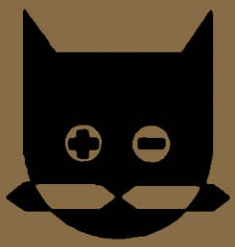

ADVANCES IN PHARMACOLOGICAL RESEARCH AND PRACTICE

General Editor: J. KNOLL

Aminergic and Peptidergic Receptors

Editors

E. S. VIZI and MÁRIA WOLLEMANN

PERGAMON PRESS

AKADÉMIAI KIADÓ

ADVANCES IN
PHARMACOLOGICAL RESEARCH
AND PRACTICE

Volume VII

AMINERGIC AND PEPTIDERGIC RECEPTORS

ADVANCES IN PHARMACOLOGICAL RESEARCH AND PRACTICE

Proceedings of the 3rd Congress of the Hungarian Pharmacological Society, Budapest, 1979

General Editor: J. KNOLL, Budapest

Volumes and Editors:

I – PHARMACOLOGICAL CONTROL OF HEART AND CIRCULATION. *Editors:* L. Tardos, L. Szekeres and J. Gy. Papp

II – MODULATION OF NEUROCHEMICAL TRANSMISSION. *Editor:* E. S. Vizi

III – CHEMICAL STRUCTURE–BIOLOGICAL ACTIVITY RELATIONSHIPS. QUANTITATIVE APPROACHES. *Editor:* F. Darvas

IV – MONOAMINE OXIDASES AND THEIR SELECTIVE INHIBITION. *Editor:* K. Magyar

V – OPIATE RECEPTORS AND THE NEUROCHEMICAL CORRELATES OF PAIN. *Editor:* Susanna Fürst

VI – PROSTANOIDS. *Editor:* Valéria Kecskeméti

(Each volume is available separately.)

Satellite Symposium of the 3rd Congress of the Hungarian Pharmacological Society, Szeged, Hungary, 1979

VII – AMINERGIC AND PEPTIDERGIC RECEPTORS. *Editors:* E. S. Vizi and Mária Wollemann

ADVANCES IN
PHARMACOLOGICAL RESEARCH AND PRACTICE

Satellite Symposium of the 3rd Congress of the Hungarian Pharmacological Society, Szeged, Hungary, 1979

Volume VII

AMINERGIC AND PEPTIDERGIC RECEPTORS

Editors:

E. S. VIZI

Department of Pharmacology
Semmelweis University of Medicine
Budapest, Hungary

and

MÁRIA WOLLEMANN

Biological Research Centre
Hungarian Academy of Sciences
Szeged, Hungary

PERGAMON PRESS

AKADÉMIAI KIADÓ

Pergamon Press is the sole distributor for all countries, with the exception of the socialist countries.

HUNGARY	Akadémiai Kiadó, Budapest, Alkotmány u. 21. 1054 Hungary
U.K.	Pergamon Press Ltd., Headington Hill Hall, Oxford OX3 0BW, England
U.S.A.	Pergamon Press Inc., Maxwell House, Fairview Park, Elmsford, New York 10523, U.S.A.
CANADA	Pergamon of Canada, Suite 104, 150 Consumers Road, Willowdale, Ontario M2 J1P9, Canada
AUSTRALIA	Pergamon Press (Aust.) Pty. Ltd., P.O. Box 544, Potts Point, N.S.W. 2011, Australia
FRANCE	Pergamon Press SARL, 24 rue des Ecoles, 75240 Paris, Cedex 05, France
FEDERAL REPUBLIC OF GERMANY	Pergamon Press GmbH, 6242 Kronberg-Taunus, Hammerweg 6, Federal Republic of Germany

British Library Cataloguing in Publication Data

Aminergic and peptidergic receptors. — (Advances in pharmacological research and practice; Vol. VII).
1. Aminergic receptors — Congresses
2. Peptidergic receptors — Congresses
I. Vizi, E S II. Wollemann Mária
III. Hungarian Pharmacological Society. *Congress, 3rd, Szeged, 1979*
IV. Series
591.1'9'27 QP363 80-41281

Pergamon Press ISBN 0-08-026839-0
ISBN 0-08-026385-2 (7 Vol set)

Akadémiai Kiadó ISBN 963 05 2479 1 (Volume VII)
ISBN 963 05 2367 1 (7 Vol set)

In order to make this volume available as economically and as rapidly 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 Hungary

CONTENTS

Aminergic and Peptidergic Receptors, Szeged 1979
E. S. Vizi and M. Wollemann (eds)

"A morphine addict's blood shows no trace of morphine. It is tempting to imagine the day when doctors will discover the hiding places of morphine and will lure it out by using some substance to which it is partial like a snake with a bowl of milk. But it will still be necessary for the organism to withstand the abrupt transition from an autumn to a spring."

