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.

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

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INVITED SPEAKERS

ORAL AND POSTERS PRESENTATIONS

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

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The Stimulatory Effects of Aprotinin on Human Endothelial and Prostate Cancer Cells Are Mediated by Pleiotrophin

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Key words: Aprotinin, pleiotrophin, angiogenesis, endothelial cells, tumour, migration

It is well known that the plasmin plays an important role in several physiological or pathological functions, among which induction or inhibition of tumor growth and angiogenesis, giving rise to active proteolytic fragments of larger molecules (1). Aprotinin belonging to the Kunitz-type family of proteins, is an inhibitor of some serine proteases, including trypsin, chymotrypsin, plasmin, tissue plasminogen activator, kallikrein, elastase, urokinase, and thrombin (2). Due to its ability to inhibit plasmin, it is being used as a hemostatic agent in coronary artery bypass grafting (CABG) surgery with CPB and cardiopulmonary operations, intended to limit blood loss in at-risk patients undergoing surgery. However serious concerns have been raised regarding the safety of aprotinin, which have limited its clinical use (3,4).

Pleiotrophin (PTN) is an 18 kDa secreted polypeptide growth factor that belongs to a novel family of heparin-binding molecules (5), which was recently identified as an important autocrine growth factor for the LNCaP prostate cancer cell line and as a paracrine growth factor implicated in prostate cancer cell-induced angiogenesis *in vivo* and *in vitro* (6). It is also angiogenic, acting directly on endothelial cells and stimulating their migration through its receptor protein tyrosine phosphatase β/ζ (RPTPβ/ζ) (7). The identification of PTN domains responsible for its angiogenic and transforming activities is considered important and the data existing so far suggest biological activities for different PTN regions (8). Proteolytic forms of PTN are found in media from endothelial and tumour cells, although their contribution to the effects of PTN is still unclear. We have recently shown that proteolysis of PTN by plasmin results in the production of five peptides with distinct activities on endothelial cell activation in vitro or angiogenesis in vivo (9) and aprotinin inhibits this proteolysis (7,9).

The goal of the present study was to evaluate the possible implication of PTN in the stimulatory effect of aprotinin on angiogenesis and human endothelial and prostate cancer cells' migration. Our data demonstrate that aprotinin is angiogenic in the in vivo model of the chicken embryo chorioallantoic membrane and induces human endothelial and prostate cancer cells' migration in vitro. Furthermore, aprotinin not only affects PTN proteolysis, but also induces the expression and secretion of PTN through transcriptional activation of the ptn gene. The latter seems to be dependent on the activation of the transcription factor AP-1. Finally, PTN seems to mediate the stimulatory effects of aprotinin on cell migration through its receptor RPTP*β/ζ* in both types of cells, strengthening the hypothesis that PTN plays an important role in cell migration induced by many factors. The stimulatory effect of aprotinin on cell migration may explain, at least partly, the problems observed with the clinical use of aprotinin.

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