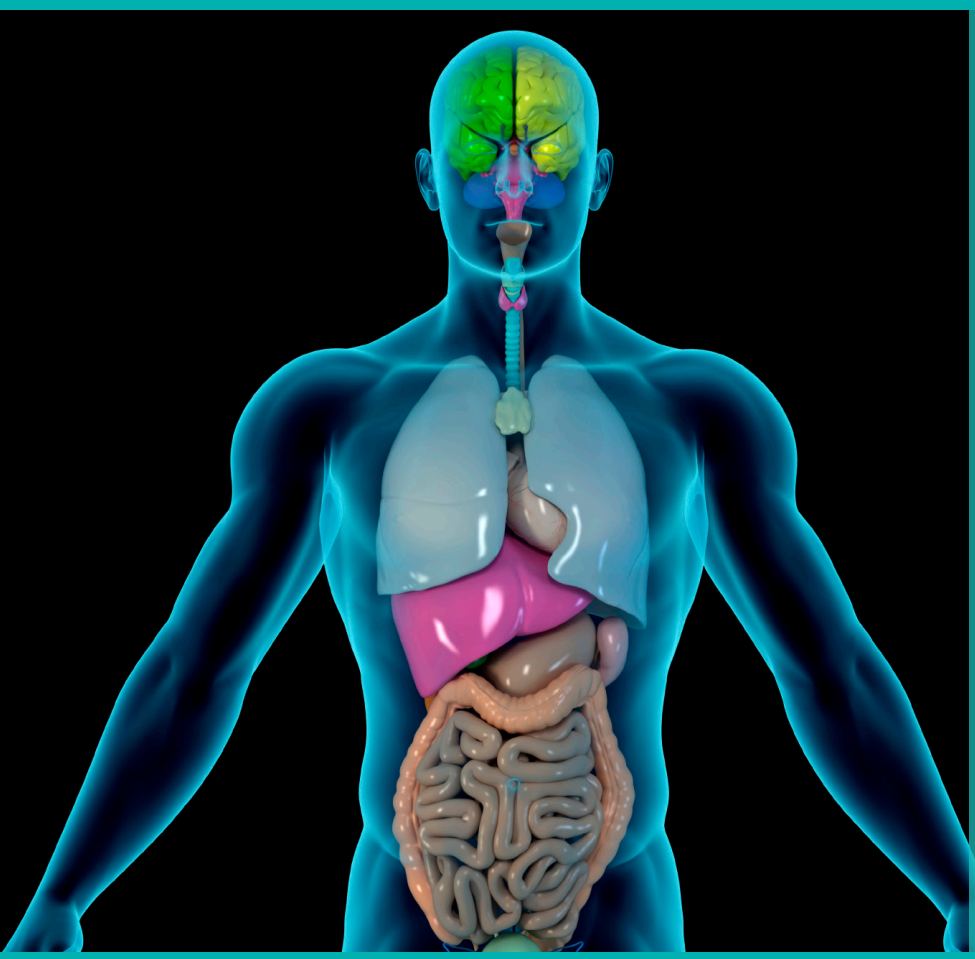
METABOLIC SYNDROME AND NEUROLOGICAL DISORDERS

Edited by
Tahira Farooqui and Akhlaq A. Farooqui



Heart Disease

Dementia

Stroke

Metabolic Syndrome

Alzheimer Disease

Depression

Parkinson Disease

WILEY Blackwell

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Editorial offices: 2121 State Avenue, Ames, Iowa 50014-8300, USA
The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK
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Dedicated to our late parents
For their unconditional love, support and understanding.

"Every human being is the author of his own health or disease."

Siddhārtha Gautama Buddha

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FOREWORD

Metabolic syndrome (MetS) is a pathologic state that most often results from a chronic positive energy balance due to an excessive energy intake (particularly refined sugars and saturated and trans fats) and a sedentary lifestyle. The defining clinical features of MetS are insulin resistance, central obesity, dyslipidemia, and hypertension. It was established several decades ago that MetS is prodromal to diabetes and that individuals with MetS have a high risk of myocardial infarction and stroke. However, within the past ten years it has become clear that MetS adversely affects brain structure and function and is a risk factor for Alzheimer disease (AD) and stroke. In *Metabolic Syndrome and Neurological Disorders* Tahira and Akhlaq Farooqui have drawn upon the knowledge of experts in the fields of neuroscience, neurology, endocrinology, cardiovascular disease, obesity, and diabetes to compile a timely review of the impact of MetS on the brain and its vulnerability to neurological disorders. This is a critically important area of research for four major reasons: (1) there is an ongoing epidemic of overweight, obesity, and MetS in modern societies; (2) due to advances in the early diagnosis and treatment of cancers and cardiovascular disease, large numbers of individuals are reaching their seventh, eighth, and ninth decades of life, the "danger zones" for AD and stroke; (3) there are no effective drugs to counteract the neuronal damage that occurs in AD and stroke; and (4) AD patients and stroke patients often require a decade or more of constant care, and therefore place a greater personal and economic burden on society than many other major diseases. Although less profound, emerging evidence also suggests that, in addition to AD and stroke, the MetS may predispose to a broader range of neurological disorders including Parkinson disease, depression, and possibly schizophrenia.

