HANDBOOK OF CHEMICAL NEUROANATOMY

VOLUME 11

NEUROPEPTIDE RECEPTORS IN THE CNS

Editors:
A. Björklund, T. Hökfelt
M.J. Kuhar

ELSEVIER

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Volume 11:

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1992

ELSEVIER

Amsterdam – London – New York – Tokyo

ISBN 0-444-89486-1 (volume)
ISBN 0-444-90340-2 (series)

This book is printed on acid-free paper.

Published by:
Elsevier Science Publishers B.V.
P.O. Box 211
1000 AE Amsterdam
The Netherlands

Library of Congress Cataloging-in-Publication Data

Neuropeptide receptors in the CNS / editors, A. Björklund, T. Hökfelt, M.J. Kuhar.
p. cm. -- (Handbook of chemical neuroanatomy ; v. 11)
Includes bibliographical references and index.
ISBN 0-444-89486-1 (alk. paper)
1. Neuropeptides--Receptors. 2. Neurochemistry. I. Björklund, Anders, 1945– . II. Hökfelt, Tomas. III. Kuhar, Michael J. IV. Series.
[DNLM: Brain--metabolism. 2. Neuropeptides--metabolism. W1 HA51J v. 11/ WL 300 N4938178]
QM451.H24 1983 vol. 11
[QP552.N39]
599'.048 s--dc20
[599'.0188]
DNLM/DLC
for Library of Congress 92-4424
CIP

Printed in The Netherlands

NEUROPEPTIDE RECEPTORS IN THE CNS

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Preface

This volume is the third in this series on neurotransmitter receptors. The first two dealt with receptors for classical neurotransmitters and with receptors for other neuropeptides. This volume extends and updates the information on peptide receptors, and it complements chapters on some of the peptides themselves in earlier volumes.

The peptides, from angiotensin to vasoactive intestinal peptide, are striking in the diversity of their origins, discoveries and actions. Atrial natriuretic peptide is produced by the cardiac atria, bombesin by the frog skin, CRH by the hypothalmus, and galanin by the small intestine; they are also found in many other organs including the brain. Angiotensin has the central action of stimulating drinking behavior but also has peripheral actions on smooth muscle and kidney. CRH acts at the pituitary but has more central behavioral effects as well. Some of these peptides such as neuropeptide Y are very abundant in brain while others are not. The fact that the brain displays such variety is both staggering and challenging.

This apparent diversity multiplies when it is realized that there are entire families of closely related peptides in many cases, and that each peptide may act at a variety of receptor subtypes. For example, calcitonin and calcitonin gene-related peptide are processing variants of the same gene, and somatostatin receptors are target sites for a family of peptides.

Regarding multiple or subtypes of receptors, it seems certain that more is to come in the future. This volume is basically a compilation of 'high affinity' receptors for agonists since we are using the neuropeptides themselves as ligands. Perhaps significant numbers of low affinity receptors exist that are not easily recognized under the binding and washing conditions employed. As peptide receptors are further understood and as antagonists are developed, additional families or subtypes of receptors may be identified and mapped with resultant increases in our ideas about their functions.

Mapping receptors helps us understand the neuronal sites of action and hence the physiological effects of the peptides. It also provides us with an additional perspective by which we view the biochemical organization of the brain. It is our hope that these organized chapters help us utilize and deal with the abundant knowledge on this topic as well as to incorporate this knowledge for future advances.

Finally we acknowledge our good fortune in having an excellent group of authors, each expert in their respective areas. They have addressed the diversity of neuropeptides and their receptors and have produced excellent state-of-the-art chapters. We thank them for their patient and thorough efforts in producing this fine volume. Also, warm thanks go to our friends at Elsevier who with never failing enthusiasm and great professional competence have made this volume possible.

Lund, Stockholm and Baltimore in May 1992

ANDERS BJÖRKLUND TOMAS HÖKFELT MICHAEL J. KUHAR

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CHAPTER I

Localization of angiotensin receptor binding sites in the rat brain

A.M. ALLEN, G. PAXINOS, K.F. SONG AND F.A.O. MENDELSOHN

1. INTRODUCTION

Angiotensin (Ang) is a circulating hormone with potent actions on vascular smooth muscle, renal function and the adrenal gland (see Peach 1977). Ang also has central actions including stimulation of drinking behaviour, regulation of the central control of the autonomic nervous system, and stimulation of the release of both anterior and posterior pituitary hormones (see Phillips 1987). Overall these actions relate to the maintenance of fluid and electrolyte homeostasis and cardiovascular function. However, some more diverse actions, including effects on learning and memory (Koller et al. 1975; Baranowska et al. 1983), have been observed following manipulation of the central renin-angiotensin system.

Initially the central actions of Ang were thought to be mediated solely by circulating Ang II acting at the circumventricular organs. These specialized brain regions are accessible to circulating Ang because they have a deficient blood–brain barrier (Simpson 1980; McKinley et al. 1990). Several of the circumventricular organs, including the subfornical organ, vascular organ of the lamina terminalis (OVLT), median eminence and area postrema, are rich in Ang receptor binding sites (Van Houten et al. 1980; Mendelsohn et al. 1984), and electrophysiological studies show that neurons in the subfornical organ are excited by Ang II administered intravenously (Ishibashi et al. 1985; Ferguson and Renaud 1986).

The discovery that all components of the renin-angiotensin system occur in brain (Yang and Neff 1972; Hirose et al. 1978; Lewicki et al. 1978; Ganten et al. 1983) led to the proposal of an endogenous brain renin-angiotensin system. Supporting this, Ang-like immunoreactive neurons, Ang receptor binding sites and Ang responsive neurons have been demonstrated at sites within the blood–brain barrier (see Lind 1987). In addition, microinjection of Ang II into several restricted regions behind the blood–brain produces pressor, dipsogenic, cardiovascular and neuroendocrine actions (see Phillips 1987).

The concept of an endogenous brain angiotensin system was not readily accepted. The isolation of Ang II from brain proved difficult, presumably due to the rapid degradation of this peptide (Harding et al. 1986; Abhold and Harding 1987) and its low concentration. However, several groups have isolated material from brain which behaves like synthetic Ang II in radioimmunoassay and radioreceptor assay (Ganten et al. 1983; Simon-

Handbook of Chemical Neuroanatomy, Vol. 11: Neuropeptide Receptors in the CNS.
A. Björklund, T. Hökfelt and M.J. Kuhar, editors.