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The importance of cytochrome P450 2B6 in the human metabolism of environmental chemicals

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Abstract

Cytochrome P450 (CYP) 2B6 (CYP2B6) is a human CYP isoform found in variable amounts in the liver and other organs. It is known to be inducible and polymorphic and has a wide range of xenobiotic substrates. Studies of CYP2B6 to date have concentrated heavily on clinical drugs. In the present communication, however, we concentrate on its role in the metabolism of environmental xenobiotics. The term environment is used, in its broadest sense, to include natural ecosystems and agroecosystems as well as the industrial and indoor domestic environments. In essence, this excludes only clinical drugs and drugs of abuse. Many of these chemicals, including agrochemicals and industrial chemicals, can serve as substrates, inhibitors and/or inducers of CYP2B6, these activities being often modified by the existence of polymorphic variants. Metabolism-based interactions between environmental chemicals are discussed, as well as the emerging possibility of metabolic interactions between environmental chemicals and clinical drugs.
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Abbreviations: CYP for cytochrome P450; XME(s) for xenobiotic-metabolizing enzymes(s).

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1. Introduction

1.1. Nature of environmental chemicals

The terms environment and environmental are in such wide use that a precise definition is probably not possible. For the purposes of this review, the term environmental is used in the broadest commonly accepted manner, that of all of the milieu external to the organism or organisms in question. The uses of the terms internal environment or cellular environment are avoided only on the grounds that they are not relevant to the present case. It should also be recognized that there are specialized environments capable of narrower definition: all of the natural climatic zones, the agroecosystem, the workplace environment, the indoor environment, and others. By including all of these, the only xenobiotics excluded are clinical drugs and drugs of abuse. These latter are, in any event, reviewed extensively and frequently while environmental chemicals are still understudied and under-reviewed.

1.2. Xenobiotic metabolism

The mode of action of toxicants, including environmental chemicals, includes a cascade of events that is initiated by exposure and culminates in the expression of a toxic endpoint. Among the various steps, metabolism and the interaction with target macromolecules are almost without exception the most important, not only for individual chemicals but also as sites for interactions between xenobiotics and either exogenous or endogenous chemicals. Metabolism can result in either detoxication or activation, the latter being the formation of products that are more reactive than the parent chemical.

1.3. Xenobiotic metabolizing enzymes

Metabolism of environmental chemicals is highly dependent on particular xenobiotic metabolizing enzymes (XME), their isoforms, and their polymorphic variants. In phase I metabolism, a polar functional group is introduced into the molecule, rendering it a suitable substrate for phase II metabolism. Phase II metabolism consists of conjugation of phase I metabolites or xenobiotics that already posses a suitable functional group with water-soluble endogenous metabolites such as sugars, amino acids, sulfate or glutathione. The products of phase I metabolism are not always conjugated by phase II enzymes since the products of phase I XME are often potent electrophiles capable of interacting with nucleophilic substituents on macromolecules and are likely to be involved in activation as well as detoxication processes. The isoforms of cytochrome P450 (CYP) are the most important of the phase I enzymes in the metabolism of xenobiotics and in the introduction of functional groups for phase II metabolism (Hodgson & Goldstein, 2001).

XME usually exist as numerous isoforms, each of which may exist in several polymorphic forms. Isoforms (or isozymes) are different forms of a given enzyme that share the same general reaction mechanism. They are coded for by different genes, which, nevertheless, share some degrees of sequence homology. Isoforms may vary from one another in substrate specificity, co-exist within a single species or cell type, and occur in different species, organs, or cells. Polymorphisms, on the other hand, are stably inherited monogenetic traits that exist in a population in at least 2 genotypes (2 or more variant alleles) that are found at the same gene locus. Polymorphisms in the coding region of the gene may affect such characteristics of the expressed enzyme as substrate specificity and/or kinetic constants or, if they occur in the regulatory regions of the gene, may affect expression of the enzyme protein. Polymorphisms frequently control whether an individual is a poor metabolizer or an extensive metabolizer of clinical drugs, but their importance vis-a-vis environmental chemicals has not yet been studied extensively.

Recently we have begun the study of human metabolism of environmental chemicals, particularly agrochemicals, industrial chemicals, and those used in military deployments (Hodgson et al., 1998; Coleman et al., 1999, 2000; Dai et al., 2001; Tang et al., 2001; Choi et al., 2002; Tang et al., 2002; Usmani et al., 2002; Hodgson, 2003; Lee et al., 2003; Usmani et al., 2003; Tang et al., 2004; Usmani et al., 2004a, 2004b; Edwards et al., 2005; Hodgson & Rose, 2005; Rose, 2002; Rose et al., 2005; Casabar et al., 2006; Cho et al., 2006; Hodgson & Rose, 2006; Usmani et al., 2006; Das et al., in press). These studies include identification of metabolic products, identification of the isoforms of the XME involved, definition of the variation between polymorphic forms, and the variation between individuals based on phenotyped liver microsomes from individual human livers.

1.4. Cytochrome P450s

CYP enzymes are a superfamily of monooxygenases, many of which are XME responsible for the oxidation of many xenobiotics. Although there are as many as 18 families of these metabolizing enzymes in humans, CYP families 1–4 appear to have the greatest involvement in the metabolism of exogenous chemicals. Within these families, there are important subfamilies and isoforms that make substantial contributions to xenobiotic metabolism. Some of the more important of these include CYP3A4, CYP1A1, CYP1A2, CYP2B6, CYP2D6, CYP2C9, CYP2C19, and CYP2E1 (Hodgson & Goldstein, 2001).

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