

# hormonal proteins and peptides

## HYPOTHALAMIC HORMONES

EDITED BY **CHOH HAO LI**

**ACADEMIC PRESS, INC.**

A Subsidiary of Harcourt Brace Jovanovich, Publishers

volume **7**

# **Hormonal Proteins and Peptides**

VOLUME VII

# **Hormonal Proteins and Peptides**

Editor CHOH HAO LI

*The Hormone Research Laboratory  
University of California  
San Francisco, California*

Vol I 1973

Vol II 1973

Vol III 1975

Vol IV Growth Hormone and Related Proteins 1977

Vol V Lipotropin and Related Peptides 1977

Vol VI Thyroid Hormones 1978

Vol VII Hypothalamic Hormones 1979

# HORMONAL PROTEINS AND PEPTIDES

Edited by CHOH HAO LI

*The Hormone Research Laboratory  
University of California  
San Francisco, California*

VOLUME VII  
Hypothalamic Hormones



ACADEMIC PRESS New York San Francisco London  
A Subsidiary of Harcourt Brace Jovanovich, Publishers

1979

COPYRIGHT © 1979, BY ACADEMIC PRESS, INC.

ALL RIGHTS RESERVED.

NO PART OF THIS PUBLICATION MAY BE REPRODUCED OR TRANSMITTED IN ANY FORM OR BY ANY MEANS, ELECTRONIC OR MECHANICAL, INCLUDING PHOTOCOPY, RECORDING, OR ANY INFORMATION STORAGE AND RETRIEVAL SYSTEM, WITHOUT PERMISSION IN WRITING FROM THE PUBLISHER.

ACADEMIC PRESS, INC.

111 Fifth Avenue, New York, New York 10003

*United Kingdom Edition published by*  
ACADEMIC PRESS, INC. (LONDON) LTD.  
24/28 Oval Road, London NW1 7DX

#### Library of Congress Cataloging in Publication Data

Main entry under title:

Hypothalamic hormones.

(His Hormonal proteins and peptides ; v. 7)

Bibliography: p.

Includes index.

1. Thyroid hormones. 2. Thyrotropin.

I. Li, Choh Hao, Date II. Series.

QP572.P77L5 vol. 7 [QP572.T5] 599'.01'927s [591.1'926]

ISBN 0-12-447207-9 (v. 7)

78-5444

PRINTED IN THE UNITED STATES OF AMERICA

79 80 81 82 9 8 7 6 5 4 3 2 1

# Contents

LIST OF CONTRIBUTORS	ix
PREFACE	xi
CONTENTS OF PREVIOUS VOLUMES	xiii

## 1. Hypothalamic Peptide Hormones: Basic and Clinical Studies

*Andrew V. Schally, David H. Coy, Chester A. Meyers,  
and Abba J. Kastin*

I. Introduction	2
II. Corticotropin-Releasing Factor (CRF)	4
III. Thyrotropin-Releasing Hormone (TRH)	6
IV. Prolactin-Releasing Factor (PRF)	14
V. Prolactin-Release-Inhibiting Factor (PIF)	15
VI. Factors Affecting the Release of Melanocyte-Stimulating Hormone (MSH)	17
VII. The LH- and FSH-Releasing Hormone (LH-RH/FSH-RH)	18
VIII. Growth Hormone-Releasing Factor (GH-RF)	35
IX. Growth Hormone Release-Inhibiting Hormone (GH-RIH, Somatostatin)	36
References	41

## 2. Gonadoliberin

*Marian Jutisz, Annette Berault, Luciano Debeljuk,  
Bernard Kerdelhué, and Madeleine Théoleyre*

I. Introduction	56
II. Extraction and Purification of Gonadoliberin from Different Sources	57
III. Determination of the Primary Structure of Gonadoliberin	60
IV. Conformational Studies on Gonadoliberin	62
V. Chemical Syntheses of Gonadoliberin	63
VI. Structure–Activity Relationship for Gonadoliberin	63
VII. Gonadoliberin Biosynthesis and Biodegradation	65
VIII. Control of Gonadoliberin Release	67

IX. Biological Effects of Gonadoliberin	68
X. Bioassay for Gonadoliberin	78
XI. Immunological Studies with Gonadoliberin	80
XII. Cellular Mechanism of Action of Gonadoliberin	86
XIII. Agonist and Antagonist Analogues of Gonadoliberin	107
XIV. Concluding Remarks	109
References	112

