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Patrick L. Kerr
Cristian Sirbu
John M. Gregg *Editors*

Endogenous Opioids

From Basic Science to Biopsychosocial Applications

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covers basic research in neurobiology and neurochemistry. It provides in-depth, book-length treatment of some of the most important topics in neuroscience including molecular and pharmacological aspects. The main audiences of the series are basic science researchers and graduate students as well as clinicians including neuroscientists (neurobiologists and neurochemists) and neurologists. *Advances in Neurobiology* is indexed in PubMed, Google Scholar, and the Thompson Reuters Book Citation Index.

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Editors
Patrick L. Kerr
West Virginia University School of Medicine-Charleston
Charleston, WV, USA

Cristian Sirbu
Center for Cancer Research
Charleston Area Medical Center
Charleston, WV, USA

John M. Gregg
Department of Surgery
VTCSOM
Blacksburg, VA, USA

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PLK
This work is dedicated…
To my wife, Kim, and our children, Jackson and Ella, who have supported my work on this book every way throughout this journey. I am eternally grateful for your love and support.
To my mom and dad, who have supported me at every step of my journey, professionally and personally.
To the memory of my sister, Sarah, who was taken from this world far too soon during the completion of this work. May the knowledge and wisdom in this book somehow prevent more lives from being lost in the same way.

JMG
Dedicated to my loving, talented and globally extended family.

CS
Dedicated to my family.

Preface

A new era and significant hope for opioid research started in 1973 with the discovery of opiates brain binding sites, identification of multiple opioid receptors, and soon after the identification and cloning of endogenous ligands binding to these receptors. For the first time after millennia of opiate compounds oscillation between glorification and demise, the scientific community was able to shed light into the complexity of the endogenous opioid system. The 1990s enhanced this promise, with two important developments: the cloning of canonical opioid receptors and the development of genetic animal models allowing the identification of their specific functional roles. A decade into the twenty-first century, the crystal structure of the opioid receptors in inactive and active forms was deciphered, and, for the first time, the scientific community is hopeful that the "holy grail" of identifying an opioid compound with morphine potency and no tolerance, emotional side effects, or respiratory depression is within reach. In an era of unprecedented public health challenges from the COVID-19 pandemic, which has only compounded the existing opioid crisis, there is an urgency for translating the massive volume of knowledge about the endogenous opioid system into lifesaving interventions.

This book (*Endogenous Opioids: From Basic Science to Biopsychosocial Applications*) is motivated by this urgency and the desire of our contributors to close the loop between the exciting basic science findings and much needed clinical applications. Our volume takes a decidedly unique trajectory to synthesize basic science, behavioral science, and social science related to endogenous opioids into a unified and useful whole. We have diligently undertaken our mandate to present an integrated "biopsychosocial" model, as our title denotes.

In the space between the basic and translational science of endogenous opioids are adjacent spaces occupied by behavioral, affective, and social science. Insights about the endogenous opioid as a critical evolutionary survival system with paramount importance in establishing homeostasis when environmental and internal challenges arise provide a glimpse into the complex molecular processes involved. The awareness that endogenous opioids are key players that act as neurotransmitters, neuromodulators, and hormones across the nervous, endocrine, and immunological systems has broad implications for understanding normal physiological

processes involved in stress and pain responses, natural immunity, social bonding, emotions, reward, feeding, reproduction, exercise, or placebo response. In pathological conditions such as cardiovascular disease, metabolic and eating disorders, and cancer, the involvement of endogenous opioid system shapes the progression of the disease and the prospect of a cure. Additionally, challenges arise when the same opioid receptors are exposed to opiates and the delicate balance of the endogenous opioid system is disrupted. Each chapter was written with the desire of synthesizing the basic science findings of the endogenous opioid system and their application to both healthy and pathological physiological processes.

In 2023, we were celebrating five decades of research since the discovery of the endogenous opioid system, and we are highly indebted to the contributions of opioid research giants and internationally renowned laboratories that added critical pieces of knowledge to the field. Prestigious journals (i.e., *Peptides*) publish summaries of endogenous opioid research outlining thousands of studies every year. When we started planning this book, we were aware of the tremendous challenges of reviewing an intimidating body of knowledge, trading across controversial topics and outlining new directions in the field. To our delight, the book contributors brilliantly addressed these challenges, bringing to life novel and exciting chapters that we hope will stimulate new ideas and conversations in the field. In such a large and complex field, we cannot claim that this work is completely comprehensive, nor was that the intention. Instead, the current volume is an attempt at reducing the distance between basic and translational research by outlining the tremendous importance of endogenous opioids across the continuum from normal to pathological processes. We believe that the distance between basic and translational science for endogenous opioids is reduced with the biopsychosocial bridge represented by the diverse yet interrelated chapters in this book.

