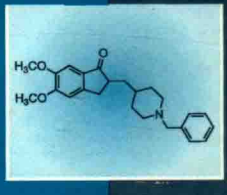
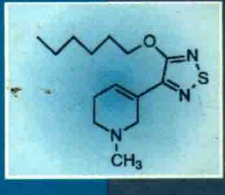
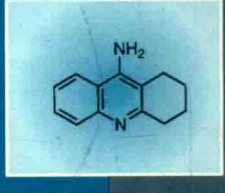
Pharmacological Treatment of Alzheimer's Disease

Molecular and Neurobiological Foundations







Edited by

JORGE D. BRIONI

MICHAEL W. DECKER

PHARMACOLOGICAL TREATMENT OF ALZHEIMER'S DISEASE

MOLECULAR AND NEUROBIOLOGICAL FOUNDATIONS

Edited by

Jorge D. Brioni and Michael W. Decker
Abbott Laboratories
Abbott Park, Illinois

WILEY-LISS
A JOHN WILEY & SONS, INC., PUBLICATION
New York • Chichester • Brisbane • Toronto • Singapore • Weinheim

Address All Inquiries to the Publisher
Wiley-Liss, Inc., 605 Third Avenue, New York, NY 10158-0012

Printed in the United States of America

Library of Congress Cataloging-in-Publication Data

Pharmacological treatment of Alzheimer's disease : molecular and
neurobiological foundations / Jorge D. Brioni, Michael W. Decker, editors.
p. cm.
Includes index.
ISBN 0-471-16758-4 (cloth : alk. paper)
1. Alzheimer's disease—Chemotherapy. 2. Alzheimer's disease—
Molecular aspects. 3. Cognition—Physiological aspects.
I. Brioni, Jorge D., 1956– . II Decker, Michael W., 1951–
[DNLM: 1. Alzheimer's Disease—drug therapy. 2. Alzheimer's
Disease—genetics. 3. Cognition—physiology. WT 155 P536 1997]
RC523.P44 1997
616.8′ 31061—dc20
DNLM/DLC
for Library of Congress

96-30137
CIP

The text of this book is printed on acid-free paper.

10 9 8 7 6 5 4 3 2 1

PHARMACOLOGICAL TREATMENT OF ALZHEIMER'S DISEASE

PREFACE

During the past several years, we have witnessed enormous growth in scientific information regarding Alzheimer's disease (AD). To this point, however, little of this information has been translated into effective treatments. In this volume, we have assembled chapters focused on potential treatments for this devastating disease, attempting to bring together basic science and industrial perspectives. In so doing, we hope to foster improved communication and understanding between the several areas of science at academic, clinical, and industrial levels and ultimately enhance our ability to find a treatment for patients suffering from AD.

Alzheimer's disease must be studied on multiple levels. A multidisciplinary approach will be the key to success. This is a critical point, and this book takes this tack, as only with a multidisciplinary understanding of AD will we be successful. Genetics, molecular and cellular biology, and biochemistry provide insights into potential causes of and treatments for AD. Basic science aimed at unraveling the neurobiological mechanisms of cognitive function will help in understanding how AD might disrupt cognitive function and, more importantly, what treatments might be helpful in ameliorating the cognitive deficits produced by this disease. The therapeutic approaches suggested by these basic science findings will yield new treatments only after extensive drug discovery and development efforts that are likely to take place within an industrial framework. Thus, diverse approaches will be required to find treatments for this uniquely human disease.

In the present book we have gathered contributions from specialists in each of these fields to cover specific topics of critical importance and have organized them into three parts: Neurobiology of Cognition, Molecular Aspects of Alzheimer's Disease, and Alzheimer's Drug Discovery and Development.

