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

# Endogenous Opioids

## From Basic Science to Biopsychosocial Applications

Springer

# Advances in Neurobiology
Volume 35

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Editors

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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.

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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.

# Introduction to the Volume: The Journey Ahead


**Patrick L. Kerr, John M. Gregg, and Cristian Sirbu**

**Abstract** The endogenous opioid system (EOS) is complex. The line of research contributing to our current body of knowledge about this system is diverse, as are the ways in which endogenous opioids affect human health and behavior. This chapter serves as an introduction to the edited volume. It includes commentary about the current public discourse related to opioids, the rationale for this book, and the unique contributions of each chapter within this volume.

**Keywords** Endogenous opioids · Opioid research

## The Present Moment

Between 2020 and 2022, the world changed in fundamental ways. The SARS-CoV-2 pandemic and its resulting illness (COVID-19) reshaped nearly every aspect of human life globally in some way. Along the way, COVID-19 became a leading cause of death, and a resulting drop in years of life expectancy was attributed to it. COVID-19 also complicated other leading causes of death that had been increasing; most notably, and relevant to this volume, deaths that were attributable to opioid poisoning or "overdose". While COVID-19 reached the rank of third leading cause of death for 2021, it was followed closely by unintentional injuries as the fourth leading cause of death (Ahmad et al., 2022). Ahmad noted about these data that "Unintentional injury deaths were largely driven by drug overdose deaths, and likely contributed to the increased death rate in younger populations." (p. 600). As

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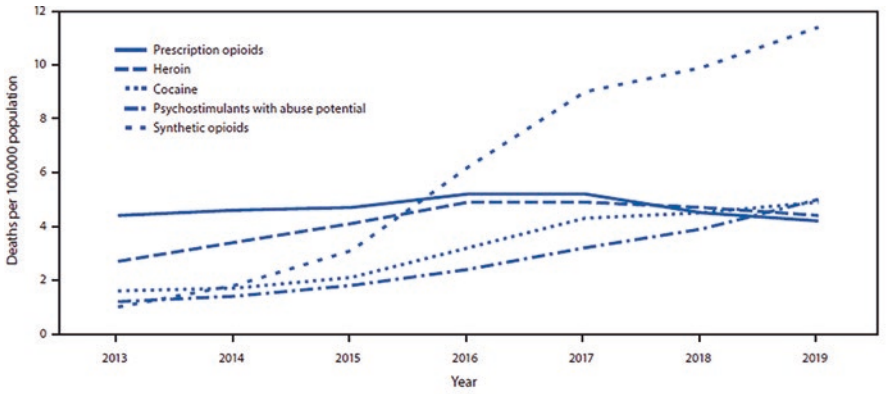



**Source:** National Vital Statistics System, Mortality File. https://wonder.cdc.gov/

* Rate per 100,000 population age-adjusted to the 2000 U.S. standard population using the vintage year population of the data year.

† Deaths were classified using the *International Classification of Diseases, Tenth Revision*. Drug overdoses are identified using underlying cause-of-death codes X40–X44 (unintentional), X60–X64 (suicide), X85 (homicide), and Y10–Y14 (undetermined).

§ Drug overdose deaths, as defined, that involve natural and semisynthetic opioids (T40.2) or methadone (T40.3).

¶ Drug overdose deaths, as defined, that involve heroin (T40.1).

** Drug overdose deaths, as defined, that involve cocaine (T40.5).

†† Drug overdose deaths, as defined, that involve psychostimulants with abuse potential (T43.6).

§§ Drug overdose deaths, as defined, that involve synthetic opioids other than methadone (T40.4).

¶¶ Because deaths might involve more than one drug, some deaths are included in more than one category. In 2019, 6.3% of drug overdose deaths did not include information on the specific type of drug(s) involved.

**Fig. 1** Age-adjusted rates* of drug overdose deaths† involving prescription opioids, §heroin, ¶cocaine, **psychostimulants with abuse potential,†† and synthetic opioids other than methadone§§,¶¶—United States, 2013–2019. (Adapted from Mattson et al. (2021))

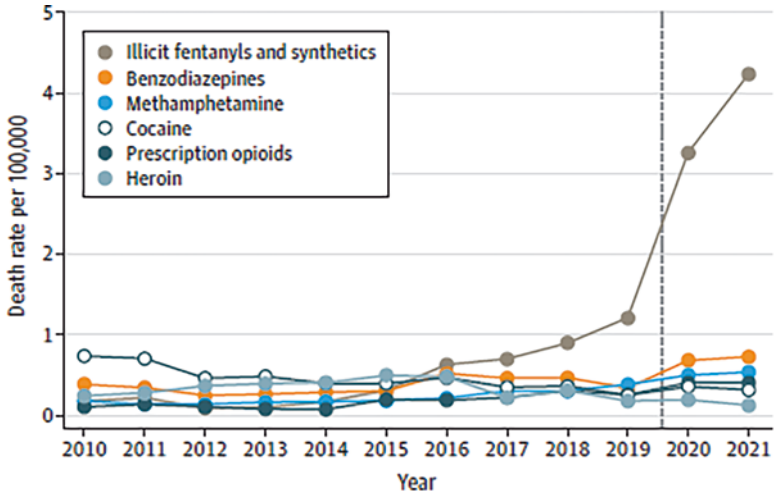
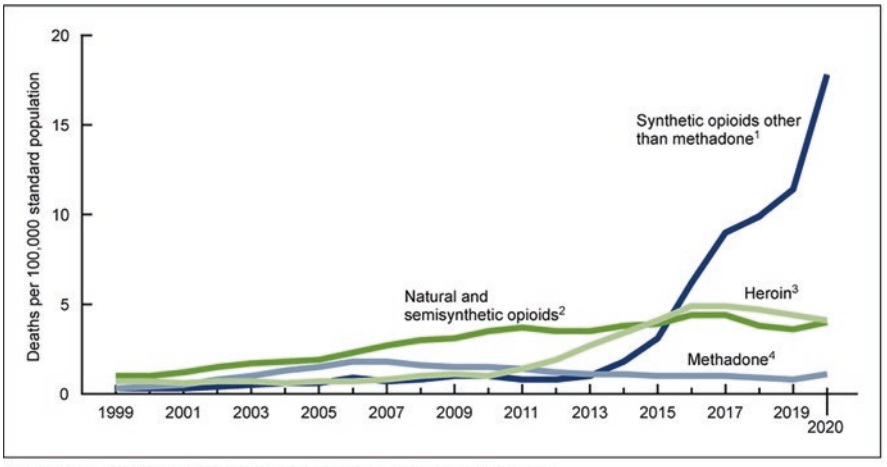



