

Review of Clinical Pharmacology and Pharmacokinetics

ΕΠΙΘΕΟΡΗΣΗ ΚΛΙΝΙΚΗΣ ΦΑΡΜΑΚΟΛΟΓΙΑΣ ΚΑΙ ΦΑΡΜΑΚΟΚΙΝΗΤΙΚΗΣ
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Τηλ.-Fax (0030)2107784700, 2107700663, 6932203802
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Letter from Guest Editor

The progress and contributions of 20th century pharmacology has been immense with over 20 pharmacologists to have received Nobel Prizes. This field of medical studies covers many areas; it is built upon and at the same time incorporates many disciplines such as biochemistry, biology physiology, pathology, anatomy, molecular biology, while the development of new analytical and experimental techniques and instruments has given a new boost in pharmacological research. Yet, although a remarkable progress has been made in developing new drugs and in understanding how they act, the challenges are endless. Integrating a depth of knowledge in many related scientific disciplines, pharmacologists offer a unique perspective to solving drug and chemical related problems which impinge on human health, with ultimate goal the treatment and prevention of major diseases.

The 5th Panhellenic Congress of Pharmacology focuses on four *hot* subjects: Regenerative Pharmacology, Herbal Medicines, Pharmacology of Abuse and Dependence, and Education in Pharmacology.

- *Regenerative Pharmacology* is one of the newest areas in Pharmacology, represents a groundbreaking field of research and has the potential to radically alter the treatment of diseases and disorders.

- *Herbal Medicines* have acquired an important percentage among the drug used; according to WHO 80% of people worldwide rely on herbal medicines for some aspect of their primary health care. This continuously increasing use of plant medicines imposes the need for establishing new regulations.

- *Pharmacology of Abuse and Dependence*, still not a well defined area, presents a lot of challenge for researchers and clinicians.

- *Education in Pharmacology* remains a hot subject in the Medical education, following the knowledge *explosion* of the last decades accompanied by a decreasing reliance on didactic teaching. The crucial question is: how and what should we teach?

We hope that the round table discussions along with the invited lectures, included in this abstract book, will raise new and intriguing ques-

tions that will further stimulate research, and will contribute to new therapeutic approaches and attitudes.

I would like to thank the Editorial Board of *Review of Clinical Pharmacology and Pharmacokinetics* in particular Journal Editors Prof. S.T. Plessas and Dr C.T. Plessas for invitation and for providing the suitable and high-standard forum through which new research findings will become available to the scientific community.

The Guest Editor

Charis Liapi

Assist. Professor in Pharmacology
Medical School, University of Athens
Chair of Hellenic Society of Pharmacology

The Role of Nuclear Receptor in Regulation of CYPs

Paavo Honkakoski

Professor in Biopharmacy, Department of Pharmaceutics, University of Kuopio, P.O.Box 1627, FI-70211 Kuopio, Finland

Drug and xenobiotic metabolism and elimination is mostly mediated by cytochrome P450 (CYP) enzymes, and aided by conjugative enzymes and transport proteins. An integral aspect of this elimination process is the induction of drug metabolism through activation of gene expression of metabolic and transport proteins. There is compelling evidence that induction is regulated mainly by drug-activated nuclear receptors constitutive androstane receptor (CAR, NR113) and pregnane X receptor (PXR, NR112) which belong to the nuclear receptor (NR) superfamily of 48 members in the human genome.

CAR and PXR have a crucial role in the disposition, metabolism and elimination of drugs, environmental contaminants and potentially toxic endogenous compounds such as bile acids and bilirubin. In addition, CAR and PXR regulate drug-induced liver hypertrophy, and they also appear to modulate glucose and lipid metabolism, respectively.

In contrast to the classical steroid hormone receptors, CAR and PXR are activated by a large repertoire of chemicals albeit at much weaker affinities. Furthermore, the activation profiles of CAR and PXR ligands are highly species-specific. This diversity in ligand-elicited activation is

caused by the flexibility and pronounced hydrophobicity of their ligand-binding domains. Finally, extensive cross-regulation of their target genes occurs due to the overlapping DNA binding specificities of CAR and PXR.

In summary, activation of CAR and/or PXR by chemical will frequently result in enhanced xenobiotic metabolism, disturbances in cellular homeostasis of endobiotics and increased toxicity. These undesired effects can not be easily extrapolated from animal studies to the human situation due to the species differences in the receptors' ligand-binding properties. Therefore, elucidation of the underlying activation mechanisms, and accurate measurement and prediction of ligand-elicited activation of CAR and PXR receptors is of high priority for drug development and toxicological research.

The presentation will highlight, with key examples, the roles of CAR and PXR in toxicity of chemicals and address the problems caused by species differences. The latest mutagenesis and functional studies have revealed pivotal residues responsible for the species-specific NR activation. The recent progress made in prediction of CAR activators in silico is also described.

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