Hormesis

Mark P. Mattson · Edward J. Calabrese
Editors

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A Revolution in Biology, Toxicology and Medicine

Springer

Editors
Mark P. Mattson
Laboratory of Neurosciences
GRC 4F01
National Institute on Aging
5600 Nathan Shock Drive
Baltimore, MD 21224
USA
mattsonm@grc.nia.nih.gov

Edward J. Calabrese
Department of Environmental Health Sciences
University of Massachusetts
Northeast Regional Environmental Public
N344 Morrill Science Center
Amherst, MA 01003-5712
USA
edward@schoolph.umass.edu

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Preface

The term *hormesis* is defined as "a process in which exposure to a low dose of a chemical agent or environmental factor that is damaging at higher doses induces an adaptive beneficial effect on the cell or organism" (Calabrese et al., 2007; Mattson, 2008). To survive and reproduce in harsh competitive environments, organisms and their cellular components have, through evolution, developed molecular mechanisms to respond adaptively to various hazards or "stressors" that they encounter. Examples of such stressors include chemicals ingested in food and water (metals, phytochemicals, etc.), increased energy expenditure (running, fighting, cognitive challenges, etc.), and reduced energy availability (food scarcity), among others. In most cases, the response of the cell or organism to the stressor exhibits a biphasic dose response, with beneficial/adaptive responses at low doses (improved function, increased resistance to damage and disease) and adverse/destructive effects (dysfunction, molecular damage, or even death) at high doses. The prevalence of the biphasic (hormetic) dose response characteristic of biological systems merits consideration of hormesis as a fundamental principle of biology.

In this book, my colleagues and I present evidence from a range of biological systems that hormesis is indeed at the epicenter of the molecular and cellular responses to their environment. Many of the thousands of examples of hormesis (biphasic dose responses with stimulatory/beneficial effects at low doses and inhibitory/toxic effects at high doses) come from the field of toxicology (Calabrese, 2008), and yet the Environmental Protection Agency (EPA) continues to largely ignore the important scientific fact of the biphasic dose response. Their approach is to reduce the levels of "toxins" in the environment as much as possible. However, it is clear that at least in some cases human health may be adversely affected by removing "toxic" chemicals from the environment. Prominent examples are metals such as selenium, zinc, and iron, all of which are toxic when consumed in high amounts but are essential for health in low amounts (Dodig and Cepelak, 2004; Frassinetti et al., 2006; Wright and Baccarelli, 2007). Other major, emerging examples are phytochemicals that function as insect repellants (toxins) in plants but stimulate adaptive stress response pathways when consumed by humans (Cheng and Mattson, 2006).

Of interest, many endogenous cellular signaling pathways exert their effects on cellular physiology (cell division, the growth of muscle and nerve cells, and even

behaviors such as learning and memory) through hormetic mechanisms. For example, the excitatory neurotransmitter glutamate is released from presynaptic terminals at synapses, where it then activates receptors that are coupled to calcium influx into the dendrites of the postsynaptic neuron. In this way glutamate plays a fundamental role in the function of neuronal circuits involved in sensory processing, motor responses, learning and memory, and emotional behaviors. These low levels of glutamate also activate adaptive stress responses that include the production of proteins that help to protect the neurons against more-severe stress. These stress resistance proteins include neurotrophic factors, antioxidant enzymes, and antiapoptotic proteins such as Bcl2. However, abnormally high levels of glutamate resulting from increased release and/or decreased removal at synapses can cause the degeneration and death of neurons. The latter neurotoxic effects of excessive activation of glutamate receptors occur in patients with epilepsy, stroke, traumatic brain and spinal cord injury, and possibly Alzheimer's, Parkinson's, and Huntington's diseases. The situation is similar with other signaling pathways in other tissues and organs. Consequently, the scientific and biomedical professions should work to elucidate the molecular components of hormetic signaling pathways and apply that knowledge to the development of novel hormesis-based preventative and therapeutic interventions for many different human diseases.

This book comprises 10 chapters, with contributions from more than a dozen authors to the writing of one or more of the chapters. The first chapter describes the concept of hormesis, the prevalence of biphasic dose responses in biological systems, and implications of hormesis for the future of science, medicine, and public policy decisions. The second chapter focuses on the role of hormesis in toxicology and risk assessment, with a focus on environmental toxins. A chapter that considers hormesis from an evolutionary perspective provides several examples of how organisms not only developed mechanisms to respond adaptively to "toxins," but also actually incorporated those chemicals into their metabolic systems. The next three chapters describe several of the most highly conserved signaling mechanisms that mediate hormetic responses of cells and organisms exposed to subtoxic doses of chemicals and other stressors. These include G protein–coupled receptors and signaling pathways that lead to the induction of genes that encode cytoprotective proteins such as heat-shock proteins, antioxidant enzymes, and growth factors. The complexity of receptor systems and cellular responses provides a rich venue for understanding the intricacies of the molecular mediators of hormesis. The health benefits of exercise and dietary modification (particularly dietary energy restriction) are well known. Two chapters provide evidence that many of the beneficial effects of exercise and dietary modification result from activation of hormetic signaling pathways in cells throughout the body.