### 3. The Control of Somatotropin Secretion

*Eugenio E. Müller*

I. Introduction	123
II. Secretion Pattern of GH in Different Animal Species	124
III. Stimuli for GH Secretion	127
IV. Central Nervous System Control of GH Secretion	146
V. Feedback Control of GH Secretion	185
VI. Concluding Remarks	187
References	188

### 4. Mechanisms of Action of Hypothalamic and Peripheral Hormones in the Anterior Pituitary Gland

*Fernand Labrie, Lisette Lagacé, Michèle Beaulieu,  
Louise Ferland, André De Lean, Jacques Drouin,  
Pierre Borgeat, Paul A. Kelly, Lionel Cusan,  
André Dupont, André Lemay, Tony Antakly,  
Georges H. Pelletier, and Nicholas Barden*

I. Introduction	206
II. Role of Cyclic AMP in the Action of TRH, LH-RH, and Somatostatin	209
III. Role of Prostaglandins in Hypothalamic Hormone Action on Adenohypophysis	216
IV. Adenohypophyseal Cyclic AMP-Dependent Protein Kinase and Its Substrates	227
V. Interactions between LH-RH, Sex Steroids, and Inhibin in the Control of LH and FSH Secretion	227
VI. Antagonism between Estrogens and Thyroid Hormone in the Control of TSH Secretion: Role of TRH Receptors	251
VII. The Pituitary Dopamine Receptor: Potent Antidopaminergic Activity of Estrogens on Prolactin Secretion	259
References	271

**5. Neurosecretion and Neuroendocrinology in Historical Perspective***Berta Scharrer*

I. Introduction	279
II. Discovery of Neurosecretory Neurons	280
III. One-Step Neurohormonal Activities	283
IV. Neuroendocrine Axis	284
V. Nonneurohormonal Functions of Peptidergic Neurons	286
VI. Biochemistry of Neurosecretory Products	288
VII. Developmental Relationships and the APUD Concept	289
VIII. Conclusions	290
References	290
AUTHOR INDEX	293
SUBJECT INDEX	321



This page intentionally left blank

## List of Contributors

Numbers in parentheses indicate the pages on which the authors' contributions begin.

- TONY ANTAKLY (205), Laboratory of Molecular Endocrinology, Le Centre Hospitalier de l'Université Laval, Québec G1V 4G2, Canada
- NICHOLAS BARDEN (205), Laboratory of Molecular Endocrinology, Le Centre Hospitalier de l'Université Laval, Québec G1V 4G2, Canada
- MICHÈLE BEAULIEU (205), Laboratory of Molecular Endocrinology, Le Centre Hospitalier de l'Université Laval, Québec G1V 4G2, Canada
- ANNETTE BERAULT (55), Laboratoire des Hormones Polypeptidiques, CNRS, 91190 Gif-sur-Yvette, France
- PIERRE BORGEAT (205), Laboratory of Molecular Endocrinology, Le Centre Hospitalier de l'Université Laval, Québec G1V 4G2, Canada
- DAVID H. COY (1), Endocrine and Polypeptide Laboratories, Veterans Administration Hospital, and Department of Medicine, Tulane University School of Medicine, New Orleans, Louisiana 70146
- LIONEL CUSAN (205), Laboratory of Molecular Endocrinology, Le Centre Hospitalier de l'Université Laval, Québec G1V 4G2, Canada
- LUCIANO DEBELJUK (55), Centro de Investigaciones en Reproduccion, Facultad de Medicina (University de Buenos Aires), 1121 Buenos Aires, Argentina
- ANDRÉ DE LEAN (205), Laboratory of Molecular Endocrinology, Le Centre Hospitalier de l'Université Laval, Québec G1V 4G2, Canada
- JACQUES DROUIN (205), Laboratory of Molecular Endocrinology, Le Centre Hospitalier de l'Université Laval, Québec G1V 4G2, Canada
- ANDRÉ DUPONT (205), Laboratory of Molecular Endocrinology, Le Centre Hospitalier de l'Université Laval, Québec G1V 4G2, Canada
- LOUISE FERLAND (205), Laboratory of Molecular Endocrinology, Le Centre Hospitalier de l'Université Laval, Québec G1V 4G2, Canada
- MARIAN JUTISZ (55), Laboratoire des Hormones Polypeptidiques, CNRS 91190 Gif-sur-Yvette, France
- ABBA J. KASTIN (1), Endocrinology Section of the Medical Service Veterans Administration Hospital, and Department of Medicine, Tulane University School of Medicine, New Orleans, Louisiana 70146
- PAUL A. KELLY (205), Laboratory of Molecular Endocrinology, Le Centre Hospitalier de l'Université Laval, Québec G1V 4G2, Canada

