Handbook of Neurochemistry

SECOND EDITION

Volume 8
NEUROCHEMICAL SYSTEMS

Edited by
Abel Lajtha

Handbook of
Neurochemistry

SECOND EDITION

Volume 8
NEUROCHEMICAL SYSTEMS

Edited by
Abel Lajtha
Center for Neurochemistry
Wards Island, New York

PLENUM PRESS · NEW YORK AND LONDON

Library of Congress Cataloging in Publication Data

Main entry under title:

Handbook of neurochemistry.

Includes bibliographical references and indexes.
Contents: v. 1. Chemical and cellular architecture—v. 2. Experimental neurochemistry—[etc.]—v. 8. Neurochemical systems—[etc.]
1. Neurochemistry—Handbooks, manuals, etc.—Collected works. 2. Neurochemistry. I. Lajtha, Abel. [DNLM: 1. Neurochemistry. WL 104 H434]
QP356.3.H36 1982 612'.814 82-493
ISBN 0-306-41579-8 (v. 8)

A Division of Plenum Publishing Corporation
233 Spring Street, New York, N.Y. 10013

Printed in the United States of America

Contributors

Bernard W. Agranoff, Neuroscience Laboratory Building and Mental Health Research Institute, University of Michigan, Ann Arbor, Michigan 48109

S. Arch, Biological Laboratories, Reed College, Portland, Oregon 97202

Nicolas G. Bazan, Lions Eye Research Laboratories, LSU Eye Center, Louisiana State University Medical Center School of Medicine, New Orleans, Louisiana 70112

M. Billingsley, Section on Biochemical Pharmacology, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland 20205

Laszlo Z. Bito, College of Physicians and Surgeons, Columbia University, New York, New York 10032

Carla Perrone Capano, Institute of General Physiology, Faculty of Sciences, University of Naples, and International Institute of Genetics and Biophysics, Naples, Italy

Priscilla S. Dannies, Department of Pharmacology, Yale University School of Medicine, New Haven, Connecticut 06510

Philippa M. Edwards, Division of Molecular Neurobiology, Institute of Molecular Biology, Laboratory of Physiological Chemistry and Rudolf Magnus Institute for Pharmacology, State University of Utrecht, 3508 TB Utrecht, The Netherlands

H. Gainer, Laboratory of Developmental Neurobiology, National Institutes of Health, Bethesda, Maryland 20205

Candace J. Gibson, Department of Pathology, University of Western Ontario, London, Ontario N6A 5C1, Canada

Willem Hendrik Gispen, Division of Molecular Neurobiology, Rudolf Magnus Institute for Pharmacology, and Institute of Molecular Biology, State University of Utrecht, 3584 CH Utrecht, The Netherlands

Antonio Giuditta, Institute of General Physiology, Faculty of Sciences, University of Naples, and International Institute of Genetics and Biophysics, Naples, Italy

László Gráf, The Institute for Drug Research, 1325 Budapest, Hungary

Roger Guillemin, Laboratories for Neuroendocrinology, The Salk Institute, La Jolla, California 92037

I. Hanbauer, Section on Biochemical Pharmacology, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland 20205

L. Hertz, Department of Pharmacology, University of Saskatchewan, Saskatoon, Saskatchewan S7N 0W0, Canada

François B. Jolicoeur, Department of Psychiatry, Faculty of Medicine, University of Sherbrooke, Sherbrooke, Quebec J1H 5N4, Canada

B.H.J. Juurlink, Department of Anatomy, University of Saskatchewan, Saskatoon, Saskatchewan S7N 0W0, Canada

E. Ronald de Kloet, Rudolf Magnus Institute for Pharmacology, Medical Faculty, University of Utrecht, 3521 GD Utrecht, The Netherlands

D. Kuhn, Section on Biochemical Pharmacology, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland 20205

Allen S. Levine, Neuroendocrine Research Laboratory, Minneapolis Veterans Administration Medical Center, Minneapolis, Minnesota 55417; and Departments of Medicine and Food Science and Nutrition, University of Minnesota, Minneapolis–St. Paul, Minnesota 55455

