Review of Clinical Pharmacology and Pharmacokinetics

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GENERAL INFORMATIONS

REVIEW OF CLINICAL PHARMACOLOGY AND PHARMACOKINETICS

publishes Applied Pharmacology and Current Therapeutics Reviews, Review Articles on Drugs and Drug Therapy, Original Papers and Practical Therapeutics Articles.

The *scientific standard* of the papers, which are accepted for publication, is controlled by the Editorial Board or by other Experts in the various fields of Pharmacology and Pharmacokinetics.

Manuscripts: These should mention, on the first page, the *Title*, *Author(s)* and the *Name of the Institution* at which the work was done. The complete *address* of the author, including Postal area code number, should be given under the rubric *Send reprint requests to*. Papers should follow the general form: *Introduction, Materials and Methods, Results, Discussion* and *References*. Drugs must be referred to by their generic or chemical name, but may be identified by trade name in parenthesis or o footnote. All papers should be submitted in duplicate.

Summary: A summary in English (maximum length 200 words) must accompany all manuscripts.

Key words: A list of key words should be submitted.

References: These should be numbered in the paper and listed under *References* in order of their appearance in the text. The author(s) surname followed by the initials should be given first, then the complete title of the article, the name of the Journal or Magazine (abbreviated according to the Index Medicus), the volume number, page numbers and year of publication in parenthesis.

Papers should be submitted to the Editors-in-Chief: Prof. S.T. Plessas or Dr C.T. Plessas.

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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

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Chair of Hellenic Society of Pharmacology

REVIEW OF CLINICAL PHARMACOLOGY AND
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Hepatic Drug Metabolizing Efficacy Modifications after Exposure to Stress

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Key words: Cytochrome P450, CYP induction, drug metabolism, stress, rat

S u m m a r y: Stress may influence the expression of certain hepatic drug metabolizing enzymes. This study investigated the effect of stress on the expression of those hepatic cytochrome CYP isozymes that have a central role in the metabolism of various therapeutic agents. For this purpose, two experimental models of psychological stress were employed, the restraint stress (RS) and the maternal deprivation stress (MDS). Our study showed that stress may alter the metabolic profile of the liver by modifying the expression of various CYPs that are involved in the metabolism of numerous drugs and toxicants, thus affecting drug therapy effectiveness and toxicity.

INTRODUCTION

Pharmacodynamics of a specific drug show depend, amongst others, on the expression and activity of drug-metabolizing enzymes. Therefore, factors modifying the expression of these drug-metabolizing enzymes may alter the pharmacodynamics of various drugs, with consequences ranging from diminished effectiveness of the drugs to increased toxicity (1,2). Among factors that hold critical roles in the regulation of various drug metabolizing enzymes including cytochrome P450s, is stress (3). The aim of this study was to investigate the effect of stress on the regulation of various cytochromes that catalyze the metabolism of toxicants and widely prescribed drugs. For this purpose, the effect of RS and early MDS were evaluated. The effect of stress was assessed on constitutive and on induced expression with PCN (specific inducer of CYP3A in rats) or Rifampicin.

METHODS

Wistar (Io/Kuo rr) rats were used in this study. In the MDS paradigm, rats were deprived from their mothers for 24hrs and then, on the basis of their performance in behavioural tests, were divided into two groups, *Responders* and *Non-Responders*. As regards to the RS paradigm, rats were exposed to restraint stress for 60min daily. Some were also administered drugs that are CYP inducers, such as Pregnenolone *16α*-carbonitrile (PCN, 50 mg/kg b.w.) and Rifampicin (10 mg/kg [RF10] and 50 mg/kg [RF50] b.w.). Cytochrome P450 activities were determined by HPLC, while CYP apoprotein levels were assessed with Western Blotting analysis.

RESULTS

RS increased some testosterone hydroxylase activities in the rat liver. On the other hand, MDS increased the activity of two testosterone metabolites, but suppressed another one. MDS also increased some CYP450 apoprotein levels in the rat liver. RS did not modify the PCN-induced CYP expression, but this type of stress, further increased some testosterone metabolite levels, after rifampicin treatment (RF10). RF50 suppressed the protein content of a CYP450 isozyme, but RS reversed this suppressive effect.

DISCUSSION

It can be suggested that, stress may affect drug metabolism through modifications in the regulation of various hepatic cytochrome P450s. It

seems that stress may modify the induction of CYPs by PCN or Rifampicin and so, stress may be a determinant factor in pharmacotherapy by affecting drug-drug interactions, drug effectiveness and toxicity.

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