ADVANCES IN THE BIOSCIENCES

Latest volumes in the series:

Volume 64: ADVANCES IN AGE PIGMENTS RESEARCH
Editors: E. Aloj Totaro, P. Glees and F.A. Pisanti
Volume 65: PEPTIDES AND PROTEASES: RECENT ADVANCES
Editors: R.L. Schowen and A. Barth
Volume 66: THE BIOLOGY OF PHAGOCYTES IN HEALTH AND DISEASE
Editors: C. Mauri, S.C. Rizzo and G. Ricevuti
Volume 67: RED BLOOD CELLS AND CARRIERS FOR DRUGS: POTENTIAL THERAPEUTIC APPLICATIONS
Editors: C. Ropars, M. Chassaigne and C. Nicolau
Volume 68: IMMUNOMODULATORS & NONSPECIFIC HOST DEFENCE MECHANISMS AGAINST MICROBIAL INFECTIONS
Editors: K.N. Masihi and W. Lange
Volume 69: ADVANCES IN PITUITARY ADENOMA RESEARCH
Editors: A.M. Landolt, J. Girard, P.U. Heitz, E. del Pozo and J. Zapf
Volume 70: NEURON, BRAIN AND BEHAVIOUR
Editor: M. Bajić
Volume 71: ALCOHOL TOXICITY AND FREE RADICAL MECHANISMS
Editors: R. Nordmann, C. Ribière and H. Rouach
Volume 72: SMALL CELL LUNG CANCER
Editors: M. Marangolo and G. Fiorentini
Volume 73: TRENDS IN CHRONOBIOLOGY
Editors: W.Th.J.M. Hekkens, G.A. Kerkhof and W.J. Rietveld
Volume 74: ALLERGY AND MOLECULAR BIOLOGY
Editors: A. Said El Shami and T.G. Merrett
Volume 75: PROGRESS IN OPIOID RESEARCH
Editors: J. Cros, J-Cl. Meunier and M. Hamon
Volume 76: FREE RADICALS IN THE PATHOGENESIS OF LIVER INJURY
Editors: G. Poli, K.H. Cheeseman, M.U. Dianzani and T.F. Slater
Volume 77: DOPAMINE AND MENTAL DEPRESSION
Editors: G.L. Gessa and G. Serra
Volume 78: EXCITATORY AMINO ACIDS AND BRAIN ISCHEMIA: PHARMACOLOGICAL AND CLINICAL ASPECTS
Editors: G. Biggio, P.F. Spano, G. Toffano and G.L. Gessa
Volume 79: CONTROL OF BREATHING AND DYSPNEA
Editors: T. Takishima and N.S. Cherniack
Volume 80: PHYSIOPATHOLOGY OF ILLICIT DRUGS: CANNABIS, COCAINE, OPIATES
Editors: G.G. Nahas and C. Latour
Volume 81: RESEALED ERYTHROCYTES AS CARRIERS AND BIOREACTORS
Editors: R. Green and J.R. DeLoach

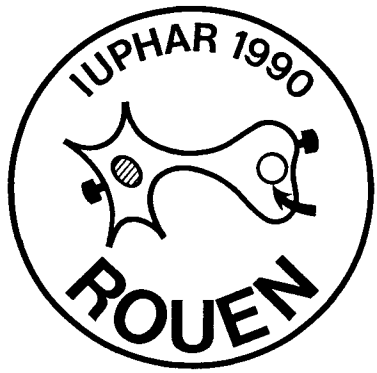
PRESYNAPTIC RECEPTORS AND NEURONAL TRANSPORTERS

Official Satellite Symposium to the IUPHAR 1990 Congress held in Rouen, France, on 26–29 June 1990

Editors:
S.Z. LANGER
A.M. GALZIN
Synthelabo-Recherche (L.E.R.S.), Paris, France

and

J. COSTENTIN
University of Rouen, St. Etienne du Rouvray, France



PERGAMON PRESS
OXFORD • NEW YORK • SEOUL • TOKYO

U.K.	Pergamon Press plc, Headington Hill Hall, Oxford OX3 0BW, England
U.S.A	Pergamon Press Inc., 395 Saw Mill Road, Elmsford, New York 10523, U.S.A.
KOREA	Pergamon Press Korea, KPO Box 315, Seoul 110-603, Korea
JAPAN	Pergamon Press, 5th Floor, Matsuoka Central Building, 1-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160, Japan

First edition 1991

ISBN: 0–08–041165–7

ISSN: 0065–3446

In order to make this volume available as economically as possible the authors' typescripts have been reproduced in their original forms. This method unfortunately has its typographical limitations but it is hoped that they in no way distract the reader.

Printed in Great Britain by BPCC Wheatons Ltd, Exeter

Preface

It has now been twenty years since the first reports on the demonstration of the existence of presynaptic inhibitory α_2-adrenoceptors on peripheral noradrenergic nerve endings and the proposal for their role in the modulation of norepinephrine (NE) release during nerve stimulation. These presynaptic inhibitory α_2-adrenoceptors are involved in a negative feed-back mechanism whereby the released neurotransmitter can regulate its own release (for review see Langer, 1981; Starke, 1981).

The role of neuronal transporters in the inactivation of monoamine neurotransmitters and GABA following their release from nerve terminals has been established for at least 30 years. It is, however, during the past 10 years that receptor binding techniques have been used to label with high affinity the sodium-dependent transporter for serotonin and subsequently, that of other monoamine transmitters. The most recent advances in the field are reviewed in the present book.