Given the prominence of the effects of AD on cognition, we have devoted a section of this book to basic research on the neurobiology of cognitive function. This section surveys relevant information on the way the brain encodes and stores information. Much of the work reviewed in this section has been conducted with rodents and nonhuman primates, but its relevance to understanding cognitive deficits in AD is made clear by the parallels between human and animal studies drawn by Kesner and Ragozzino in Chapter 1. Neurochemical systems important in modulating rodent memory are discussed extensively in Chapter 2 by Guzowski and McGaugh. An understanding of this content will be important in developing symptomatic treatments for the cognitive deficits associated with AD, and further consideration of this topic from the perspective of nonhuman primate studies and their potential

relevance to work in humans is found in Chapter 3 by Arnsten and van Dyck. The cholinergic hypothesis, which has been central in attempts to understand and treat AD in the last 20 years, is the topic of two chapters in this section. Chapters 4 by Baxter and Gallagher and Chapter 5 by Sarter and Bruno make the case that the idea that cholinergic dysfunction underlies the memory deficits in AD is no longer tenable. Instead, they propose that cholinergic dysfunction in AD produces marked deficits in attentional processes. Finally, this section concludes with Chapter 6 by Salmon, surveying the neuropsychological findings in Alzheimer's patients. This information, when combined with our knowledge of brain structures involved in cognitive processes, provides hypotheses regarding the relative importance of pathological changes observed in AD for producing cognitive deficits. Identification of the types of memory deficits present in AD patients (declarative, procedural, attentional, etc.) is also important in validating animal models of AD, which goes back to a major theme of Chapter 1.

The topic of brain pathology observed in AD and the relevance of these changes for producing cognitive deficits is the focus of Chapter 7 by Solodkin and Van Hoesen, which provides a transition between the behavioral studies of the first section and the mechanisms of AD explored in the second section. This section emphasizes investigations of possible etiological factors. To begin this analysis, in Chapter 8 Grewal and Finch discuss a major etiological question: is Alzheimer's just an acceleration of normal aging or is it a separate condition? The answer to this question will have important public health and treatment implications. In Chapter 9 by Clark and Goate, the genetics of AD are reviewed. Genetic studies can reveal the location of mutations associated with the disease, and molecular biology can be used to identify the candidate mechanisms involved in producing the disease. The potential role of the classical histopathological features of the disease, neurofibrillary tangles and senile plaques, are discussed in separate chapters. In Chapter 10 Clark, Trojanowski, and Lee review evidence that neurofibrillary tangles are an important causal factor in AD and reflect on some implications for treatment. Interestingly, no animal models overexpressing tangles have been reported yet. In Chapter 11 Mattson, Bruce, Mark, and Blanc provide an extensive review of potential mechanisms of the toxicity of β-amyloid, the primary component of senile plaques. The recent discovery that the apolipoprotein E genotype may be a risk factor for AD is the topic of Chapter 12 by Falduto and LaDu. The authors describe the relationship between apolipoprotein E and AD and discuss potential mechanisms involved. In Chapter 13 Borchelt, Martin, Hsiao, Gearhart, Lamb, Sisodia, and Price review novel animal models of AD, particularly animal models based on recent findings in the molecular biology of the disease. Transgenic models are being developed exclusively in mice for practical reasons, but we will need to develop transgenic models in rats or other higher mammals in the near future.

The lack of good animal models for AD has hampered efforts both to understand disease processes and to test potential treatments. Conversely, the lack of effective treatments precludes the pharmacological validation of the animal models under consideration. By analogy to other central nervous system (CNS) disorders such as epilepsy or anxiety, we are at a stage equivalent to the prebarbiturate or prebenzodi-

azepine era with respect to AD. Thus, we should not be hypercritical of the small advances or limited efficacy of present treatments. As was true for other CNS disorders, even incremental progress in therapeutics will likely accelerate future advances.

The need for animal models to test potential therapeutics provides transition from basic science approaches to AD to treatments, the topic of the last section of the book. In this last section, a variety of issues important in developing treatments are discussed. Chapter 14 by Whitehouse opens the section with a discussion of AD as a public health concern and regulatory issues related to developing a drug for treating AD. Improved ability to diagnose AD and to develop surrogate markers for the disease are clearly important in conducting clinical trials, and these issues are the subject of Chapter 15 by Seubert, Galasko, and Boss on biochemical markers. Clinical trials for AD are complex, and proper design is critical for providing appropriate information on compounds in clinical development. Cutler and Sramek tackle this important issue in Chapter 16 on clinical trials and assessment.