Bruce S. McEwen, The Rockefeller University, New York, New York 10021

Henry McIlwain, Department of Biochemistry, St. Thomas's Hospital Medical School, London SE1 7EH, England

John E. Morley, Neuroendocrine Research Laboratory, Minneapolis Veterans Administration Medical Center, Minneapolis, Minnesota 55417; and Departments of Medicine and Food Science and Nutrition, University of Minnesota, Minneapolis–St. Paul, Minnesota 55455

Jacques Nunez, Unité de Recherche 35 de l'INSERM, and Equipe de Recherche sur la Biochimie de la Régulation Hormonale, CNRS, Hospital H. Mondor, 94 Creteil, France

Chandan Prasad, Departments of Medicine (Section of Endocrinology) and Biochemistry, Louisiana State University Medical Center, New Orleans, Louisiana 70112

Thomas C. Rainbow, Department of Pharmacology, University of Pennsylvania, Philadelphia, Pennsylvania 19104

T. Sanjeeva Reddy, Lions Eye Research Laboratories, LSU Eye Center, Louisiana State University Medical Center School of Medicine, New Orleans, Louisiana 70112

Francis Rioux, Department of Physiology and Pharmacology, Faculty of Medicine, University of Sherbrooke, Sherbrooke, Quebec J1H 5N4, Canada

Serge St.-Pierre, Department of Physiology and Pharmacology, Faculty of Medicine, University of Sherbrooke, Sherbrooke, Quebec J1H 5N4, Canada

Peter Schotman, Division of Molecular Neurobiology, Institute of Molecular Biology, Laboratory of Physiological Chemistry and Rudolf Magnus Institute for Pharmacology, State University of Utrecht, 3508 TB Utrecht, The Netherlands

Loes H. Schrama, Division of Molecular Neurobiology, Institute of Molecular Biology, Laboratory of Physiological Chemistry and Rudolf Magnus Institute for Pharmacology, State University of Utrecht, 3508 TB Utrecht, The Netherlands

Hitoshi Shichi, Institute of Biological Sciences, Oakland University, Rochester, Michigan 48063

S. Szuchet, Department of Neurology, University of Chicago, Chicago, Illinois 60637

Gyula Telegdy, Institute of Pathophysiology, University Medical School, Szeged, Hungary

Yasuzo Tsukada, Department of Physiology, Keio University School of Medicine, Tokyo, Japan

H. Dick Veldhuis, Rudolf Magnus Institute for Pharmacology, Medical Faculty, University of Utrecht, 3521 GD Utrecht, The Netherlands

Tony L. Yaksh, Department of Neurosurgical Research, Mayo Clinic, Rochester, Minnesota 55905

Gigliola Grassi Zucconi, Institute of Cell Biology, Faculty of Sciences, University of Perugia, Perugia, Italy

Henk Zwiers, Division of Molecular Neurobiology, Rudolf Magnus Institute for Pharmacology, and Institute of Molecular Biology, State University of Utrecht, 3584 CH Utrecht, The Netherlands

Preface

The content of Volume 8 of the *Handbook of Neurochemistry* is a perfect example and sample of what occupies neurochemists in the late 1980s. What occupies them are questions, concepts, and technology that either did not start with the nervous system, or rapidly moved out of its exclusivity (see, for instance, chapters on neurotensin, beta-lipotropin, behavioral and neurochemical effects of ACTH, cholecystokinin, etc.). Thus, the neurochemist is more and more seen as a biochemist occupied by questions, concepts, and technology that are not unique to the nervous system, even though the ultimate substrate of these questions, as well as the ultimate functions so studied and occasionally explained, are of the nervous system.