- BERNARD KERDELHUÉ (55), Laboratoire des Hormones Polypeptidiques, CNRS, 91190 Gif-sur-Yvette, France
- FERNAND LABRIE (205), Laboratory of Molecular Endocrinology, Le Centre Hospitalier de l'Université Laval, Québec G1V 4G2, Canada
- LISETTE LAGACÉ (205), Laboratory of Molecular Endocrinology, Le Centre Hospitalier de l'Université Laval, Québec G1V 4G2, Canada
- ANDRÉ LEMAY (205), Laboratory of Molecular Endocrinology, Le Centre Hospitalier de l'Université Laval, Québec G1V 4G2, Canada
- CHESTER A. MEYERS (1), Endocrine and Polypeptide Laboratories, Veterans Administration Hospital, and Department of Medicine, Tulane University School of Medicine, New Orleans, Louisiana 70146
- EUGENIO E. MÜLLER (123), Department of Pharmacology and Pharmacognosy, University of Cagliari, 69100 Cagliari, Italy
- GEORGES H. PELLETIER (205), Laboratory of Molecular Endocrinology, Le Centre Hospitalier de l'Université Laval, Québec G1V 4G2, Canada
- ANDREW V. SCHALLY (1), Endocrine and Polypeptide Laboratories, Veteran's Administration Hospital, and Department of Medicine, Tulane University School of Medicine, New Orleans, Louisiana 70146
- BERTA SCHARER (279), Department of Anatomy, Albert Einstein College of Medicine, Bronx, New York 10461
- MADELEINE THÉOLEYRE (55), Laboratoire des Hormones Polypeptidiques, CNRS, 91190 Gif-sur-Yvette, France

## **Preface**

Studies of the midbrain of fishes during the period of 1928 to 1932 led E. Scharrer to the concept of neurosecretion. This was followed by the discovery that neurohypophysial hormones are produced in the cell bodies of the supraoptic and paraventricular nuclei of the hypothalamus and transported to the posterior pituitary for storage and secretion. Hence, the hypothalamus may be considered to be an endocrine gland like the hypophysis.

In 1937, G. W. Harris induced ovulation in the rabbit by electrical stimulation of the hypothalamohypophyseal mechanism. Later work of Harris and others demonstrated that the hypothalamus regulates the secretion of anterior pituitary hormones. The final proof of the hypothalamohypophyseal systems came from the isolation and synthesis of thyrotropin releasing hormone by A. V. Schally and others in 1969.

This volume opens with a critical and detailed review by Schally and his collaborators on basic and clinical studies of corticotropin releasing factor (CRF), thyrotropin releasing hormone (TRH), prolactin releasing factor, prolactin-release inhibiting factor, factors affecting the release of melanotropin, luteinizing hormone release hormone (LHRH), growth hormone release factor, and somatostatin. This is followed by a chapter by Jutisz *et al.* on LHRH. In the early 1960s, Jutisz was among the first to obtain highly purified TRH from ovine hypothalamus. In his chapter, Jutisz offers a comprehensive discussion of various aspects of LHRH.

In Volume IV of this series, Clements and Meites discussed the control of prolactin secretion. In this volume, Müller reviews various factors that control the secretion of growth hormone, with particular emphasis on brain neurotransmitters. A review of the mechanism of action of hypothalamic hormones is presented by Labrie and co-workers. In addition, these authors also discuss effects of androgens, estrogens, and other peripheral hormones on the hypothalamus function.

The final contribution by B. Scharrer is on historical perspectives of neurosecretion and neuroendocrinology, a subject in which she has played an important role. Scharrer is one of the pioneers responsible for opening the new discipline of biology—neuroendocrinology. It is fitting that the last chapter on historical perspectives of neurosecretion and neuroendocrinology is written by her.

I wish to express my appreciation for the cooperation of the authors and the staff of Academic Press in the preparation of this volume.

Choh Hao Li

## Contents of Previous Volumes

### Volume I

1. The Chemistry of Glycoproteins  
*Richard J. Winzler*
  2. The Chemistry of Pituitary Thyrotropin  
*John G. Pierce, Ta-Hsiu Liao, and Robert B. Carlsen*
  3. The Chemistry of the Interstitial Cell-Stimulating Hormone of Ovine Pituitary Origin  
*Harold Papkoff*
  4. The Biology of Pituitary Interstitial Cell-Stimulating Hormone  
*M. R. Sairam and Choh Hao Li*
  5. Chemistry of Human Chorionic Gonadotropin  
*Om P. Bahl*
  6. Chemistry and Biosynthesis of Thyroid Iodoproteins  
*G. Salvatore and H. Edelhoeh*
- Author Index—Subject Index

