolizes naphthalene and it is likely that these P450s are responsible for metabolic activation of several different kinds of xenobiotic chemicals and contribute to extrahepatic toxicity and carcinogenesis.

Keywords: Extrahepatic P450; Vitamin D; Naphtalene; Arachidonic acid; all-*trans* retinoic acid; Lung toxicity

Contents

Introduction . . . S57
CYP2S1 . . . S58
CYP2R1 . . . S58
CYP2U1 . . . S59
CYP2W1 . . . S60
Conclusions . . . S60
Acknowledgments . . . S61
References . . . S61

Introduction

The cytochrome P450 enzymes constitute a superfamily of heme-containing monooxygenases. In the human genome approximately 57 cytochrome P450 genes that encode active enzymes as well as 58 pseudogenes have been identified (Nelson et al., 2004). Many of the previously well-characterized mammalian P450s are expressed primarily in liver, and only at much lower or undetectable levels in extrahepatic tissues. The hepatic P450 enzymes belonging to the cytochrome P450 families 1–3 are mainly involved in the metabolism of foreign compounds, and are of major importance for metabolism of drugs and other xenobiotics. The importance of extrahepatic P450s for drug clearance is relatively small compared to the hepatic P450s. By contrast, the known extrahepatic P450s often exhibit important endogenous functions, e.g., in the regulation of the levels of steroid hormones, bile acids, lipids and other signaling molecules.

Many P450s are expressed in the respiratory tract, including nasal mucosa, lung, and trachea. This region is

* Corresponding author. Fax: +46 8 337 327.
E-mail address: Maria.Karlgren@imm.ki.se (M. Karlgren).

0041-008X/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.taap.2004.12.022

exposed to both inhaled and blood-borne xenobiotic compounds, and is therefore an important target in extrahepatic xenobiotic metabolism. A common subsets of P450s are expressed preferentially in the respiratory tract, for example, the P450 genes located on the CYP2 gene cluster on chromosome 19, including CYP2A13 (Su et al., 2000) and CYP2F1 (Nhamburo et al., 1990). Both CYP2A13 and CYP2F1 are important for the bioactivation of xenobiotics. CYP2A13 has been shown to activate the tobacco-specific nitrosamine, NNK, which has been suggested to play a role in human tobacco-related cancers (Su et al., 2000), and CYP2F1 has been shown to metabolize naphthalene (Lanza et al., 1999), a pulmonary toxicant in mice (Plopper et al., 1992).

The brain contains very low P450 levels and the amount in brain homogenate is only about 0.5–2% of that in liver microsomes (Hedlund et al., 2001). The P450 levels vary between different brain regions, with an exceptionally high overall P450 content in cerebellum (Warner et al., 1988). There are a few P450s that are predominantly expressed in brain. These include CYP7B, expressed in particular in hippocampus of rat and mouse (Stapleton et al., 1995), CYP26B, expressed in cerebellum and pons of the human brain (White et al., 2000) and CYP46, showing a widespread expression in brain (Lund et al., 1999). These three brain-specific enzymes are not involved in the metabolism of foreign compounds, but are important for endogenous functions like in the regulation of neurosteroids, cholesterol and vitamin A metabolism (Hedlund et al., 2001).

Because of the completion of the sequence of the humane genome and the initiatives related to this project, there has recently been a remarkable progress in the identification and characterization of novel P450 genes, which have been found to be expressed mainly in extrahepatic tissues. Here, we present some of the lately identified cytochrome P450s with potential importance for metabolic activation of xenobiotics.

CYP2S1

CYP2S1 is a newly identified cytochrome P450 enzyme localized on chromosome 19q13.2 close to the previously known CYP2 cluster. The other P450s in that cluster are also the enzymes with highest identity to CYP2S1 (Fig. 1). When the CYP2S1 mRNA expression was investigated, extrahepatic tissues such as the respiratory and gastrointestinal tracts were found to contain significant amounts. The CYP2S1 protein was also detected by Western blotting analysis in human lung (Rylander et al., 2001). In another study CYP2S1 mRNA and protein were found in human skin, where it was shown to be induced by ultraviolet radiation, coal tar, and all-*trans* retinoic acid (Smith et al., 2003). All-*trans* retinoic acid was found to be a substrate of CYP2S1.

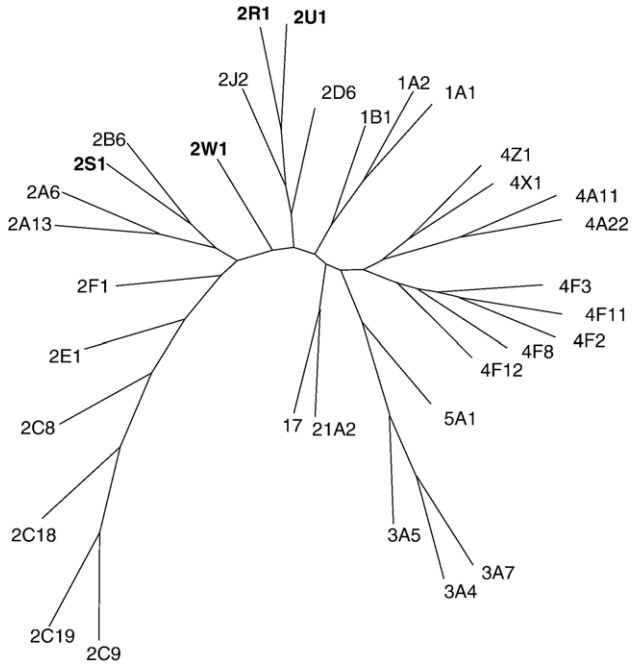

Fig. 1. Unrooted phylogenetic tree of human cytochrome P450s. CYP2S1, CYP2R1, CYP2U1 and CYP2W1 are shown in bold.

An unusual feature of CYP2S1 is that it is induced by dioxin in both mouse and human (Rivera et al., 2002). Such an induction via the Ah-receptor (AhR) by dioxin or polycyclic aromatic hydrocarbons (PAHs) usually affects the expression of members within the CYP1 family. This opens the possibility that CYP2S1 participates in the metabolism of aromatic hydrocarbons. Naphthalene has been shown to be metabolized into reactive intermediates by the murine enzyme Cyp2f2 (Shultz et al., 1999) and by the human homologue CYP2F1 (Lanza et al., 1999). CYP2S1 is closely related to CYP2F1 (47.2% identity), and is expressed in lung. It has also been shown to be induced by dioxin and PAHs trough activation of the AhR. Indeed, we found that CYP2S1 is capable to metabolize naphthalene. CYP2S1 was heterologously expressed in yeast and examination of the CYP2S1-dependent activity of the microsomes revealed that the enzyme converted naphthalene into two different metabolites, as revealed by HPLC analysis of the incubates (Fig. 2). This finding indicates that CYP2S1 might play a role in naphthalene-induced lung cytotoxicity (Buckpitt et al., 2002).

CYP2R1

The *CYP2R1* gene is localized on chromosome 11p15.2 and has five exons. Thus, it differs from most other members of the CYP2 family, carrying nine exons. CYP2R1 is also highly conserved across species with human CYP2R1 showing 89% and 66% sequence identity at the amino acid level to mouse and fugu fish CYP2R1, respectively.