

---

## Neuroimmunoendocrinology

---

# Chemical Immunology

Vol. 52

Series Editors

*Kimishige Ishizaka*, La Jolla, Calif.

*Peter J. Lachmann*, Cambridge

*Byron H. Waksman*, New York, N.Y.

**KARGER**

---

Basel · München · Paris · London · New York · New Delhi · Bangkok · Singapore · Tokyo · Sydney

---

# Neuroimmunoendocrinology

2nd, revised and enlarged edition

Volume Editor

*J. Edwin Blalock*, Birmingham, Ala.

22 figures, 3 color plates and 14 tables, 1992

**KARGER**

---

Basel · München · Paris · London · New York · New Delhi · Bangkok · Singapore · Tokyo · Sydney

---

# Chemical Immunology

Formerly published as 'Progress in Allergy'

Founded 1939 by Paul Kallós

Vol. 43 (1st edition)

Neuroimmunoendocrinology

Editors: J. Edwin Blalock; Kenneth L. Bost, Birmingham, Ala.

X+166 p., 17 fig., 1 cpl., 13 tab., hard cover, 1988. ISBN 3-8055-4774-9

---

## Bibliographic Indices

This publication is listed in bibliographic services, including Current Contents® and Index Medicus.

---

## Drug Dosage

The authors and the publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.

---

## All rights reserved.

No part of this publication may be translated into other languages, reproduced or utilized in any form or by any means, electronic or mechanical, including photocopying, recording, microcopying, or by any information storage and retrieval system, without permission in writing from the publisher.

- © Copyright 1992 by S. Karger AG, P.O. Box, CH-4009 Basel (Switzerland)  
Printed on acid-free paper.  
ISBN 3-8055-5488-5

---

## Contents

Introduction to the 1st Edition . . . . .	IX
Introduction to the 2nd Edition . . . . .	XI
 <i>Production of Peptide Hormones and Neurotransmitters by the Immune System</i>	
Blalock, J.E. (Birmingham, Ala.) . . . . .	1
Introduction . . . . .	1
Production and Structure of Leukocyte-Derived Peptide Hormones . . . . .	1
Pituitary Hormones . . . . .	1
Hypothalamic Releasing Hormones . . . . .	6
Neuropeptides . . . . .	7
New Proteins . . . . .	8
Regulation of Leukocyte-Derived Peptide Hormones . . . . .	8
Processing of Leukocyte-Derived Peptide Hormones . . . . .	13
Immunologic Cell Types that Produce Peptide Hormones . . . . .	15
Functions of Leukocyte-Derived Peptide Hormones . . . . .	15
Acknowledgments . . . . .	18
References . . . . .	19
 <i>Noradrenergic and Peptidergic Innervation of Lymphoid Organs</i>	
Felten, S.Y.; Felten, D.L.; Bellinger, D.L.; Olschowka, J.A. (Rochester, N.Y.)	25
Introduction . . . . .	25
General Patterns of Innervation of Lymphoid Organs . . . . .	29
Innervation of the Bone Marrow and Thymus . . . . .	36
Innervation of the Spleen . . . . .	37
Innervation of Lymph Nodes . . . . .	39
Gut-Associated Lymphoid Tissue (GALT) . . . . .	40
Criteria for Neurotransmission . . . . .	41
References . . . . .	42