Look at the case of the hypothalamic hypophysiotropic peptides, also called hypothalamic releasing factors, or hypothalamic releasing hormones. These are all small-to-medium-size polypeptides originally characterized in extracts of the hypothalamus on the basis of bioassays directed at studying their effects on one or another of the secretions of the adenohypophysis. We know now that TRFs (See Chapter 8), the thyrotropin and prolactin releasing factor, somatostatin, the hypothalamic inhibitor of the secretion of growth hormone, as well as LRF, the hypothalamic decapeptide stimulating the secretion of pituitary gonadotropins, are to be found in parts of the brain other than the hypothalamus, where their function is obviously not hypophysiotropic. Such is also the case for CRF—the corticotropin and beta-endorphin releasing factor. Our original statement about the uniquely hypothalamic location of the growth hormone releasing factor—GRF, somatocrinin, has recently been challenged by colleagues using polyclonal antisera different from those used by us, and they may well be right.

Furthermore, we know that these peptides, first of the hypothalamus, then of the brain, are also found in the spinal cord, peripheral nerves, and in various tissues of the gastrointestinal tract including the pancreas, and, in some forms with relatively minor structural variation, the skin of amphibians and even in various anatomical structures of invertebrates.

Similarly, all the biologically active peptides originally characterized in the gastrointestinal tract, the lungs, the kidney, and the teguments (of amphibians) have been recognized as such or with minor structural variations in the brain, the spinal cord, and the peripheral nervous system of mammalians.

There is excellent evidence that in all locations we are dealing with the same polypeptide sequence or molecule.

In one location, these peptides will be called hormones, and will be called neuromediators or neuromodulators in other locations. I have already alluded to the fact that the hypothalamic hypophysiotropic peptides are also called hypothalamic hormones. We obviously have a problem of terminology. Should we ignore it?

The word hormone was originally introduced into the literature by Ernest Henry Starling on June 20, 1905, in the first of his Croonian Lectures delivered before the Royal College of Physicians in London on "The Chemical Correlation of the Functions of the Body". Starling frames the thinking within which the definition of hormones will appear: "The chemical adaptation or adaptations of the body, like those which are carried out through the intermediation of the central nervous system, can be divided into two main classes: 1) those which are involved in consequence of changes impressed upon the organism as a whole from without; and 2) those which, acting entirely within the body, serve to correlate the activities, in the widest sense of the term, of the different parts and organs of the body." Then, after some discussion of the first category, he moves on to the second and says the following: "These chemical messengers, however, or hormones (from *ormao*, I excite, or arouse) as we might call them, have to be carried from the organ where they are produced to the organ which they affect, by means of the bloodstream, and the continually recurring physiological needs of the organism must determine their repeated production and circulation through the body".

Most of the substances which we call hormones to this day do meet these criteria; this is the case for the secretory products of all the endocrine glands. These circulate far and wide from their organ of production to the receptors of their target organs, where they somehow excite, stimulate, or cause some positive effect in the cells of that tissue. Physiologically meaningful levels of these hormones can now be measured by all sorts of exquisitely sensitive methods in the peripheral blood with the added feature that there is always a demonstrable arterial/venous difference in the concentration of these substances when measured in the inflow or outflow blood to and from the organ known to be the source of the hormone in question.

In the case of the hypothalamic peptides involved in the control of pituitary functions, there is reliable evidence that they can be demonstrated by bioassay or radioimmunoassay in the effluent blood from the hypothalamus when tapped in the portal vessels along the pituitary stalk. There is also no doubt that there is a difference in the concentrations found in the hypothalamic portal blood when compared to peripheral blood. This, however, is where the problems begin in calling these substances hormones. Reliable methodology shows that the peripheral levels of circulating thyrotropin releasing factor (TRF) or gonadotropin releasing factor (LRF) are so low as to be of no physiological significance. In the case of somatostatin, the matter is even more complex. First, somatostatin is universally an inhibitor (of one secretion or another), and thus can hardly be called a "hormone", a name that etymologically implies "stimulation, excitation". But perhaps more important, it is now well recognized

