

Review of Clinical Pharmacology and Pharmacokinetics

ΕΠΙΘΕΟΡΗΣΗ ΚΛΙΝΙΚΗΣ ΦΑΡΜΑΚΟΛΟΓΙΑΣ ΚΑΙ ΦΑΡΜΑΚΟΚΙΝΗΤΙΚΗΣ
ΕΠΙΘΕΩΡΗΣΗ ΚΛΙΝΙΚΗΣ ΦΑΡΜΑΚΟΛΟΓΙΑΣ ΚΑΙ ΦΑΡΜΑΚΟΚΙΝΗΤΙΚΗΣ
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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
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Changes in Pharmacological and Functional Properties of Human 5-HT Receptors by Genetic, Splice and Subunit Variation

Manfred Göthert

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Serotonin (5-hydroxytryptamine 5-HT) plays an important role as a tissue hormone and a neurotransmitter in the organism. More than 90% of the body 5-HT is stored in the enterochromaffin cells (ECCs) of the gastrointestinal tract from where it can be released in response to, e.g., anticancer drugs such as cisplatin and radiotherapy. Released 5-HT triggers the vomiting reflex by stimulating 5-HT₃ receptors on afferent vagal nerve fibres in the vicinity of the ECCs. The fraction of this 5-HT diffused into the blood is taken up into thrombocytes and is, thus, inactivated. Most importantly, 5-HT is a neurotransmitter in the CNS. The cell bodies of the serotonergic neurons are located in the raphe nuclei of the brain stem from where they project into virtually all regions of the brain and into the spinal cord. Accordingly, 5-HT is involved in many important CNS functions such as emotional behaviour, anxiety, blood pressure regulation, perception of pain and vomiting reflex. The effects of 5-HT are mediated via 14 5-HT receptors grouped in 7 5-HT receptor families named 5-HT₁ - 5-HT₇, among which only the 5-HT₃ receptor is a ligand-gated ion channel whereas the others are G protein-coupled receptors.

Heterogeneity of 5-HT receptors is further increased by expression of genetic variants (single nucleotide polymorphisms, SNPs) and alternative splicing. Genetic or splice variation of 5-HT receptors may play a role in the pathogenesis of, e.g., neuropsychiatric disorders and/or may induce quantitative or qualitative changes in drug action or, finally, may have no such consequences. The present report mainly based on

work carried out in Bonn, will focus on variants in human (h) 5-HT_{1A}, 5-HT_{1B} and 5-HT₃ receptors.

The 5-HT_{1A} receptor (negatively coupled to adenylyl cyclase) has been suggested to play a role in the development of anxiety and hypertension. Accordingly, the 5-HT_{1A} receptor agonists buspirone and urapidil are used as antianxiety and antihypertensive drugs, respectively. Radioligand binding to membrane from HEK 293 cells transfected with the cDNA of either the wild -type (WT) or the naturally occurring Arg219Leu variant in the third intracellular loop of the h5-HT_{1A} (identified in a patient with Tourette's syndrome) revealed no differences between both isoforms. However, in cells expressing the variant receptor, there was a decrease by 60-90% in the ability of 5-HT to stimulate [³⁵S] GTPγS binding (a measure of G protein coupling) to the variant receptor and of 5-HT, buspirone and urapidil to inhibit forskolin-stimulated cAMP accumulation. In conclusion, the Arg219Leu variant of the h5-HT_{1A} receptor does not change the ligand binding properties, but is associated with a drastic impairment of signal transduction. In patients carrying this variant, diminished, responses to drugs acting via this receptor may occur.

Vasoconstrictor 5-HT_{1B} receptors (also negatively coupled to adenylyl cyclase) are the therapeutic targets of triptans such as sumatriptan in migraine attack. The pharmacological and transductional properties of the variant (Phe124Cys) h5-HT_{1B} receptor expressed in C0S-7 or C6 glioma cells were determined in comparison with the WT receptor. In radioligand binding experiments 5-HT, sumatriptan and other 5-HT_{1B} re-

ceptor agonists exhibited 2 to 3 times higher affinity for the mutant receptor.

In agreement with this, the potencies of the agonists in inducing G protein coupling and in inhibiting cAMP accumulation were about 3 times higher in the mutant receptor. Human temporal arteries from patients undergoing neurosurgery were used to examine whether *in vivo* expression of the 124Cys 5-HT_{1B} receptor (Cys/Phe genotype) modifies 5-HT-induced constriction mediated not only by 5-HT_{1B} but also by coexpressed 5-HT_{2A} receptors. In arteries from Cys/Phe individuals the contribution of 5-HT_{1B} receptors to the mediation of the effects of 5-HT is increased. Whether or not this modifies the therapeutic or undesired triptan-induced constriction of dura mater arteries and coronary arteries, respectively, cannot yet be decided.

In addition to several 5-HT₃ receptor subunits among which only the 5-HT_{3A} subunit can form functional homopentameric receptor, a short truncated (h5-HT_{3AT}) and a long (h5-HT_{3AL}) splice variant of the h5-HT_{3A} receptor have been identi-

fied. Both splice variants are expressed together with the 5-HT_{3A} subunit in the amygdale and hippocampus. Coexpression of the short variant with the 5-HT_{3A} subunit in HEK293 cells considerably decelerates the desensitization of the heteromeric receptor compared to the homomeric 5-HT_{3A} receptor, as shown in patch clamp investigations in outside-out patches. As a result, heteromeric assemblies of the h5-HT_{3A} and h5-HT_{3AT} subunit exhibit much larger 5-HT-induced cation fluxes. In contrast, heteromeric complexes containing the h5-HT_{3AL} subunit display reduced cation fluxes. Recombinantly expressed h5-HT₃ receptors could help to identify new and possibly therapeutically useful drugs specifically recognizing such heteromeric receptor complexes. In view of probable occurrence of these splice variants as components of heteromeric 5-HT₃ receptors in limbic structures of the brain (see above), selective antagonists at these receptors may be effective as new drugs in psychiatric disorders.

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