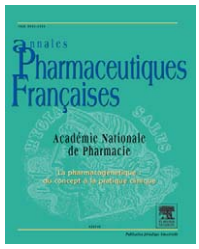
Annales Pharmaceutiques Françaises (2011) **69**, 45—52

Disponible en ligne sur
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com



SÉANCE THÉMATIQUE : MÉTABOLISME DES XÉNOBIOTIQUES

FAD-dependent enzymes involved in the metabolic oxidation of xenobiotics☆

Enzymes FAD-dépendantes impliquées dans l'oxydation métabolique des xénobiotiques

M. Strolin Benedetti

UCB Pharma SA, 420, rue d'Estienne-d'Orves, 92705 Colombes, France

Received 5 July 2010; accepted 6 October 2010
Available online 28 December 2010

KEYWORDS
Flavin-containing monooxygenases;
Molybdenum hydroxylases;
Aldehyde oxidase;
Xanthine oxidase;
Monoamine oxidases;
Polyamine oxidases

Summary Although the majority of oxidative metabolic reactions are mediated by the CYP superfamily of enzymes, non-CYP-mediated oxidative reactions can play an important role in the metabolism of xenobiotics. Among the major oxidative enzymes, other than CYPs, involved in the oxidative metabolism of drugs and other xenobiotics, the flavin-containing monooxygenases (FMOs), the molybdenum hydroxylases [aldehyde oxidase (AO) and xanthine oxidase (XO)] and the FAD-dependent amine oxidases [monoamine oxidases (MAOs) and polyamine oxidases (PAOs)] are discussed in this minireview. In a similar manner to CYPs, these oxidative enzymes can also produce therapeutically active metabolites and reactive/toxic metabolites, modulate the efficacy of therapeutically active drugs or contribute to detoxification. Many of them have been shown to be important in endobiotic metabolism (e.g. XO, MAOs), and, consequently, interactions between drugs and endogenous compounds might occur when they are involved in drug metabolism. In general, most non-CYP oxidative enzymes (e.g. FMOs, MAOs) appear to be noninducible or much less inducible than the CYP system. Some of these oxidative enzymes exhibit polymorphic expression, as do some CYPs (e.g. FMO3). It is possible that the contribution of non-CYP oxidative enzymes to the overall metabolism of xenobiotics is underestimated, as most investigations of drug metabolism have been performed using experimental conditions optimised for CYP activity, although in some cases the involvement of non-CYP oxidative enzymes in xenobiotic metabolism has been inferred from not sufficient experimental evidence.

☆ Cet article a fait l'objet d'une communication orale à l'Académie nationale de pharmacie lors de la séance thématique du 19 mai 2010.

E-mail address: largeron@pharmacie.univ-paris5.fr

0003-4509/$ — see front matter
doi:10.1016/j.pharma.2010.10.004

MOTS CLÉS
Monooxygénases à flavine ;
Hydroxylases à molybdène ;
Aldéhyde oxydase ;
Xanthine oxydase ;
Monoamine oxydases ;
Polyamine oxydases

Résumé Même si la majorité des réactions métaboliques oxydatives sont catalysées par la superfamille d'enzymes à cytochrome P-450, les réactions oxydatives contrôlées par les enzymes non-CYP ont un rôle important dans le métabolisme des xénobiotiques. Parmi les enzymes oxydatives non-CYP impliquées dans le métabolisme oxydatif des médicaments et d'autres xénobiotiques, on discute dans cette minirevue les monooxigénases à flavine (FMO), les hydroxylases à molybdène (aldéhyde oxydase [AO] et xanthine oxydase [XO]) et les amines oxydases FAD-dépendantes (monoamine oxydases [MAOs] et polyamine oxydases [PAOs]). Comme les CYP, ces enzymes oxydatives peuvent aussi générer des métabolites thérapeutiquement actifs et des métabolites réactifs/toxiques, moduler l'efficacité des médicaments ou contribuer à leur détoxification. Un bon nombre d'entre elles est important pour le métabolisme des produits endogènes (par exemple XO, MAOs), et par conséquence des interactions entre médicaments et molécules endogènes peuvent se produire quand ces enzymes sont impliquées dans le métabolisme des médicaments. En général, la plupart des enzymes oxydatives non-CYP (par exemple FMOs, MAOs) n'est pas inductible ou beaucoup moins inductible que les CYPs. Certaines de ces enzymes oxydatives (FMO3) montrent un polymorphisme, comme il est le cas pour certains CYPs. Il est possible que la contribution des enzymes oxydatives non-CYP à l'ensemble du métabolisme des xénobiotiques ait été sous-estimée, car la plupart des investigations dans le domaine du métabolisme des médicaments a été effectuée en utilisant des conditions expérimentales optimales pour l'activité des CYPs, même si dans certains cas l'implication des enzymes oxydatives non-CYP dans le métabolisme des xénobiotiques a été attribuée à partir des données expérimentales non suffisantes.