that somatostatin has a ubiquitous distribution (though not random) ranging from the central nervous system to multiple locations of the gastrointestinal tract and the pancreas as we discussed above. Immunoreactive and bioactive somatostatin, in fact forms of somatostatin of various molecular sizes, can be demonstrated to circulate in peripheral blood (jugular vein in laboratory animals, antecubital vein in man), but in concentrations that appear to be far below what can be calculated to be its binding or affinity constants. There is, however, excellent evidence that much larger concentrations of immunoreactive and bioactive somatostatin can be shown in more localized circulation such as in the effluent vein of the pancreas, where we know that somatostatin is present in the delta cells. There is also good evidence that these local plasma concentrations of local somatostatin can vary considerably as a function of physiological or experimental situations (absorption of meals, injection of various peptides, such as cholecystokinin, or endorphins, or drugs such as opiates, or arginine). If TRF, LRF, and somatostatin are to be called hormones and considered as such, then it must be said that they do not qualify as the classical hormones.

But things are even more complex. We know now that immunoreactive, as well as bioactive, TRF, LRF, somatostatin, the "gut hormones" cholecystokinin (see Chapter 5), VIP (vasoactive intestinal peptide), gastrin, etc., are found within discrete neurons, either in the cell body or in peripheral endings from which they certainly have to be released for physiological purposes which are not well understood at the moment. In such circumstances and setups, neither TRF, LRF, nor somatostatin or any of the other "gut hormones" behaves as, or meets the criteria of, hormones. They seem to be involved in localized controls. It is probably also the case when trying to understand how pancreatic somatostatin could modify the secretion of insulin and glucagon by the nearby cells of the islets.

Because of their neuronal locations, TRF, LRF, somatostatin (and perhaps the other biologically active peptides such as neurotensin, endorphins, enkephalins, VIP, etc.) have been proposed as neurotransmitters, as are catecholamines or acetylcholine. But somatostatin is not a neurotransmitter when released by the delta cells of the endocrine pancreas to affect the glucagon secretion by a nearby alpha cell, reaching either through gap junctions or extracellular space. Noradrenalin in and out of neurons is the neurotransmitter, while adrenalin is the hormonal form in and from the adrenal medulla, with the small amounts of noradrenalin found in the adrenal medulla leaving us in a quandary.

It is thus obvious that the current terminology is wanting. Either we have to redefine what it is that we mean by hormone or some additional terminology has to be proposed.

The question is what to do with these ubiquitous molecules which have local effects that can range from angstroms to microns (gap junctions, extracellular spaces) in and from cells which include neurons, to centimeters, when dealing with local either splanchnic or pituitary locations. Such substances do not fit in well with the definition of a hormone or of a neurotransmitter. We have the word *paracrine*, as originally proposed by Feyrter to describe pre-