The final seven chapters of this section deal with specific treatments. Since cholinergic-based treatments have been prominent in efforts to develop therapeutics for AD, this approach is the topic of three separate chapters. Gracon and Berghoff (Chapter 17) describe the clinical results with tacrine, a cholinesterase inhibitor that was the first compound approved in the United States for the treatment of AD. Jaen and Schwarz (Chapter 18) review the development of muscarinic cholinergic agonists for AD, and our chapter (Chapter 19) describes efforts to develop compounds acting as nicotinic cholinergic receptors. Pelleymounter and Williams (Chapter 20) provide information on neurotrophins and discuss the therapeutic potential of this approach. The next two chapters are devoted to classes of compounds approved for other therapeutic targets but that may also be useful in treating AD. Rogers (Chapter 21) focuses on issues related to the role of neuroinflammation in AD and the therapeutic potential of anti-inflammatory agents. Simpkins, Green, and Gridley (Chapter 22) discuss the possible therapeutic role of estrogens and suggest some potential mechanisms underlying these apparent beneficial effects. Finally, this section concludes with Chapter 23 by Williams and Arneric that provides an overview and an update on the status of a variety of treatment approaches currently under development in industry.

We are indebted to our colleagues who agreed to participate in this endeavor and allowed us to cover so many areas of importance in understanding AD. We are deeply grateful to Dr. James McGaugh and Dr. Michela Gallagher for all the lessons learned from them, to Dr. Michael Williams for guidance in the development of our original book proposal, and to Dr. Williams and to Dr. Stephen Arneric for their support. We would also like to acknowledge the help of the staff at Wiley for their excellent editorial work.

This book is dedicated to our wives, Elsa Daprati-Brioni and Elisa Trombetta Decker, as they have shared with us this long journey from graduate school, years full of dreams and sacrifice, doubts and accomplishments, in essence and in retrospect, a gratifying adventure.

JORGE D. BRIONI
MICHAEL W. DECKER

CONTRIBUTORS

Stephen P. Arneric, Neuroscience Discovery, Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, Illinois 60064-3500

Amy F. T. Arnsten, Section of Neurobiology, Yale Medical School, New Haven, Connecticut 06510-8001

Mark G. Baxter, Curriculum in Neurobiology, University of North Carolina, Chapel Hill, North Carolina 27599

William G. Berghoff, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, Michigan 48105

Emmanuelle M. Blanc, Sanders-Brown Research Center on Aging and Department of Anatomy & Neurobiology, University of Kentucky, Lexington, Kentucky 40536

David R. Borchelt, Departments of Pathology and Neuropathology Laboratory, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205

Michael A. Boss, Athena Diagnostics, Inc., Four Biotech Park, 377 Plantation Street, Worcester, Massachusetts 01605

Jorge D. Brioni, Neuroscience Discovery, Abbott Laboratories, Abbott Park, Illinois 60064-3500

Annadora J. Bruce, Sanders-Brown Research Center on Aging and Department of Anatomy & Neurobiology, University of Kentucky, Lexington, Kentucky 40536

John P. Bruno, Department of Psychology and Neuroscience Program, Ohio State University, Columbus, Ohio 43210

Christopher M. Clark, Department of Neurology, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104

Robert F. Clark, Department of Psychiatry, Washington University School of Medicine, St. Louis, Missouri 63110

Neal R. Cutler, California Clinical Trials, Beverly Hills, California 90211

Michael W. Decker, Neuroscience Discovery, Abbott Laboratories, Abbott Park, Illinois 60064-3500

Michael T. Falduto, Immunoscience Discovery, Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, Illinois 60064

Caleb E. Finch, Department of Neurology, School of Medicine, and Division of Neurogerontology, Andrus Gerontology Center, University of Southern California, Los Angeles, California 90089-0191

Katsutoshi Furukawa, Sanders-Brown Research Center on Aging and Department of Anatomy & Neurobiology, University of Kentucky, 40536

Douglas Galasko, Department of Neurosciences, University of California at San Diego and Veteran's Affairs Medical Center, San Diego, California 92161

Michela Gallagher, Department of Psychology, University of North Carolina, Chapel Hill, North Carolina 27599

John D. Gearhart, Departments of Obstetrics & Gynecology and the Division of Reproductive & Developmental Biology, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205

