Introduction

H. REIN and K. RUCKPAUL

Volume 2 of the series "Frontiers in Biotransformation" is focussed on the induction of enzymes involved in biotransformation. Induction as an effector mediated stimulation of the biosynthesis of distinct enzymes represents a regulation mechanism of enzymatic activity which is controlled on the cellular level. Thus the content of volume 2 continues and extends the scope of volume 1, which dealt with problems of regulation of cytochrome P-450 catalysed reactions on the molecular and membrane level of integration.

Biological and medical consequences of induction resulting in changed biotransformation activities are manifold and important for toxification and detoxification as well. In addition, inducing agents have become to be seen as promoters and may thus initiate malignant transformation. Therapeutic effects can be altered by inducing drugs and in this way, e.g., the protective effect of contraceptive steroids may vanish. Induction modifies the isozymic pattern, which originates from the genetically determined polymorphism. The changed isozymic pattern determines their individual capability of metabolizing endogenous and exogenous compounds alike.

A huge number of articles dealing with the induction of enzymes involved in biotransformation have generated a real need for reviews. Therefore the interest of the editors in selecting the contributions for this volume was not to look for outstanding casuistic articles but rather to put together such papers which would comprehend and condense problems more general in character. Volume 2 is introduced by an article by PARKE, summarizing the general principles and biological consequences of induction. More detailed studies of molecular orbitals of inducers have revealed that the type of cytochrome P-450 induced is governed by the spatial dimensions and electronic structures of the inducing agents. Corresponding to the different types of inducers there exist different mechanisms of induction. An increase of the monooxygenase concentration but also of the NADPH dependent cytochrome P-450 reductase and further enzymes is observed at induction by the phenobarbital type inducers. Moreover, proliferation of the endoplasmic reticulum

and cellular hypertrophy of liver is observed. Obviously, phenobarbital increases both the transcriptional and translational activity.

The amino acid sequences of about 100 cytochromes P-450 led to a proposal for a unified nomenclature of the P-450 gene superfamily described by NEBERT and GONZALEZ in this volume. Most members of these families are inducible, with the assignment to a distinct family being mainly determined by the degree of homology but also by the specific inducer. The considerable increase in molecular biological studies on cytochrome P-450 in the last few years has led to a better understanding of constitutive and inducible gene expression of these key enzymes of biotransformation. The identification and characterization of *cis*-acting DNA regulatory elements, and the cloning of genes that encode *trans*-acting regulatory proteins interacting with these elements, are important steps in our knowledge of gene expression as well as of the developmental, sex and tissue specificities.

In the review of BRESNICK and HAUSER the polycyclic hydrocarbon specific cytochrome P-450 is described in detail. The gene of cytochrome P-450c was isolated and its DNA sequence determined. By genetic construction of specific gene segments their importance for interaction with the 4S polycyclic hydrocarbon-binding protein could be shown. The authors suggest that this protein could be the transcriptional factor which shuttles between the cytosolic compartment and the nucleus.

Already very early a sex-specific effect of inducers was observed, especially concerning the sex-related metabolism, such as hexobarbital hydroxylation and aminopyrine N-demethylation. The molecular basis of these differences is now understood in terms of a sex-specific induction of cytochrome P-450 isozymes in female and male animals. In the review of KATO and YAMAZOE not only this aspect of sex-dependent regulation of cytochrome P-450 expression is described but also a detailed analysis of sex-related cytochrome P-450 forms is given. The authors developed an immunoquantitative method for quantitation of cytochrome P-450-male and cytochrome P-450-female. These sex-specific forms clearly differ from each other in catalytic activity, molecular weight, physico-chemical properties and amino acid sequence too. Their specificity in drug oxidation was well documented by use of highly specific antibodies. Such inhibition studies offer an excellent method for classification of isozyme specific contributions in drug metabolism.

Doubtless the ontogenetic development of biotransformation activity is regulated and, or moreover, determined by the induction since it is known that the administration of phenobarbital to neonates has been shown to "imprint" or "programme" the microsomal enzymes of the adult. Distinct forms of cytochrome P-450 are induced in the foetal liver after administration of selected inducers to pregnant rats and treatment of neonates with inducers or their uptake via the maternal milk increases distinct cytochrome P-450 dependent enzyme activities. These facts are considered in the review of

KLINGER describing the biotransformation during the ontogenetic development. Although the total cytochrome P-450 concentration is a function of age, evidently, this enzyme concentration is responsible neither for the age dependence of drug oxidation, nor for the age dependent induction by the inducers of the phenobarbital and 3-methylcholanthrene group. Several reasons determine this behaviour. Different developmental patterns are observed for the multiple forms of cytochrome P-450. For the activity of a relevant isozyme, however, developmental changes in the microenvironment of the enzyme are of importance, i.e. phospholipids and their fatty acid composition which change with age, thereby changing structural and functional properties of the membrane and the cytochrome P-450 reducibility likewise. This knowledge is of importance to understand the prolonged half-life times in blood for most drugs in human neonates and to avoid therapeutic accidents as observed after chloramphenicol administration in newborns.

From the toxicological point of view, postoxidation reactions of xenobiotics are of importance because by these reactions, not in all cases highly water soluble metabolite of decreased pharmacological activity but also more toxic products are formed. Examples of such activation pathways are given in the chapter of LANGNER, BORCHERT and PFEIFER who describe the sulfo-, methyl-, and acetyltransferases in detail, including a lot of substrates which are conjugated by these enzymes. The fact that postoxidation enzymes are also inducible by different inducers is of interest in medicinal practice because enhanced bilirubin blood levels can be normalized by induction of glucuronosyltransferase which conjugates bilirubin. Instead of phenobarbital with many undesired side effects, the development of specific inducers for glucuronosyltransferase is necessary which requires deep insight into its structure and regulation. Definite data currently available for rat cDNA are the basis of the review of MACKENZIE dealing with the analysis of structural features, substrate preferences and regulation of glucuronosyltransferases predominantly of this species.

One of the main conjugation pathways is catalysed by glutathione transferases. These multifunctional enzymes are associated with the detoxification of drugs and carcinogens, the reduction of organic hydroperoxides and nitrate, the binding and intracellular transport of lipophiles and the biosynthesis of the local hormone leucotriene C. In the review of KETTERER and TAYLOR the reader will not only find a broad account of reactions with GSH which are catalysed by GSH transferases but the current situation regarding the distribution of these enzymes in the animated world, their structure and, finally, what is known at present of their genetic regulation.

In a last chapter THOMAS and OESCH deal with the most recent findings about the enzyme epoxide hydrolase which catalyses the hydration of epoxides. Normally this reaction is considered a step of detoxification. However, in the special case when dihydrodiol is formed from benzo(a)pyrene 7,8-oxide, a

further activation by a monooxygenase takes place resulting in the ultimate carcinogen, i.e. benzo(a)pyrene 7,8-diol-9,10-oxide. Biotransformation of foreign compounds is a complex process including steps of both toxification and detoxification. Clearly, the balance between the toxification and detoxification pathways depends on several factors; most importantly the genetically determined concentration of individual enzymes involved in biotransformation steps and their inducibility, too.