It is possible to differentiate between presynaptic terminal autoreceptors, acted upon by transmitters which can regulate their own release and in some cases their synthesis, and presynaptic heteroreceptors sensitive to endogenous compounds other than the neuron's own transmitter. In addition, a neuron may possess somato-dendritic autoreceptors controlling the generation of action potentials in the perikarya as well as autoreceptors controlling release or synthesis of transmitter in the axon terminals. Therefore, one should differentiate between presynaptic somato-dendritic autoreceptors and presynaptic terminal autoreceptors.

The first section of the book deals with the extensive and still increasing list of presynaptic release-modulating auto and heteroreceptors and the different articles represent the current state of the art in the field of presynaptic modulation of neurotransmission. It should be emphasized that the various subtypes of presynaptic receptors have been characterized by functional studies, both in vitro and in vivo, using a number of experimental approaches including electrophysiology, microdialysis, biochemical and behavioral studies.

The second section of the book is devoted to the molecular pharmacology of presynaptic receptors. The biochemical events triggered by the activation of presynaptic receptors represent an area of intensive research. It is now well established that presynaptic receptors can interfere with G proteins, and modify the activity of adenylate cyclase, guanylate cyclase or protein kinase C. Direct effects of presynaptic receptor activation on Ca^{++} channels, leading to inhibition of Ca^{++} influx, have also been reported, as well as modification of K^+-channel conductance. New developments are likely to occur in this field in a near future.

A third part of the book is devoted to recent progress on the purification and molecular biology of transporter systems. The cloning and sequencing of the neuronal sodium-ion coupled

GABA transporter is reported. This protein of 67 kD in its unglycosylated form contains 12 transmembrane spanning α-helices and has 3 putative protein kinase C phosphorylation sites.

Progress made on the purification of other sodium-ion coupled transporters (for 5-HT, DA, NA and choline) is also a major topic of interest, and this area opens the way towards the cloning of these transporters in the near future. In the meanwhile the cloning of the norepinephrine transporter was recently reported.

Pharmacological and biochemical studies of the proton-ion coupled monoamine transport system found in chromaffin granules of the adrenal medulla are included, indicating that the purification of this system should be obtained in the near future.

In conclusion, this book provides new insights on the function of presynaptic receptors and neuronal transporters both in the periphery and in the CNS, with their obiquitous locations and physiological roles. Clearcut pharmacological differences between presynaptic auto- and heteroreceptors for the same transmitter open up the possibility of designing new drugs more selective than those currently available, which could become a novel generation of drugs with different and hopefully useful therapeutic properties. It can be concluded that considerable progress was achieved in this field since the publication of the proceedings of the first International Symposium on Presynaptic Receptors (Pergamon Press, 1979). In the field of neuronal transporters, the impressive progress made in terms of molecular biology of these systems should contribute to a better understanding of the mechanism of action and the therapeutic effects of antidepressant drugs acting specifically on such macromolecular complexes, as for instance NE or 5-HT transport inhibitors.

References

Langer S.Z.: Presynaptic regulation of the release of catecholamines. Pharmacol. Rev. 32, 337-362 (1981).

Langer S.Z., Starke S. and Dubocovich M.L. (eds.): Presynaptic receptors. Advances in the Biosciences, Vol. 18, Pergamon Press, 1979.

Starke K.: Presynaptic receptors. Ann. Rev. Pharmacol. Toxicol. 21, 7-30 (1981).

S.Z. Langer, A.M. Galzin and J. Costentin

Physiological and Pharmacological Relevance of Presynaptic Receptors in Neurotransmission

S.Z. Langer, I. Angel and H. Schoemaker

Synthélabo Recherche (L.E.R.S.), 58 rue de la Glacière, 75013 Paris, France

Abstract

During the last twenty years, the concept that noradrenaline can regulate its own release through an action on presynaptic autoreceptors, has been confirmed and extended to several neurotransmitters in the periphery and in the central nervous system. In addition, many nerve terminals possess presynaptic heteroreceptors which can be acted upon by transmitters released from adjacent terminals, by cotransmitter neuropeptides or by locally produced or blood-borne endocoids to either inhibit or facilitate transmitter release. In the noradrenergic system, the concept of presynaptic modulation of transmitter release developped in parallel with pharmacological evidence for the existence of α_1-and α_2-adrenoceptor subtypes. In the meanwhile three different α_2-adrenoceptor clones were identified by molecular biologists that may correspond to pharmacologically different subtypes of α_2-adrenoceptors. The heterogeneity of presynaptic release-modulating α_2-adrenoceptors may offer the opportunity of developping selective drugs with novel and useful therapeutic properties.

Keywords

Presynaptic autoreceptors. Transmitter release. Alpha adrenoceptor subtypes. Presynaptic heteroreceptors. Noradrenaline. Neuropeptide cotransmitters.

Introduction

Neurotransmitters can regulate their own release through an action on inhibitory autoreceptors located on the synaptic nerve terminal (for recent reviews see Langer and Lehmann, 1988 ; Starke et al, 1989). The physiological role of presynaptic inhibitory autoreceptors was first established for noradrenaline in the peripheral nervous system through the demonstration of a negative feed-back mechanism through which this transmitter can modulate its own release (Langer, 1974). The pharmacological possibilities for intervention through selective agonists, partial agonists or antagonists acting on presynaptic, release modulating receptors, resulted from the characterization of the autoreceptor subtype for each of the neurotransmitters. In addition to presynaptic autoreceptors, many nerve terminals