INDIVIDUAL SUSCEPTIBILITY TO TOXIC COMPOUNDS: ROLE OF CYTOCHROMES P450

Pavel ANZENBACHER [a], Roman ZUBER[a], Josef FUSEK [b]
[a] Palacky University, Faculty of Medicine, Institute of Pharmacology, Olomouc
[b] Purkyne Military Medical Academy, Department of Toxicology, Hradec Králové

The response of an organism to xenobiotic, often toxic, compounds is determined by various factors. One of the most important ones is the presence of enzymes metabolizing the xenobiotics; among them, the most prominent enzymes are cytochromes P450 (abbrev. CYP). The CYP enzymes metabolizing xenobiotics are present in the liver as well as in other parts of the gastrointestinal tract, in the lung, kidney, heart, nasal epithelium, leukocytes and other tissues. Their localization is expected to be connected with their yet unknown physiological function(s).

The role of cytochromes P450 in toxicity of xenobiotics is given by the fact that the products of P450-mediated reactions are often more harmful than the parent compound itself. There are four ways by which the P450s may cause or promote toxic effects of a given compound:

i. by direct activation of e.g. a chemical carcinogen – typical examples are polycyclic aromatic hydrocarbons or nitrosamines
ii. by formation of reactive intermediates – e.g. reactive oxygen species or quinones
iii. by interactions at the level of CYP enzymes – an example may be an increased plasmatic level of dihydropyridine calcium channel blockers (causing hepatotoxicity) due to competitive interaction with erythromycin (at the level of CYP3A4)
iv. due to slow or impaired metabolism of a compound metabolized by CYP enzyme whose levels may vary in individuals as a result of genetic polymorphism – as in the case of cardiotoxic effects of an overdose of tricyclic antidepressant caused by its slow metabolism in an individual lacking a „correct" allele of the respective CYP gene (here CYP2D6)

Differences in the individual susceptibility to toxic compounds (at the level of cytochromes P450) may thus be determined by the genotype of an individual as well as by factors given by interactions with other compounds or factors from the environment. Among these factors, interactions with drugs, with compounds present at the workplace or factors of dietary or social origin (e.g. alcohol, smoking habit) are the most prominent. In the next part, examples of these factors will be given together with individual cytochrome P450 enzymes involved.

The most important cytochrome P450 for man is the CYP3A4 enzyme. Its levels and activities may vary by one order of magnitude. The reason for this is most probably the presence of different alleles of this enzyme (www. imm.ki.se/CYPalleles). The CYP3A4 is responsible for metabolism of the majority of known xenobiotics. This determines its importance in toxicology and in drug interactions. It is the enzyme, which is responsible for metabolic activation of aflatoxins, namely, of the aflatoxins B1 and G1 as well as of some polycyclic aromatic hydrocarbons. It is involved in toxic side effects of several classes of drugs due to interactions.

As examples of toxic effects of compounds formed from pro-toxicants by CYP enzymes, the activation of polycyclic aromatic hydrocarbons and aromatic amines by cytochromes P450 of the CYP1A subfamily and formation of reactive quinones or quinoneimines by CYP2E1 may be presented.

Carcinogenicity of polycyclic aromatic hydrocarbons and of aromatic amines is widely known. The structurally very close forms CYP1A1 and 1A2 are responsible for their activation to ultimate carcinogens. The 1A1 form is mostly extrahepatic, typically located in lung, placenta, and leukocytes. The CYP1A2 is typically hepatic; both are induced by aromatic hydrocarbons and related compounds. CYP1A enzymes are uniquely suitable for binding of aromatic systems, as their active site seems to be rather planar. In the chemical reactions leading to formation of ultimate carcinogens (the electrophilic, positively charged structures which are able to bind directly to biological macromolecules) the CYP1A enzymes are involved in the first step mediating the hydroxylation reaction.

The CYP2E1 is another cytochrome P450 enzyme that takes part in the activation of protoxicants. As typical examples, the activation of nitrosamines, acrylonitrile, halogenderivatives of methane or ethane, of styrene and benzene may be mentioned here. The formation of reactive quinones and related compounds from aromatic structures are the basis of hepato- and nephrotoxicity of one of the most poular over-the-counter drug in the world, of paracetamol (acetaminophen).

Genetically determined effects on metabolism of drugs and toxic compounds are the bases of pharmaco- and toxicogenetics, in recent terms, pharmaco- and toxico-genomics. Genetic polymorphism is supposed to exist in all cytochromes P450 important for metabolism of xenobiotics and recent developments in genomics lead to findings of new alleles coding for variants of known CYP enzymes. The most is known for the CYP2D6 with nearly eighty alleles known to-date. Here, a gene duplication (leading to quick metabolism of xenobiotics in the so-called ultrarapid metabolizers) has been found as well as formation of many mutant proteins with lower activity for substrates; alternatively, formation of inactive proteins or no formation of a CYP2D6 protein at all has been also detected. The resulting phenotype of slow metabolizers (approximately 7 % of Caucasians) exhibits toxic side effects with many drugs. The cardiotoxicity of tricyclic antidepressants has been already mentioned as an example; life-threatening arrythmias after antiarrythmics (propafenone), neuropathy (after perhexilin) or nausea (after serotonin reuptake inhibitors) is another example.

During the studies on the CYP function, general relevance of xenobiotic metabolism to toxicity should be studied to reveal the links between molecular mechanisms and disease. To fully understand this, studies on (i) the effective levels of active compounds at the site of action, (ii) the influence of competing agents at the site, (iii) the mechanisms of attack of the reactive compounds on the macromolecules, (iv) the response of the organism to the altered structure at various levels of organization as well as epidemiologic studies on the relation of the disease to particular alteration of the genome are necessary. Hence, the progress does not seem to bring the simplification; on the other hand, the problems to be solved may be more sharply formulated and directed.

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Correspondence: Pavel Anzenbacher
Palacky University
Faculty of Medicine
Institute of Pharmacology
Hněvotínská 3
775 15 Olomouc
Czech Republic
e-mail: anzen@tunw.upol.cz

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