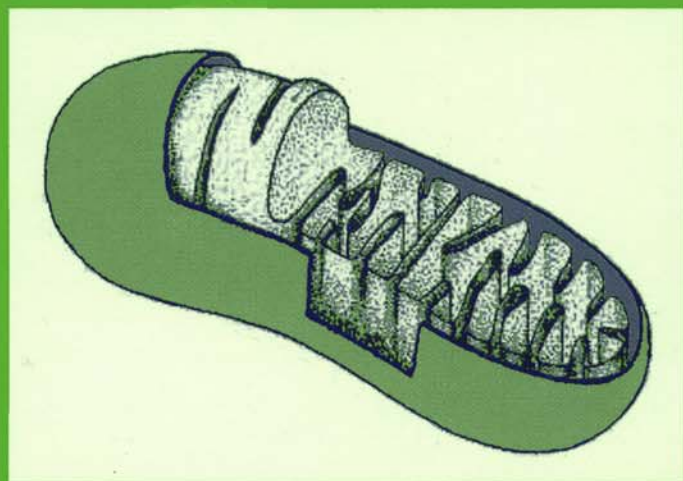


Mitochondrial Inhibitors AND Neurodegenerative Disorders



Edited by

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 **Humana Press**

Mitochondrial Inhibitors and Neurodegenerative Disorders

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Humana Press
Totowa, New Jersey

© 1999 Humana Press Inc.
999 Riverview Drive, Suite 208
Totowa, New Jersey 07512

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ANSI Z39.48-1984 (American Standards Institute) Permanence of Paper for Printed Library Materials.

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Printed in the United States of America. 10 9 8 7 6 5 4 3 2 1

Library of Congress Cataloging in Publication Data

Main entry under title:

Mitochondrial inhibitors and neurodegenerative disorders / edited by Paul R. Sanberg, Hitoo Nishino, Cesario V. Borlongan.

p. cm.—(Contemporary neuroscience)

Includes index.

ISBN 0-89603-805-X (alk. paper)

1. Nervous system—Degeneration—Pathophysiology. 2. Nervous system—Degeneration—Animal models. 3. Mitochondrial pathology. 4. Neurotoxic agents. I. Sanberg, Paul R. II. Nishino, Hitoo. III. Borlongan, Cesario V. IV. Series.

[DNLM: 1. Neurodegenerative Diseases—chemically induced. 2. Propionic Acids—toxicity. 3. Mitochondria—metabolism. 4. Neurotoxins—toxicity. WL 359 M684 1999]

RC394.D35M56 1999

616.8'047—dc21

DNLM/DLC

for Library of Congress

98-55467

CIP

Dedications

To my father and best friend, Bernard Sanberg, in memorium—Paul

To my wife, Akiko, and loving mother and father—Hitoo

To my inspirations, Christine Stahl and Mia Borlongan—Cesar

Foreword

Mitochondria have long been the Rodney Dangerfield of cellular organelles. Believed to be the remnants of bacterial infection of eukaryotic cells eons ago, the mitochondrion evolved a symbiotic relationship in which it dutifully served as the efficient source of ATP for cell function. The extraordinary dependence of cells on the energy provided by mitochondrial oxidative metabolism of glucose, especially through critical organs such as the heart and brain, is underlined by the fatal consequences of toxins that interfere with the mitochondrial electron transport system.

Consistent with their ancestry, the mitochondria have their own DNA that encodes many but not all of their proteins. The mitochondria and their genes come from the mother via the ovum since sperm do not possess mitochondria. This extranuclear form of inheritance derived exclusively from the female side has proved to be a powerful tool for tracing the evolution by the number of base substitutions in mtDNA.

That mitochondrial gene mutations might be a source of human disease became evident a decade ago with the characterization of a group of multisystem disorders typically involving the nervous system, which are transmitted from mother to child. Specific point mutations in mtDNA have been associated with the different syndromes.

The central role of mitochondria in neurodegenerative disorders has become apparent over the last decade as the molecular mechanisms causing cell death have come under scientific scrutiny. Reactive oxygen species were shown to be mediators of delayed neuronal degeneration caused by activation of ionotropic glutamate receptors. Oxidative stress was also shown to precipitate programmed cell death or apoptosis. The linkage between these two phenomena related to the facts that the mitochondria are the source of 80% or more of the oxyradicals generated in the neuron and that Ca^{2+} dysregulation causing excessive activation of glutamate ionotropic receptors disrupts the mitochondrial electron.

In this context, *Mitochondrial Inhibitors and Neurodegenerative Disorders* provides a timely, in-depth review of the effects of mitochondrial toxins on the nervous system. What is particularly interesting about

the clinical manifestations of the mitochondrial poisons is the uneven vulnerability of neurons, with neurons of the extrapyramidal system exhibiting particular susceptibility. This selective vulnerability mimics that of hereditary neurodegenerative disorders such as Huntington's and Parkinson's Disease. Furthermore, experimental studies indicate that activation of the receptor, mediates this selective vulnerability. The insights derived from this line of research suggest novel therapeutic approaches that could prevent the onset of these disorders in individuals at risk.

Joseph T. Coyle, MD

Preface

Mitochondrial Inhibitors and Neurodegenerative Disorders critically surveys all the recent work on the utilization of mitochondrial inhibitors to deepen understanding of the various mechanisms involved in neurodegenerative disorders. The many facets of advances in this field can be divided into the three major areas that we have included here. The first section is concerned with the role of mitochondrial inhibitors in neurodegenerative disorders, a topic that has been the subject of much research this past decade; many neurotoxins that disrupt normal mitochondrial energy metabolism have been identified. The chapters tackled in this first section deal largely with discovery of environmental mitochondrial toxins. A short historical background of these neurotoxins is presented to provide the reader with an understanding of the basic neurochemistry and mode of action of these drugs as they relate to mitochondrial dysfunction.

The second section deals with the development of animal models of those human diseases that in recent years have been suggested to be caused by abnormal mitochondrial function. At the forefront of these mitochondrial deficiency-related disorders is Huntington's disease, and the chapters in this section have thus been written by investigators who have examined these neurotoxic models [specifically 3-nitropropionic acid (3-NP)] into replicating the cellular and anatomical, as well as the behavioral, alterations seen in this disorder. Because of our own keen interest and significant increase in the recent literature validating the utility of 3-NP in modeling many of the symptoms of Huntington's disease, we have chosen to review the many studies on this neurotoxin. The bulk of information on 3-NP is the concentration of this book and should provide "proof of principle" that mitochondrial inhibitors, in general, play an important role in the etiology of central nervous system disorders.

Finally, any validation of the usefulness of a drug for modeling specific human disease leads to the development of treatment strategies. The third section of *Mitochondrial Inhibitors and Neurodegenerative Disorders* thus discusses recent therapeutic modalities directed toward

rescuing the central nervous system from abnormal mitochondrial functioning.

We very much hope that *Mitochondrial Inhibitors and Neurodegenerative Disorders* will guide students and researchers alike in further establishing the neurobehavioral foundations of the human disorders that are mimicked by administration of mitochondrial inhibitors.

Paul R. Sanberg, PhD, DSc

Hitoo Nishino, MD

Cesario V. Borlongan, MD

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I

Mitochondrial Toxins

Symptomatology, Origin, and Chemistry
