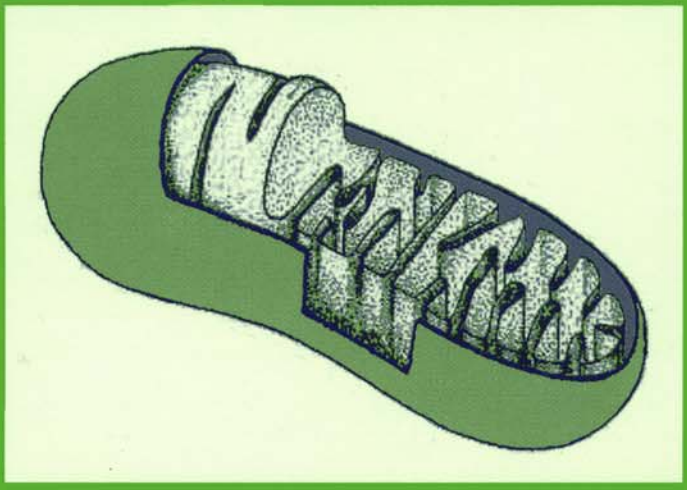
Mitochondrial Inhibitors AND Neurodegenerative Disorders



Edited by

Paul R. Sanberg, PhD, DSc

Hitoo Nishino, MD, PhD

Cesario V. Borlongan, PhD

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Mitochondrial Inhibitors and Neurodegenerative Disorders

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Edited by

Paul R. Sanberg, PhD, DSc
Univeristy of South Florida College of Medicine, Tampa, FL

Hitoo Nishino, MD, PhD
Nagoya City University Medical School, Nagoya, Japan

Cesario V. Borlongan, MD
National Institutes of Health, Baltimore, MD

Foreword by
Joseph T. Coyle, MD

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Totowa, New Jersey 07512

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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 eukarytotic 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 mitochrondria have their own DNA that encodes many but not all of their proteins. The mitchondria 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 mitochrondrial 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

Mitochondial Inhibitors and Neurodegenerative Disorders critically surveys all the recent work on the utilization of mitochodrial 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***

Contents

Contributors

ROGER ALBIN • *Department of Neurology, University of Michigan & Geriatrics Research Education and Clinical Center, Ann Arbor VAMC, Ann Arbor, MI*

TAJRENA ALEXI • *Department of Pediatrics, RCDMB Starship Hospital, Garfton, Auckland, New Zealand*

SAFIA BAGGIA • *Portland State University, Portland, Oregon*

TERRENCE J. BAZZETT • *Department of Psychology, SUNY Geneseo, Geneseo, NY*

JILL B. BECKER • *Department of Psychology, Reproductive Sciences Program, Neuroscience Program, University of Michigan, Ann Arbor, MI*

MARÍA ISABEL BEHRENS • *Las Condes Santiago, Chile*

ZBIGNIEW BINIENDA • *Division of Neurotoxicology, National Center for Toxicological Research, Jefferson, AR*

VIMALA BONDADA • *Sanders-Brown Center on Aging and Department of Anatomy and Neurobiology, University of Kentucky, Lexington, KY*

CESARIO V. BORLONGAN • *Cellular Neurophysiology, Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD*

D. ALLAN BUTTERFIELD • *Director, Center of Membrane Sciences, and Faculty Associate, Sanders-Brown Center on Aging, Lexington, KY*

JOHN M. CARNEY • *Centaur Pharmaceuticals, Sunnyvale, CA*

MIKE CHIUEH • *Laboratory Chief, Unit on Neurodegeneration and Neuroprotection, LCS, NIMH, NIH, Bethesda, MD*

SHRIPAD B DESHPANDE • *Department of Physiology, Nagoya City University Medical School, Mizuho-cho, Mizuho-ku, Nagoya, Japan*

JIE DONG • *Brain Research Laboratory, Psychology Department, Central Michigan University, Mt. Pleasant, MI*

GARY L. DUNBAR • *Department of Psychology, Director, Brain Research Laboratory, Central Michigan University, Mount Pleasant, MI*

STEPHEN B. DUNNETT • *MRC Cambridge Centre for Brain Repair and Department of Experimental Psychology, University of Cambridge, Cambridge, UK*

Barry J. Everitt • *MRC Cambridge Centre for Brain Repair and Department of Experimental Psychology, University of Cambridge, Cambridge, UK*

Richard L. M. Faull • *Department of Anatomy with Radiology, School of Medicine, University of Auckland, Auckland, New Zealand*