Particularly intriguing are the prominent hormetic effects of exercise and dietary energy restriction on brain health. Data suggest that hormetic mechanisms may be compromised during aging, and such impairments may contribute to the development of a range of age-related diseases. We are in the midst of an epidemic of obesity and diabetes in the United States, and this major health problem is spreading to industrialized countries in all continents. A chapter describes evidence that

the "couch potato" lifestyle that causes obesity and diabetes does so, in part, by suppressing the activation of hormetic response pathways. The book concludes with a chapter entitled The Hormetic Pharmacy that considers the role of hormesis-based mechanisms of action in the future of natural products and man-made drugs for disease prevention and treatment. Early in the 16th century, Paracelsus recognized that all drugs are poisonous at high doses and that careful evaluation of dose-response relationships are necessary for optimizing treatments. In this book we emphasize our newer recognition of the great potential of hormesis-based approaches for drug discovery, as well as for the optimization of dietary and lifestyle factors to improve the quality of life.

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Baltimore, Maryland Mark P. Mattson

Contents

About the Editors

Mark P. Mattson, Ph.D., is Chief of the Laboratory of Neurosciences at the National Institute on Aging in Baltimore, where he leads a multifaceted research team that applies cutting-edge technologies in research aimed at understanding molecular and cellular mechanisms of brain aging and the pathogenesis of neurodegenerative disorders. He is also a professor in the Department of Neuroscience at Johns Hopkins University School of Medicine. He has published more than 450 original research articles and numerous review articles and has edited 10 books in the areas of mechanisms of aging and neurodegenerative disorders. Dr. Mattson has trained more than 60 postdoctoral and predoctoral students and is the most highly cited neuroscientist in the world.

Edward J. Calabrese, Ph.D., is a professor and Program Director of Environmental Health Science at the University of Massachusetts in Amherst. His research focuses on environmental toxicology, with an emphasis on biological factors, including genetic and nutritional factors that enhance susceptibility to pollutant toxicity and the environmental implications of toxicological hormesis. Dr. Calabrese has researched extensively in the area of host factors affecting susceptibility to pollutants and is the author of more than 600 papers in scholarly journals, as well as 24 books in the field of toxicology and environmental pollution. Dr. Calabrese has received numerous awards, including, most recently, the prestigious Marie Curie Prize.

Contributors

Mark P. Mattson Laboratory of Neurosciences, National Institute on Aging, Intramural Research Program, Baltimore, MD 21224, USA, mattsonm@grc.nia.nih.gov

Edward J. Calabrese Department of Environmental Health Sciences, School of Public Health and Health Sciences, University of Massachusetts, Amherst, MA 01003, USA, edwardc@schoolph.umass.edu

Tae Gen Son Laboratory of Neurosciences, National Institutes of Health, National Institute on Aging, Baltimore, MD 21224, USA, sont2@grc.nia.nih.gov

Roy G. Cutler Laboratory of Neurosciences, National Institutes of Health, National Institute on Aging, Baltimore, MD 21224, cutlerro@grc.nia.nih.gov

Simonetta Camandola Laboratory of Neurosciences, National Institute on Aging, Intramural Research Program, Baltimore, MD 21224, camandolasi@grc.nia.nih.gov

Wayne Chadwick Receptor Pharmacology Unit, National Institute on Aging, National Institutes of Health, Biomedical Research Center, Baltimore, MD 21224, USA, chadwickwa@nia.nih.gov

Stuart Maudsley Laboratory of Neurosciences, National Institutes of Health, National Institute on Aging, Baltimore, MD 21224, USA, maudsleyst@grc.nia.nih.gov

Alexis M. Stranahan Department of Psychological and Brain Sciences, Johns Hopkins University, Baltimore, MD 21218, USA, alexis.stranahan@jhu.edu

Bronwen Martin Laboratory of Clinical Investigation, National Institutes of Health, National Institute on Aging, Baltimore, MD 21224, USA, martinbro@mail.nih.gov

Sunggoan Ji Laboratory of Neurosciences, National Institutes of Health, National Institute on Aging, Baltimore, MD 21224, USA, jis2@mail.nih.gov

Caitlin M. White Laboratory of Neurosciences, National Institutes of Health, National Institute on Aging, Baltimore, MD 21224, USA, whitecm2@mail.nih.gov

Suresh I. S. Rattan Laboratory of Cellular Aging, Department of Molecular Biology, University of Aarhus, DK 8000 Aarhus C, Denmark, rattan@mb.au.dk

Dino Demirovic Laboratory of Cellular Aging, Department of Molecular Biology, University of Aarhus, DK8000 Aarhus C, Denmark, rattan@mb.au.dk