Contents	VI
<i>Neuroendocrine Peptide Hormone Regulation of Immunity</i>	
Johnson, H.M.; Downs, M.O.; Pontzer, C.H. (Gainesville, Fla.) . . . . .	49
Introduction . . . . .	49
POMC and Proenkephalin Products . . . . .	50
Arginine Vasopressin . . . . .	55
Thyroid-Stimulating Hormone (Thyrotropin, TSH) and Related Hormones . . . . .	58
Substance P . . . . .	60
Vasoactive Intestinal Peptide . . . . .	62
Growth Hormone . . . . .	66
Prolactin . . . . .	68
Somatostatin . . . . .	70
Second Messenger Signals for Neuroendocrine Hormones . . . . .	70
Conclusions . . . . .	74
References . . . . .	74
<i>Neuroendocrine Peptide Receptors on Cells of the Immune System</i>	
Carr, D.J.J. (Birmingham, Ala.) . . . . .	84
Introduction . . . . .	84
Arginine Vasopressin Receptors . . . . .	85
Corticotropin Receptor . . . . .	86
$\beta$ -Endorphin Receptors . . . . .	87
Growth Hormone Receptors . . . . .	88
Nerve Growth Factor Receptors . . . . .	89
Opioid Receptors . . . . .	90
Prolactin Receptor . . . . .	91
Somatostatin Receptors . . . . .	92
Substance P Receptors . . . . .	92
Thyrotropin Receptor . . . . .	93
Vasoactive Intestinal Peptide Receptor . . . . .	93
Other Neuropeptide Receptors . . . . .	94
Hypothalamic Releasing Hormone Receptors . . . . .	95
In Summary . . . . .	96
References . . . . .	99
<i>Cytokines: Influence on Glial Cell Gene Expression and Function</i>	
Benveniste, E.N. (Birmingham, Ala.) . . . . .	106
Introduction . . . . .	106
Glial Cells: Classification, Lineage and Function . . . . .	107
Astrocytes . . . . .	107
Astrocyte Lineage . . . . .	107
Astrocyte-Specific Antigens . . . . .	109
Astrocyte Function . . . . .	110

Oligodendrocytes . . . . .	112
Oligodendrocyte Lineage . . . . .	112
Oligodendrocyte-Specific Antigens . . . . .	112
Oligodendrocyte Function . . . . .	114
Microglia . . . . .	114
Microglia Markers . . . . .	115
Microglia Functions . . . . .	115
Abnormal Glial Cell Function in Neurological Diseases . . . . .	116
In vivo CNS Sources of Cytokines . . . . .	117
Cytokines . . . . .	118
Tumor Necrosis Factor- $\alpha$ . . . . .	119
Interleukin-1 . . . . .	120
Interleukin-6 . . . . .	121
Interleukin-2 . . . . .	121
Interferon- $\gamma$ . . . . .	122
Components of the Immune System . . . . .	122
Immune Cell-Derived Cytokines and Their Effect on Glial Cells . . . . .	124
Interleukin-1 and Glial Cells . . . . .	126
Biological Effects of IL-1 on Glial Cells: Astrocytes . . . . .	126
IL-1 Production by Glial Cells . . . . .	127
Role of IL-1 in EAE . . . . .	128
Interleukin-2 and Glial Cells . . . . .	128
Biological Effects of IL-2 on Glial Cells: Oligodendrocytes . . . . .	128
Interferon- $\gamma$ and Glial Cells . . . . .	129
Biological Effects of IFN- $\gamma$ on Glial Cells . . . . .	129
Expression of Class II Antigens on Astrocytes: Correlation with EAE . . . . .	133
Modulation of Astrocyte Gene Expression by IFN- $\gamma$ . . . . .	133
Role of IFN- $\gamma$ in EAE . . . . .	134
Tumor Necrosis Factor- $\alpha$ and Glial Cells . . . . .	135
Biological Effects of TNF- $\alpha$ on Glial Cells . . . . .	135
TNF- $\alpha$ Production by Glial Cells . . . . .	136
Expression of TNF- $\alpha$ by Astrocytes: Correlation with EAE . . . . .	137
Role of TNF- $\alpha$ in EAE . . . . .	138
Interleukin-6 and Glial Cells . . . . .	139
Biological Effects of IL-6 on Glial Cells . . . . .	139
IL-6 Production by Glial Cells . . . . .	139
Regulation of IL-6 Gene Expression in Glial Cells . . . . .	140
Conclusion . . . . .	141
Acknowledgments . . . . .	142
References . . . . .	142

*Hormonal Activities of Cytokines*

Smith, E.M. (Galveston, Tex.) . . . . .	154
Introduction . . . . .	154
Interleukin-1 . . . . .	155
Neuroendocrine Action . . . . .	155