We are in the midst of an "omics" era. Our knowledge of the molecular aspects of the endogenous opioid system is evolving at light speed. Analytical methods for big data generate hypotheses that were unfathomable just a decade ago. New clinical and scientific tools allow research findings on endogenous opioids to be built upon in unparalleled rapid succession. As we look to the journey ahead of meaningfully applying this knowledge, we hope that basic scientists and clinicians alike will find this book useful in their efforts to build much needed translational bridges.

Charleston, WV, USA — Patrick L. Kerr
Charleston, WV, USA — Cristian Sirbu
Blacksburg, VA, USA — John M. Gregg
May 1, 2023

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About the Editors

Patrick L. Kerr, PhD, completed his Master's and doctoral degrees in clinical psychology at the University of North Dakota. He completed his pre-doctoral internship training at the West Virginia University School of Medicine-Charleston campus and Charleston Area Medical Center. Dr. Kerr is a clinical psychologist, specializing in the treatment of severe psychopathology, suicidality, and traumatic stress. He is currently an Associate Professor in the Department of Behavioral Medicine and Psychiatry at West Virginia University School of Medicine-Charleston. He serves as Director of the WVU Behavioral Science and Psychopathology Research Division, and as Director of the WVU Dialectical Behavior Therapy Services Program.His main lines of research and academic work emphasize common mechanisms of severe psychiatric disorders, emotion regulation, suicide risk, trauma, and the psychobiological mechanisms of psychopathology.

Cristian Sirbu, DDS, PhD, PsyD, is a Clinical Associate Professor at West Virginia University School of Medicine-Charleston campus and Charleston Area Medical Center (CAMC) and a Research Scientist at the CAMC Center for Cancer Research. He completed his dental and psychology doctoral degrees in Romania and a clinical psychology doctoral degree at Marshall University.His scholarly and clinical works are focused on assessment and treatment of anxiety, mood disorders, and chronic pain across multiple populations and the enhancement of psychosocial interventions using pharmacological and technology-based approaches. He is interested in immunological mechanisms of psychopathology and the implementation of patient-reported outcomes in oncology.

John M. Gregg, DDS, MS, PhD, is a retired oral and maxillofacial surgeon and who served in academic positions at multiple institutions during his career. Dr. Gregg's academic career has included appointments as Professor of Surgery at University of North Carolina, Virginia Tech University, and Virginia Commonwealth University. During his academic and professional training, he completed five degrees as well as clinical residency in Oral and Maxillofacial surgery at the University of Michigan. Dr. Gregg's preclinical research was the first to demonstrate

that peripheral injury of rodent trigeminal nerves may produce neuroanatomic pathoses in the transganglionic and central spinal trigeminal complex. He continues his active program of clinical research post-retirement, with an emphasis on mechanisms of neuropathic pain and microsurgical management of trigeminal nerve injuries.

Endogenous Opioids in the Homeostatic Regulation of Hunger, Satiety, and Hedonic Eating: Neurobiological Foundations

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Marcela Rodriguez Flores & Sylvana Stephano Zúñiga

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Abstract

This chapter (part one of a trilogy) summarizes the neurobiological foundations of endogenous opioids in the regulation of energy balance and eating behavior, dysregulation of which translates to maladaptive dietary responses in individuals with obesity and eating disorders, including anorexia, bulimia, and binge eating disorder. Knowledge of these neurobiological foundations is vital to researchers' and clinicians' understanding of pathophysiology as well as the science-based development of multidisciplinary diagnoses and treatments for obesity and eating disorders. We highlight mechanisms of endogenous opioids in both homeostatic and hedonic feeding behavior, review research on the dysregulation of food reward that plays a role in a wide array of obesity and disordered eating, and the clinical implications of neurobiological responses to food for current science-based treatments for obesity and eating disorders.