cisely the suspected secretory activities of what we now know to be the peptide-secreting cells of the gut. The etymology of the word is obvious and implies a local or nearby use or function for what is being secreted. I personally think that the word paracrine is excellent and should be used often in relation to the problem we are discussing here. But paracrine is an adjective, and to my knowledge Feyrter, in his difficult German, used it exclusively as such, referring to paracrine secretory cells and paracrine secretion. We could perhaps coin the word "parahormone" or "parhormone", but neither is euphonic or easy to pronounce in either French or English, or German for that matter. Several years ago I proposed the word *cybernin*, from the Greek "kurbenetes", meaning "pilot" or "rudder" of a boat, implying the local nature of the command or information involved. This is also the root of the well-known word cybernetics, even though I could never ascertain whether Norbert Wiener implied any localization (of information) when he decided to use the word (according to Littré, the word "cybernétique" was coined by Ampère to define "la partie politique qui s'occupe des moyens de gouverner"). I never pushed very hard for the implantation of the word cybernin, feeling that it was another word, another root, without a clearly defined mission. The word. however, is being used by more and more people, thus appearing to fulfill a role. So, how should we use it? First of all, what is a cybernin? A cybernin is a polypeptide biosynthesized, processed, and released by a cell or group of cells, that represents information that will affect the function of another cell or group of cells in the vicinity of the first cell or group of cells. Such a simple definition excludes all steroids, prostaglandins, or molecules such as cyclic-AMP. Would bèta-endorphin, ACTH, which certainly are hormones when secreted by the pituitary, be considered as cybernins when relating to their presence in hypothalamic neurons and when released either at nerve endings from these neurons (a statement which is only a proposal at the moment, albeit a logical one) or when released in the portal vessels of the pituitary of the median eminence and as measured in the down-flow blood along the pituitary stalk? The answer is yes. I would say that, in these circumstances, beta-endorphin and ACTH are seen, act, and should be considered, as cybernins. When we describe their action it will be referred to as a cybernin action rather than a hormonal action. Somatostatin will act as a cybernin when it modifies the secretion of insulin and glucagon in nearby pancreatic cells and originates from pancreatic delta cells; it will also be acting as a cybernin when proceeding to the adenohypophysis, inhibiting the secretion of growth hormone, when originating from the hypothalamus. I would prefer to consider somatostatin as a cybernin rather than as a neurotransmitter if it can be shown that it is actually released at some axonal or dendritic ending and that it modifies the response of another neuron to any one of the classical neurotransmitters. In fact, the word cybernin may turn out to be the optimal noun for the adjective paracrine. The polypeptidic growth factors recently proposed by Sporn and Todaro as "autocrine" secretions in the ultimate of paracrine function could also be considered as cybernins.

The success of any nomenclature is based on need. The need for the use of the word cybernin is probably not compelling. However, since the words hormone, neuromediator, mediator, modulator, are either too restrictive or too

vague in their definition or implied use, maybe there will be some feeling of comfort in the use of the word cybernin.

I have discussed above the ubiquity of these biologically active peptides. There is also evidence, though not so widely established, that the "receptor" molecules for these peptides in their ubiquitous locations are identical or share extensive common binding properties for related ligands. Thus what is specific (for the nervous system) if are neither the ligands, nor the receptors? There is evidence that not even the post- receptor-binding *type* of response is. What *may be* specific is the final result of the activation of a highly specialized neuron. What *is* specific finally is the functional response as seen in a system of neurons. And while (neuro)chemistry is necessary to understand the function of each cellular unit of that system, (neuro)chemistry does not tell us what will be the function of that system or how that function will take place. This is where the power, the immense power of reductionism as we know it currently comes to a halt, a pause, possibly a standstill—an "impossibility to proceed owing to exhaustion", says the Oxford dictionary. Rather than accepting this latest meaning of the word I'd rather use it as implying standing still, as in wait of some new paradigm, a true revolution in science, according to the terminology of Thomas Kühne. How else could we engage in the neurochemical study of sleep while at the same time attempting to characterize sleep peptides?

Perhaps one of those new ways will be found in the emerging studies of what I will simply call nonlinear dynamics to refer to the mode of thinking or the concept that complexity when it reaches such a height that it is seen as chaos or apparent randomness can still generate its own periodic order. Physicists, chemists, and mathematicians like Haken, Prigogine, and Thom have all proposed mathematics to support this vastly novel way of thinking for the biologist and have already shown the powerful predictive value of such mathematics in "explaining" the emergence of complex biological structures in embryogenesis, complex periodic functions in multicompartmental biological systems, etc. Psychiatrists like Mandell have already proposed that such thinking could lead to new approaches to understand normal and abnormal patterns of behaviour, in some ways defining normal brain functions and behaviour from the absence of the characteristics of mental disorders.

And this is where so much of the subject matter of this volume comes back in focus: Many of the molecules discussed here have already been shown to affect the amplitude or frequency of one or another of these nonlinear dynamics events as observed in the central nervous system. Perhaps here will be found a new generation of still reductionist questions, unless some genial holist takes us away from modern obscurantism in its glorious achievements.

Roger Guillemin

Contents

Chapter 8

Thyrotropin-Releasing Hormone
Chandan Prasad