

# Preface

This book deals with various clinical aspects of cytochrome P4502E1 (CYP2E1) which is a potent source for oxidative stress. Cytochrome P-450 (CYP) enzymes are proteins that essentially contain a heme moiety and are involved in diverse oxidative metabolism of a wide spectrum of endogenous compounds as well as xenobiotics. Further, they are induced by several stimuli which include pathophysiological conditions, thus emphasizing their critical role in human physiology and diseases.

Ethanol-inducible CYP2E1 which forms the key enzyme in the microsomal ethanol-oxidizing system, besides metabolizing ethanol to acetaldehyde, also catalyzes oxidative metabolism of substrates primarily through acting as a monooxygenase and generating reactive oxygen species in the process. Oxidative stress is critical for pathogenesis of diseases and CYP2E1 is a major contributor for oxidative stress. Several clinical disorders are associated with changes in regulation of CYP2E1 and the consequent abnormalities which include alcoholic liver disease, alcoholic pancreatitis, carcinogenesis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, obesity, hepatitis C virus infection, reproductive organ toxicity, hepatocellular and cholestatic injury.

The list for the involvement of clinical and metabolic disorders associated with changes in regulation of CYP2E1 is extensive which includes bone loss, cross-tolerance in smokers and people treated with nicotine (e.g., smokers, patients with Alzheimer's disease, ulcerative colitis, neuropsychiatric motor disorders), disorders of central nervous system due to exposure to certain environmental chemicals and changes in the metabolism of protoxicants in the circulatory system.

Changes in regulation of CYP2E1 may occur due to endotoxemia, inflammatory stimuli, complex endocrine regulation by pituitary and testicular hormones, expression of methionine adenosyltransferase genes, nicotine or environmental tobacco smoke exposure, polymorphic gene expression, transcription factor hepatocyte nuclear factor 1 alpha, calmodulin dependent protein kinase, protein kinase C and cAMP dependent protein kinase, drugs such as isoniazid and clofibrate, starvation, insulin, diabetes or alcohol consumption.

The several mechanisms through which CYP2E1 exerts its damaging effects include increased oxidative stress, acetaldehyde formation and accumulation, increased hepatotoxicity of carcinogens like nitrosodimethylamine, urethane and acrylamide, oxidative DNA damage, augmentation of iron induced hepatotoxicity, priming of Kupffer cells to lipopolysaccharide-induced toxicity, affecting therapeutic index of drugs, i.e. potentiating acetaminophen mediated toxicity, increasing polyunsaturated fat mediated injury, depletion of the levels of the major cellular antioxidant glutathione and increase in collagen expression. Other mechanisms for clinical abnormalities associated with CYP2E1 include mitochondrial dysfunction, apoptotic cell death, potentiation of lipopolysaccharide or cisplatin mediated injury, inhibition of microsomal  $\text{Ca}^{2+}$ -ATPase, formation of carcinogenic etheno-DNA adducts, modulation of the immune response, increases in proinflammatory cytokines, polymorphic gene expression and increased hydroxyethyl radical formation.

Further, CYP2E1 causes metabolic abnormalities through formation of autoantibodies against CYP2E1, necroinflammation, increased degradation of retinoic acid and vitamin A, JNK activation, decrease in proteasome activity with subsequent accumulation of oxidized proteins, formation of cytokeratin aggresomes and Mallory body-like inclusions. Several other mechanisms through which CYP2E1 exerts toxicity include increased formation of Kupffer cell-generated metabolites, which may contribute to Kupffer cell toxicity; elevated c-fos mRNA; oxidative modifications of heat shock protein 60; protein disulfide isomerase; mitochondrial aldehyde dehydrogenases, prohibitin, and other proteins; formation of 3-nitrotyrosine adducts and high molecular weight microsomal ubiquitin conjugates; increased levels of endoplasmic reticulum stress marker tribbles-related protein 3 and chemokine CXCL-2; impairment of insulin signaling; formation of protein adducts of aldehydes such as acetaldehyde, malondialdehyde and 4-hydroxy-nonenal; suppression of activities of antigen-trimming enzymes, thereby decreasing the cleavage of C-extended and N-extended peptides which may potentially result in decreased MHC class I-restricted antigen presentation on virally infected liver cells; impairment of interferon gamma signaling; irreversible inhibition of fatty acid oxidation, potentially through suppression of PPARalpha-regulated pathways; and potentiation of thioacetamide mediated hepatotoxicity.

The first chapter gives an overview of the research on different aspects of CYP2E1 and the aim of the chapter is to acquaint the readers with a general picture regarding CYP2E1 before they delve deeper into further chapters which are specialized research findings discussed in detail by the different experts with respect to the studies being performed in their own respective laboratories. The subsequent chapters deal with some of the research activities dealing with CYP2E1 in major laboratories around the world.

Dr. Arthur I. Cederbaum discusses about the role of the transcription factor Nrf2, the key regulator of cytoprotective enzymes as a protective mechanism against CYP2E1 mediated oxidative stress in a human hepatoma cell line transfected with CYP2E1. Dr. Helmut K. Seitz discusses about the important role of ethanol inducible CYP2E1 in promoting alcohol mediated carcinogenesis. Dr. Samuel W. French deals with CYP2E1 mediated drug metabolism and the consequent drug mediated

hepatitis due to co-administration of ethanol and drugs. Also, epigenetic effects due to induction of CYP2E1 are discussed.

Dr. Ann K. Daly discusses about the role of CYP2E1 as a genetic risk factor for non-alcoholic fatty liver disease- evidences in favour and against it, as documented in studies involving genetic analyses. Drs. Terence M. Donohue and Natalia A. Osna discuss about the role of CYP2E1 in regulating cytokine signaling, antigen presentation, and macromolecular degradation leading to liver injury. Dr. M. Raj Lakshman discusses about the role of CYP2E1 and ethanol mediated oxidative stress in downregulating the hepatic expression of paraoxonase 1, a multifunctional antioxidant enzyme that prevents LDL oxidation and detoxifies the homocysteine metabolite, homocysteinethiolactone. Dr. Vasilis K. Vasiliou discusses about the role of CYP2E1 in ethanol metabolism in the central nervous system, including its regulation and expression and its influence on sensitivity to ethanol in the brain.

Thus, CYP2E1 is implicated in several clinical disorders through diverse mechanisms of injury. It is interesting to explore some of these pathways which shed light on the several other aspects linked with this enzyme. The different biochemical, toxicological and clinical aspects of CYP2E1 and the underlying mechanisms through which CYP2E1 plays a critical and indispensable role in modulating the therapeutic effects of drugs, and in development and pathogenesis of clinical disorders, form the core of the book.

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