Thomas B. Freeman • *Division of Neurological Surgery, Deparment of Surgery, University of South Florida College of Medicine, Tampa, FL*

Atsuo Fukuda • *Department of Physiology, Nagoya City University Medical School, Mizuho-cho, Mizuho-ku, Nagoya, Japan*

S. Prasad Gabbita • *Sanders Brown Center on Aging, Department of Chemistry and Center of Membrane Sciences, University of Kentucky, Lexington, KY*

James W. Geddes • *University of Kentucky Medical Center, Lexington, KY*

Daniel H. Gould • *Department of Pathology, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO*

David L. Gustine • *USDA-ARS PSWMRL, USDA Pasture Laboratory, University Park, PA*

Kristi L. Haik-Creguer • *Brain Research Laboratory, Psychology Department, Central Michigan University, Mt. Pleasant, MI*

Bradley F. Hamilton • *Bayer Corporation, Agriculture Division, Stilwell, KS*

Robert A. Hauser • *Division of Neurological Surgery, Deparment of Surgery, University of South Florida College of Medicine, Tampa, FL*

Paul E. Hughes • *Department of Pharmacology and Clinical Pharmacology, School of Medicine, University of Auckland, Auckland, New Zealand*

Gopal Krishna • *Unit on Neurodegeneration and Neuroprotection, Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, MD*

Michiko Kumazaki • *Department of Physiology, Nagoya City University Medical School, Mizuho-ku, Nagoya, Japan*

Wen Lin • *Department of Neurology, University of Wisconsin School of Medicine and Veterans Administration Medical Center, Milwaukee, WI*

Albert C. Ludolph • *Direktor der Neurologischen, Department of Neurology, University of Ulm, Ulm, Germany*

Alicia Meldrum • *MRC Cambridge Centre for Brain Repair, Cambridge, UK*

Keiya Nakajima • *Department of Physiology, Nagoya City University Medical School, Mizuho-cho, Mizuho-ku, Nagoya, Japan*

Hitoo Nishino • *Department of Physiology, Nagoya City University Medical School, Mizuho-cho, Mizuho-ku, Nagoya, Japan*

KEITH J. PAGE • *MRC Cambridge Centre for Brain Repair and Department of Experimental Psychology, University of Cambridge, Cambridge, UK*

ZHEN PANG • *Sanders-Brown Center on Aging and Department of Anatomy and Neurobiology, University of Kentucky, Lexington, KY*

NORMAN C. REYNOLDS, JR. • *Department of Neurology, University of Wisconsin School of Medicine and Veterans Administration Medical Center, Milwaukee, WI*

MATTHIAS RIEPE • *Department of Neurology, University of Ulm, Ulm, Germany*

MOHAMMAD SABRI • *Oregon Health Sciences University, Portland, OR*

PAUL R. SANBERG • *Division of Neurological Surgery, Program in Neuroscience, Department of Surgery, University of South Florida School of Medicine, Tampa, FL*

ANDREW C. SCALLET • *Division of Neurotoxicology, National Center for Toxicological Research/FDA, Jefferson, AK*

DEBORAH A. SHEAR • *Brain Research Laboratory, Psychology Department, Central Michigan University, Mt. Pleasant, MI*

YASUNOBU SHIMANO • *Department of Physiology, Nagoya City University Medical School, Mizuho-cho, Mizuho-ku, Nagoya, Japan*

PETER S. SPENCER • *Center for Research on Occupational and Environmental Toxicology and Department of Neurology, Oregon Health Sciences University, Portland, OR*

CHRISTINE E. STAHL • *Uniformed Services University of Health Sciences, Bethesda, MD 20814*

KUNIO TORII • *Department of Physiology, Nagoya City University Medical School, Mizuho-cho, Mizuho-ku, Nagoya, Japan*

CHUCHARIN UNGSUPARKORN • *Department of Physiology, Nagoya City University Medical School, Mizuho-ku, Nagoya, Japan*

YUN WANG • *Cellular Neurophysiology, Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD*

MOUSSA B. H. YOUDIM • *NIH Fogarty International Center for Advance Studies in Human Health, Unit on Neurodegeneration and Neuroprotection, Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, MD*

GAIL D. ZEEVALK • *Department of Neurology, UMDNJ-Robert Wood Johnson Medical School, Piscataway, NJ*

I

Mitochondrial Toxins

Symptomatology, Origin, and Chemistry