Introduction

Although the cytochrome P-450 (CYP) system would appear to rank first in terms of catalytic versatility and of the wide range of xenobiotics that are detoxified or activated to reactive intermediates, the contribution of flavine-adenine dinucleotide (FAD)-dependent enzymes to the oxidative metabolism of drugs or other xenobiotics is far from negligible [1]. Among these enzymes the flavin-containing monooxygenases (FMOs), the molybdenum hydroxylases and the amine oxidases will be reviewed.

The contribution of these enzymes to the oxidative metabolism of xenobiotics has been overlooked in the past for a number of reasons, e.g. the subcellular fractions used for investigating drug metabolism were generally selected for maximal CYP activity (liver microsomes), whereas some of the FAD-dependent oxidatives enzymes are more prevalent in cytosol, mitochondria or peroxisomes. In addition, experimental conditions, e.g. temperature and pH, were frequently chosen to optimise CYP activity rather than the activity of the FAD-dependent oxidative enzymes. Moreover enzymes such as monoamine oxidases were considered important mainly for the metabolism of biogenic amines rather than for that of xenobiotics.

As it occurs when the CYP system is involved in the oxidative metabolism of drugs, also when metabolism is due to FAD-dependent enzymes, the metabolites produced can be inactive, active, toxic or reversible, e.g. the isoenzyme of monoamino oxidases called MAO-B generates a toxic metabolite when metabolising N-methylphenyl-4-tetrahydro-1,2,3,6-pyridine (MPTP) whereas FMOs can produce reversible N-oxides. When the N-oxides of drugs are reduced back to the parent amines they may serve as storage forms of the active drugs. Subsequent excretion of the parent drugs may not reflect the extent of N-oxidation that has occurred in vivo. This alternate oxidation/reduction of amines can lead to futile cycling of a drug resulting in a long half-life [2,3].

As for a number of CYPs also for FAD-dependent isoenzymes polymorphisms have been reported, e.g. polymorphisms of FMO3 [4].

Flavin-containing monooxygenases

FMOs are microsomal enzymes having as prosthetic group FAD, which is an integral part of the protein, and as cofactor oxygen and nicotinamide-adenine dinucleotide phosphate (NADPH). FMOs are not haemoproteins. The catalytic cycle of FMOs, according to Krueger and Williams [5], is presented in Fig. 1.

Both FMOs and CYPs catalyze the NADPH-dependent N-or S-oxygenation of heteroatom-containing compounds. Both FMOs and CYPs generally convert lipophilic compounds to more hydrophilic materials.

While FMOs require nucleophiles as substrates, CYPs can oxidize non-nucleophilic substrates.

FMOs are much more sensitive to temperature than CYPs (e.g. in the absence of NADPH, FMOs are quite unstable at 50 °C, while under similar conditions about 85% of the functional activity of CYPs is retained). CYPs are often inducible, whereas very few reports of FMOs induction have appeared, although the effect of hormones on modulating FMO activity has been described [6]. In contrast to CYPs, FMOs are rarely inhibited. Therefore, potential adverse drug-drug interactions are minimized for drugs prominently metabolized by FMOs. Compared with FMOs, CYPs appear to participate in more metabolic reactions that result in