Jean Cocteau: *Opium. The Diary of a Cure*

INTRODUCTION

The research whereby neurotransmitters, hormones and drugs act at the plasma membrane is reaching an exciting period. Over the past decade the experimental methods have been developed enough precisely to measure the binding of radioactive ligands to high affinity binding sites in intact cells as well as in particulate and soluble membrane preparations. A further advantage of the biochemical approach is the possibility to measure also the effect of some ligands on the molecular level by determining adenylate cyclase activity. This offers a unique occasion to investigate the coupling processes between receptors and enzyme activation.

Moreover such complex processes as desensitization of the receptors which are connected with important pharmacological and pathological events as drug resistance and dependency, schizophrenia and mental illnesses, can be studied directly at the cell membrane by these methods.

The Symposium on aminergic and peptidergic receptors offered us an opportunity to gather highly trained specialists in such different fields as biochemistry, pharmacology, chemistry, physiology, morphology, biophysics and pathology to elucidate one of the currently most interesting problems: the state of the art in the receptor research.

The readers of the book will judge how far science succeeded to "discover the hiding places of morphine" and other drugs and how and why one can help "the organism to withstand the abrupt transition from an autumn to a spring".

Szeged, September 1979

Maria Wollemann

This page intentionally left blank

Aminergic and Peptidergic Receptors, Szeged 1979
E. S. Vizi and M. Wollemann (eds)

PRESYNAPTIC RECEPTORS IN CHEMICAL NEUROTRANSMISSION

Klaus Starke

Pharmakologisches Institut, Hermann-Herder-Strasse 5
D-7800 Freiburg i.Br., Bundesrepublik Deutschland

In an article in the Handbuch der experimentellen Pharmakologie Dixon (1924) published a figure showing the effect of nicotine on the isolated perfused heart of the rabbit. The alkaloid first decreased and then increased the rate of beat. The negative chronotropic effect was explained by excitation of vagal ganglia. The positive effect was thought to be due either to stimulation of intracardiac sympathetic ganglion cells or to direct stimulation of cardiac muscle, with the first view seeming more likely. We now know, on the one hand, that nicotine releases noradrenaline in the heart; and on the other hand, that the rabbit heart does not contain sympathetic ganglion cells but only postganglionic sympathetic axons. The receptors involved, therefore, are not nicotine receptors on the postganglionic cell bodies, but are presynaptic receptors presumably located on the axon terminals themselves (Löffelholz, 1979). To my knowledge, this is the first published experiment that retrospectively must be explained by the existence of presynaptic receptors.

As illustrated by this example, presynaptic receptors are

receptors which, unlike soma-dendritic receptors, do not influence the electrical activity of the neuronal perikarya, but initiate or modify calcium-dependent release processes (and in some cases transmitter biosynthesis) in the nerve terminals. A distinctive feature of this definition is that primarily it is not topographical but functional, describing which effects are triggered by the activation of the receptors. There is now evidence to show that some presynaptic receptors are in fact located directly on the axon terminals. For other receptors, evidence is lacking or controversial. The emphasis on function and the caution concerning localization thus faithfully reflect our present state of knowledge (Starke and Langer, 1979).

Biochemical investigations have by now revealed the existence of a large number of presynaptic receptor systems. Since it is impossible to discuss in detail here all members of this numerous family, an up-to-date summary is presented in Table 1. The references will allow the reader an easy access to the relevant literature (see also the book edited by Langer et al., 1979).

Soma-dendritic receptors, which control the rate of neuronal firing, and postsynaptic receptors, which recognize the transmitter and mediate the response of the postsynaptic cell, are essential for the neuronal transfer of information. Why do we have presynaptic receptors in addition? Three possible functions can be distinguished. Firstly, these receptors allow modulation of transmitter release and biosynthesis by blood-borne agents. For instance, many postganglionic sympathetic neurones are en-

dowed with presynaptic ß-adrenoceptors and angiotensin receptors, activation of which facilitates the release of noradrenaline. It seems possible, although by no means certain, that one task of the renin-angiotensin system and of adrenal medullary adrenaline is to reinforce the activity of the sympathetic nervous system through these presynaptic sites.

Secondly, presynaptic receptors allow presynaptic modulation by agents secreted from adjacent neurones or other cells. Examples are the inhibition of the release of noradrenaline from post-ganglionic sympathetic neurones by acetylcholine secreted from neighbouring parasympathetic fibres, and the inhibition of the release of various neurotransmitters by enkephalins.

Thirdly, presynaptic receptors may be links of synaptic feed-back mechanisms. In general, these feedbacks are negative: the higher the concentration of transmitter in the synaptic cleft, the lower the release per action potential. Major feedback loops are mediated by presynaptic autoreceptors, i.e., receptors presumably located on the axon terminals and sensitive to the neurone's own transmitter. For instance, at all noradrenergic synapses studied so far extracellular noradrenaline inhibits further release by activation of presynaptic α-adrenoceptors. There are, however, feedback mechanisms not mediated by auto-receptors. The best-known one is the prostaglandin-mediated feedback mechanism controlling noradrenaline release.

Finally, there are many presynaptic receptors for which no physiological function whatsoever is known. One example are