Biochemical Pharmacology, Vol. 37, No. 1, p. 103, 1988.
Printed in Great Britain.

0006-2952/88 $3.00 + 0.00

Chairman's Summary of Session C
Chirality and cytochrome P-450: a perspective

Cytochromes P-450 are the key enzymes of the mixed-function oxygenase system and are responsible for the metabolism of a vast variety of xenobiotics and endobiotics. As such, the cytochromes P-450 are the key enzymatic interface between xenobiotics such as drugs, carcinogens, mutagens and other environmental chemicals and biological organisms ranging phylogenetically from man to prokaryotes. In addition, the cytochromes P-450 metabolize a variety of classes of endobiotics such as steroids, prostaglandins, leukotrienes and fatty acids. There are a multiplicity of cytochrome P-450 isozymic forms and the genes for some of these have been cloned. The sequence homology of the P-450 forms of known sequence range from 30% to more than 90%. The different forms of cytochrome P-450 exhibit variable substrate and product specificity. In some cases a chemical may be a substrate for only a single P-450, in other cases several P-450s may exhibit activity toward the same substrate. Overlapping substrate and product regio-and stereo-specificity are common features of many of the P-450s.

Cytochrome P-450 enzyme activity may result in beneficial detoxification of xenobiotics such as drugs and carcinogens or detrimental activation of xenobiotics to toxic, carcinogenic or mutagenic products. Cytochromes P-450 also may play an important regulatory role related to their key position in the metabolism of steroids, prostaglandins and leukotrienes, all metabolites important in mammalian regulatory processes.

A large percentage of cytochrome P-450 substrates and products are chiral molecules. Although there has been some minimal awareness of this fact, the stereochemistry of both substrates and product cytochrome P-450 has largely been ignored. Several years ago, Yang and Gelboin elucidated the high stereochemical specificity of activation of benzo(*a*)pyrene to its carcinogenic diol epoxide form. This set of reactions involved two cytochrome P-450 steps and one reaction catalyzed by epoxide hydrolase. The methods used to isolate the enantiomorphic intermediates and products were laborious, cumbersome and relatively inefficient. Yang has presented new data on the highly effective use of chiral stationary phase HPLC columns to separate simply and efficiently numerous enantiomorphs of chiral compounds formed during the metabolism of several polycyclic hydrocarbons. He demonstrated the relative ease of these methods and the enantiomorphic abundance of epoxides and dihydrodiols formed, reflecting the stereochemical specificity of cytochrome P-450 catalyzed metabolism of three planar and three non-planar hydrocarbons. The varying degree of regio- and stereo-selectivity likely reflects the sum of the selectivity of the individual P-450s contributing to each reaction. Eichelbaum examined the stereoselective aspects of the metabolism of certain drugs. He found that the L-form of verapamil, a cytochrome P-450 substrate and calcium channel blocker behaved far differently than the D-form in pharmacokinetic, therapeutic and bioavailability character. In other studies, Eichelbaum found that in the polymorphic oxidation of debrisoquin there are large differences between the enantiomeric ratio of metabolites in the efficient metabolizers where one enantiomer product predominates compared to the poor metabolizers where the products are closer to racemic mixtures. Waxman discussed the role of cytochrome P-450s in regio and stereospecific metabolism of a variety of steroids and how these reactions can be crucial in steroid regulatory processes.

Testa discussed the cytochrome P-450 catalyzed metabolism of chiral styrene as well as other P-450 drug substrates many of which have chiral centers. In some cases, drugs such as mephenytoin, are known to be oxidized by a P-450 which is polymorphic in the human populations.

The chirality of a vast abundance of P-450 substrates offers exciting challenges to pharmacology, drug design, pharmacogenetics, chemical carcinogenesis and cellular regulatory processes related to cytochrome P-450 action. With the introduction of chiral solid phase HPLC, the needed methodology has matured to a point where a variety of questions can now be experimentally posed. These relate to the biological activity and metabolism of enantiomeric forms of drugs and carcinogens and other cytochrome P-450 substrates such as steroids. The use of pure cytochromes P-450 obtained by the expression of cloned cDNA in expression vectors such as vaccinia virus can precisely determine the stereospecificity of a pure cytochrome P-450. Cytochrome P-450 specific monoclonal antibodies can now be used to determine the contribution of epitope related cytochrome P-450s to the enantiomeric ratios of a product obtained in a crude tissue preparation containing a mixture of cytochromes P-450. Another promising approach is to use the enantiomeric ratios of products of drug or carcinogen metabolism to detect genetic polymorphisms in the human population. The stereospecific analysis of cytochrome P-450 activity sharpens indeed the precision of our knowledge of cytochrome P-450 based metabolism, detoxification and activation of a vast variety of cytochrome P-450 substrates. These lie in the broad classes of xenobiotics such as drugs and carcinogens and potent endobiotic regulatory substances that include steroids and prostaglandins.

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