Because of its adverse effects on essentially all organ systems including the brain, an understanding of the molecular and cellular alterations that cause the MetS, and the mechanisms by which the MetS promotes dysfunction and degeneration of brain cells, will be required to develop novel approaches for preventing and treating MS and associated diseases. As detailed in *Metabolic Syndrome and Neurological Disorders*, alterations resulting from a chronic positive energy balance that are involved in the genesis of the MetS include oxidative stress and inflammation and associated dysregulation of lipid (sphingolipids, cholesterol, and others) metabolism. As a result, signaling pathways that normally protect brain cells and promote their optimal functionality are impaired, including pathways activated by the hormones insulin, leptin, adiponectin, and brain-derived neurotrophic factor (BDNF). In addition, oxidative stress, inflammation, and abnormal lipid metabolism

can increase the production and/or reduce the removal of the neurotoxic amyloid beta-peptide, which likely contributes to the dysfunction and degeneration of neurons in AD. With regards to the pathogenesis of stroke, hypertension, dyslipidemia, and local oxidative stress and inflammation in cerebral blood vessels result in a narrowing and weakening of the vessels.

The good news for those with motivation is that the MetS can be effectively prevented and treated by adherence to prescriptions for exercise and dietary energy restriction. Exercise and energy restriction (particularly intermittent fasting) can prevent or reverse MetS by enhancing insulin sensitivity, increasing utilization of fats, stimulating antioxidant and anti-inflammatory pathways, and enhancing parasympathetic tone, which decreases blood pressure. Recent findings from animal research, and epidemiological and clinical studies, suggest that AD and stroke may also be prevented or delayed by regular exercise and moderation in energy intake during adult life. In addition to protecting the brain by reversing all of the peripheral manifestations of the MetS, exercise and energy restriction have been shown to have direct effects on brain cells that optimize brain function and may forestall AD and stroke. These include increased production of neurotrophic factors, improved cellular bioenergetics, and reduced oxidative stress.

For those unwilling or unable to exercise regularly and restrict their calorie intake so as to maintain a normal body weight *Metabolic Syndrome and Neurological Disorders* reviews potential dietary and drug interventions that are being developed and tested in clinical studies. As with research toward understanding disease mechanisms, translational research for MetS and neurodegenerative disorders is accelerated by the use of animal models. Studies of animal models of AD and stroke have demonstrated beneficial effects of insulin, leptin, incretin peptides such as glucagon-like peptide 1 analogs, and PPAR-γ agonists that are insulin-sensitizing agents such as metformin and rosiglitazone. Many of these drugs are now in clinical trials in patients with mild cognitive impairment or early AD. Targeting lipid metabolism is also being pursued via studies of dietary supplementation with omega-3 fatty acids or the use of cholesterol-lowering drugs. Other approaches that might prove beneficial for protecting the brain in subjects with MetS include drugs that suppress appetite, such as cannabinoid receptor antagonists. This book will provide a valuable resource to guide future research projects to disentangle the complex cellular and molecular underpinnings of MetS-related neuropathologies, and to thereby inform the development of novel therapeutic interventions for neurological disorders.

MARK P. MATTSON

National Institute on Aging
Intramural Research Program
Baltimore, MD

PREFACE

At the end of 2011, the United Nations declared for the first time in the history of humanity that non-communicable diseases had outpaced infectious diseases as the main global threat to human health. Among non-communicable diseases, metabolic syndrome (MetS), cardiovascular diseases, and Alzheimer disease (AD) are of paramount importance. MetS is a condition characterized by clustering of insulin resistance, hyperinsulinemia, hypertension, dyslipidemia, impaired glucose disposal, type 2 diabetes, abnormal blood fat levels, fatty liver disease, and abdominal obesity. Changes in human dietary habits in recent decades have led to the consumption of hypercaloric diets that are rich in saturated fats and simple sugars (sucrose, glucose, and fructose). The MetS is a highly prevalent pathological condition that affects a considerate number of adult humans. Approximately one-fourth of European, American, and Canadian adults suffer from MetS. Clustering of insulin resistance, hyperinsulinemia, hypertension, dyslipidemia, impaired glucose disposal, type 2 diabetes, and abdominal obesity reflects overnutrition, sedentary lifestyles, physical inactivity, and resultant excess adiposity. At the molecular level, MetS is accompanied not only by dysregulation in the expression of adipocytokines and chemokines, but also by increase in levels of lipids and lipid mediators (free fatty acids, di- and triacylglycerols, and ceramide). These changes modulate immune response and inflammation that lead to alterations in the hypothalamic body-weight/appetite/satiety set point, resulting in the initiation and development of MetS.

MetS is a risk factor for neurological disorders such as stroke, depression, and AD. The molecular mechanism underlying the relationship between MetS and neurological disorders is not fully understood. However, major mechanisms through which MetS may influence stroke, AD, and depression include insulin resistance, impairment in insulin receptor, and insulin growth factor signaling, glucose toxicity, elevated levels of phospholipid-, sphingolipid-, and cholesterol-derived lipid mediators, generation of advanced glycation endproducts, activation of receptor for advanced glycation endproducts, cerebrovascular injury, and vascular inflammation that may represent a pathological bridge between MetS and neurological disorders such as stroke, AD, and depression.

Information on molecular links between MetS and neurological disorders is scattered throughout the literature mainly in the form of original papers and some reviews. Although, many books are published on biochemistry of MetS and neurological disorders separately, at present there are no books on the relationship between MetS and neurological disorders.