### Volume II

1. The Structure and Function of Adrenocorticotropin  
*J. Ramachandran*
2. Gastrointestinal Hormones  
*Miklos Bodanszky*

## 3. Peptide Synthesis: A Review of the Solid-Phase Method

*Johannes Meienhofer*

Author Index—Subject Index

## Volume III

## 1. The Chemistry of Human Pituitary Growth Hormone: 1967–1973

*Choh Hao Li*

## 2. Immunochemical and Biological Studies with Antisera to Pituitary Growth Hormones

*T. Hayashida*

## 3. Clinical Studies of Human Growth Hormone in Children with Growth Problems

*Roberto F. Escamilla*

## 4. Acromegaly

*John A. Linfoot, Claude Y. Chong, John H. Lawrence, James L. Born, Cornelius A. Tobias, and John Lyman*

## 5. Endocrinology and Herbert M. Evans

*Leslie L. Bennett*

Author Index—Subject Index

## Volume IV Growth Hormone and Related Proteins

## 1. Bioassay of Pituitary Growth Hormone

*Choh Hao Li*

## 2. Growth Hormone and the Regulation of Lipolysis

*A. Jagannadha Rao and J. Ramachandran*

## 3. The Chemistry of Human Choriomammotropin

*Thomas A. Bewley*

## 4. Control of Prolactin Secretion

*James A. Clemens and Joseph Meites*

## 5. Hypophysectomy and Philip E. Smith

*James H. Leatham*

Author Index—Subject Index

## Volume V Lipotropin and Related Peptides

## 1. The Chemistry of Melanotropins

*Choh Hao Li*

2.  $\beta$ -Endorphin: A New Biological Active Peptide from Pituitary Glands

*Choh Hao Li*

## 3. Lipotropins

*M. Chrétien and M. Lis*

## 4. The Neurophysins

*B. T. Pickering and C. W. Jones*

## 5. Separation Methods and Arne Tiselius

*Jerker Porath*

Author Index—Subject Index

## Volume VI

## 1. Chemistry of Human Pituitary Thyrotropin

*M. R. Sairam and Choh Hao Li*

## 2. Thyroid Hormones and Analogs, I. Synthesis, Physical Properties, and Theoretical Calculations

*Eugene C. Jorgensen*

## 3. Thyroid Hormones and Analogs, II. Structure-Activity Relationships

*Eugene C. Jorgensen*

## 4. The Mechanism of Thyroxine Action

*Mary Bagan Dratman*



5. Cellular and Molecular Aspects of Thyroid Hormone Action during Amphibian Metamorphosis

*Philip P. Cohen, Robert F. Brucker, and Sidney M. Morris*

6. Evolution of Thyroid Function

*Aubrey Gorbman*

7. The Thyroid Hormones: Historical Aspects

*Rosalind Pitt-Rivers*

Author Index—Subject Index

# Hypothalamic Peptide Hormones: Basic and Clinical Studies

ANDREW V. SCHALLY, DAVID H. COY, CHESTER A. MEYERS, AND ABBA J. KASTIN

I. Introduction .....	2
II. Corticotropin-Releasing Factor (CRF) .....	4
A. Historical Background .....	4
B. Recent Studies on CRF .....	4
III. Thyrotropin-Releasing Hormone (TRH) .....	6
A. Isolation, Structure, and Synthesis .....	6
B. Physiological and Biochemical Studies .....	9
C. Metabolism .....	10
D. Radioimmunoassay for TRH .....	10
E. Regional Distribution of Immunoreactive TRH in the Brain .....	11
F. TRH and Prolactin Release .....	11
G. Analogues of TRH .....	12
H. Clinical Studies with TRH .....	12
IV. Prolactin-Releasing Factor (PRF) .....	14
V. Prolactin-Release-Inhibiting Factor (PIF) .....	15
A. Hypothalamus and Prolactin Secretion .....	15
B. Effect of Catecholamines on the Release of Prolactin .....	15
C. Effect of $\gamma$ -Aminobutyric Acid on Prolactin Release .....	16
D. Other Hypothalamic Substances with PIF Activity .....	17
E. Possible Clinical Uses of PIF .....	17
VI. Factors Affecting the Release of Melanocyte-Stimulating Hormone (MSH) .....	17
VII. The LH- and FSH-Releasing Hormone (LH-RH/FSH-RH) .....	18
A. Isolation, Structure, and Synthesis .....	18
B. Concept of One Hormone Controlling the Release of Both LH and FSH .....	20
C. Biological Properties of LH-RH/FSH-RH .....	21