Contents	VIII
Central Nervous System (CNS) Action	157
Interleukin-2	159
Other Interleukins and IL-6	160
Tumor Necrosis Factor	161
Interferons	162
Conclusion	163
Acknowledgments	164
References	164
<i>Signaling Pathways of the Neuroendocrine-Immune Network</i>	
Roszman, T.L.; Brooks, W.H. (Lexington, Ky.)	170
Introduction	170
Can the Pituitary Gland Modulate the System?	171
Are There Receptors for Neurohormones Present on Cells of the Immune System?	173
Can Neurohormones Influence the Immune System?	175
How Do Neurohormones Modulate Lymphocyte Function?	175
Neurohormone-Lymphocyte Interactions: Signaling Models	177
Neurohormone Modulation of Immune Function-Future Directions	183
Conclusions	184
References	185
Subject Index	191



---

## Introduction to the 1st Edition

The study of interactions between the immune and neuroendocrine systems is a currently popular and rapidly advancing field which had its foundation in anecdotal observations of the association between 'personality' and disease. A measure of scientific credence was afforded to the area by the observation that, like many other physiologic responses, immune reactions could be conditioned in a classical Pavlovian fashion [1]. A possible mechanism was then found in Selye's [2] observation of thymic involution during 'stress'. The concept of the effects of stress on immunity turned out to be a two-edged sword. On the one hand, it provided a molecular basis, in the form of adrenal glucocorticoids, for neuroendocrine control of immunity. On the other hand, it led to the general and often currently held notion that steroid hormones are the sole players in neuroendocrine modulation of the immune system. Of course, recent studies have shown that this is clearly not the case since stressed adrenalectomized animals are functionally immunosuppressed [3]. Another impediment to the development of the area was the ability to have immunologic responses proceed *in vitro*. This inadvertently led to the idea that the immune system is a totally autonomous and self-regulating unit. If this were the case, then the immune system would be unlike all other organ systems. Furthermore, this view overlooks the rich hormonal milieu in which many *in vitro* immune responses occur. The end result of this series of events is the thought that if immune neuroendocrine interactions occur, they are mediated by steroid hormones. The picture has been further clouded by the predominance of studies of the psychological aspects of immune neuroendocrine interactions. Though it is not necessarily our view, such studies have given the field an aura of being a 'soft' science, thus the intent of *Neuroimmunoendocrinology* is to highlight the cellular and molecular aspects of this field.

*References*

- 1 Ader R: A historical account of conditioned immunobiologic responses; in Ader (ed): Psychoneuroimmunology. New York, Academic Press, 1981, pp 321–349.
- 2 Selye H: Thymus and adrenals in the response of the organism to injuries and intoxications. *Br J Exp Pathol* 1936;17:234–248.
- 3 Keller SE, Weiss JM, Schleifer SJ, Miller NE, Stein M: Stress-induced suppression of immunity in adrenalectomized rats. *Science* 1983;221:1301–1304.

---

## Introduction to the 2nd Edition

In the 3 years since the first publication of this volume, we have witnessed an explosion of information on immune neuroendocrine interactions. This has been evidenced by numerous international congresses, the inclusion of many symposia at the annual meetings of immunology, endocrinology, and neuroscience societies and the initiation of at least two new journals on the subject (i.e., *Progress in NeuroEndocrinImmunology* and *Advances in Neuroimmunology*). Among the highlights which have fueled the scientific growth of this discipline are: the tremendous increase in the number of neuroendocrine hormones and peptide neurotransmitters as well as their receptors which are endogenous to the immune system; the finding of cytokines such as IL-1 and IL-6 as well as their receptors in neural and endocrine tissues; and the profound effects of bidirectional communication between the immune and neuroendocrine systems on an animal's physiology. As an example, it is interesting to note that IL-1 is probably a more potent activator of the hypothalamic pituitary adrenal axis than is corticotropin releasing factor (CRF). Thus the paradox that without knowing it immunologists discovered a most potent 'hypothalamic releasing factor'. Contrariwise, CRF is a very effective inducer of IL-1. Thus, endocrinologists without knowing it discovered a cytokine. Such are the strange but exciting ironies of the development of a new discipline.

As a result of the great accumulation of new knowledge and the overwhelming success of the first edition, myself, and the coauthors have written

the present revised edition of *Neuroimmunoendocrinology*. Once again, the emphasis is on the molecular, cellular, and physiologic aspects of immune neuroendocrine interactions. Because of the expansion of the literature in this area, most chapters and bibliographies are longer. It is our fondest hope that this volume will be a valuable resource to the evolution of this exciting new discipline.