Alison M. Goate, Department of Psychiatry, Washington University School of Medicine, St. Louis, Missouri 63110

Stephen I. Gracon, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, Michigan 48105

Pattie S. Green, Department of Pharmacodynamics and the Center for the Neurobiology of Aging, University of Florida, Gainesville, Florida 32610

Raji P. Grewal, Department of Neurology, School of Medicine, and Division of Neurogerontology, Andrus Gerontology Center, University of Southern California, Los Angeles, California 90089-0191

Kelly E. Gridley, Department of Pharmacodynamics and the Center for the Neurobiology of Aging, University of Florida, Gainesville, Florida 32610

John F. Guzowski, Center for the Neurobiology of Learning and Memory, University of California, Irvine, California 92717-3800

Anne Marie Himmelheber, Department of Psychology and Neuroscience Program, Ohio State University, Columbus, Ohio 43210

Karen K. Hsiao, Department of Neurology, University of Minnesota Medical School, Minneapolis, Minnesota 55455

Juan C. Jaen, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, Michigan 48105

Raymond P. Kesner, Department of Psychology, University of Utah, Salt Lake City, Utah 84112

Mary Jo LaDu, Department of Pathology, University of Chicago, Chicago, Illinois 60637

Bruce T. Lamb, Departments of Obstetrics & Gynecology and the Division of Reproductive & Developmental Biology, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205

Virginia M.-Y. Lee, Department of Pathology and Laboratory Medicine, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104

Robert J. Mark, Sanders-Brown Research Center on Aging and Department of Anatomy & Neurobiology, University of Kentucky, Lexington, Kentucky 40536

Lee J. Martin, Departments of Pathology and Neuroscience and the Neuropathology Laboratory, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205

Mark P. Mattson, Sanders-Brown Research Center on Aging and Department of Anatomy & Neurobiology, University of Kentucky, Lexington, Kentucky 40536

James L. McGaugh, Departments of Psychology and Pharmacology, University of California, Irvine, California 92717-3800

Mary Ann Pelleymounter, Department of Neurobiology, Amgen Inc., 1840 DeHavilland Drive, Thousand Oaks, California 91320

Donald L. Price, Departments of Pathology, Neuroscience, Neurology, and the Neuropathology Laboratory, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205

Michael E. Ragozzino, Department of Psychology, University of Utah, Salt Lake City, Utah 84112

Joseph Rogers, Sun Health Research Institute, 10515 West Santa Fe Drive, Sun City, Arizona 85372

David P. Salmon, Department of Neurosciences, School of Medicine, University of California, San Diego, La Jolla, California 92093-0948

Martin Sarter, Department of Psychology and Neuroscience Program, Ohio State University, Columbus, Ohio 43210

Roy D. Schwarz, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, Michigan 48105

Peter Seubert, Athena Neurosciences, Inc., 800 Gateway Boulevard, South San Francisco, California 94080

James W. Simpkins, Department of Pharmacodynamics and the Center for the Neurobiology of Aging, University of Florida, Gainesville, Florida 32610

Sangram S. Sisodia, Departments of Pathology, Neuroscience, and the Neuropathology Laboratory, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205

Ana Solodkin, Departments of Anatomy and Neurology, University of Iowa, Iowa City, Iowa 52242

John J. Sramek, California Clinical Trials, Beverly Hills, California 90211

John Q. Trojanowski, Department of Pathology and Laboratory Medicine, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104

Christopher H. van Dyck, Department of Psychiatry, Yale Medical School, New Haven, Connecticut 06510-8001

Gary W. Van Hoesen, Departments of Anatomy and Neurology, University of Iowa, Iowa City, Iowa 52242

Peter J. Whitehouse, University Hospitals of Cleveland, Case Western Reserve University, Cleveland, Ohio 44120

Lawrence R. Williams, Department of Neurobiology, Amgen Inc., 1840 Dehavilland Drive, Thousand Oaks, California 91320

Michael Williams, Neuroscience Discovery, Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, Illinois 60064-3500

PHARMACOLOGICAL TREATMENT OF ALZHEIMER'S DISEASE

CONTENTS

PART I

NEUROBIOLOGY OF COGNITION