**Fig. 2** Adolescent overdose deaths, 2010–2021: Overdose mortality among adolescents by substance type. (Adapted from Friedman et al. (2022))

the data in Figs. 1 and 2 make clear, the majority of these drug poisoning deaths in both adults and adolescents were driven by opioids and increasingly by a sharp rise in the availability of synthetic opioids (Friedman et al., 2022; Mattson et al., 2021).

However, these data do not reflect a new phenomenon. In November 2018, data from the US Centers for Disease Control and Prevention (Murphy et al., 2018) reported two alarming data points: that life expectancy in the United States decreased between 2016 and 2017; and that drug overdose deaths were a significant contributing factor to this. Moreover, overdose deaths from synthetic opioids, which increased by 45% in that time period, appear to be leading this trend. Since that initial report, the trend has continued and has only been exacerbated by the COVID-19 pandemic (Hedegaard et al., 2021; see Fig. 3). Nearly 4 years later in 2022, the CDC (2022) reported further declines in life expectancy from 2020 (77.4 years) to 2021 (76.4 years), with approximately one in six deaths attributable to accidental/unintentional injuries, and at least half of those deaths attributable to unintentional drug poisonings (i.e., "overdoses"). It is possible that the intersecting pandemics of the COVID-19 pandemic and unrelenting rates of opioid use disorder will constitute one of the most deadly syndemics in human history. Only time and data will tell.

These reports, along with the panoply of media coverage they have spawned, have painted a stark picture of the ways in which opioids have wreaked havoc on human lives. However, missing from these reports and the media descriptions of them is any discussion of two fundamental questions: Why? and How? These questions necessitate science and not speculation.




[1]Significant increasing trend from 1999 through 2020, with different rates of change over time, $p < 0.05$.
[2]Significant increasing trend from 1999 to 2010, and stable trend from 2010 through 2020, $p < 0.05$.
[3]Significant increasing trend from 2005 to 2016, with different rates of change over time, and significant decreasing trend from 2016 through 2020, $p < 0.05$.
[4]Significant increasing trend from 1999 to 2006, with different rates of change over time, significant decreasing trend from 2006 through 2017, and stable trend from 2017 through 2020, $p < 0.05$.
NOTES: Drug overdose deaths are identified using the *International Classification of Diseases, 10th Revision* (ICD–10) underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Drug overdose deaths involving selected drug categories are identified by specific multiple-cause-of-death codes: any opioid, T40.0–T40.4 and T40.6; heroin, T40.1; natural and semisynthetic opioids, T40.2; methadone, T40.3; and synthetic opioids other than methadone, T40.4. Deaths involving more than one opioid category (such as a death involving both methadone and a natural or semisynthetic opioid) are counted in both categories. The percentage of drug overdose deaths that identified the specific drugs involved varied by year, ranging from 75%–79% from 1999 through 2013 and increasing from 81% in 2014 to 94% in 2020. Access data table for Figure 4 at: https://www.cdc.gov/nchs/data/databriefs/db428-tables.pdf#4.
SOURCE: National Center for Health Statistics, National Vital Statistics System, Mortality.

**Fig. 3** Age-adjusted drug overdose death rates involving opioids, by type of opioid: United States, 1999–2020. (Adapted from Hedegaard et al. (2021))

## Endogenous Opioids: The Journey Ahead

Our goal in developing this book is to provide a thoughtful and scientifically based exploration of the multifaceted world of opioids, with a distinct emphasis on endogenous opioids, e.g., endorphins, enkephalins, and dynorphins. At the time of this writing, the term "opioid" has achieved household name status, commonly connected to the phrases "opioid epidemic" or "opioid crisis". Data from Google Trends alone suggest a five- to ten-fold increase in interest based on search patterns worldwide over the past decade. There is no shortage of interest in this topic. With the most recent data from CDC described above, there is likely to be enduring interest for some time.

Despite this increase in interest, the general public's understanding of opioids, and especially endogenous opioids, has not kept pace. There are understandable reasons for this. References to opioids, especially in popular culture, often focus on medications (e.g., hydrocodone) or substances to which people become addicted (e.g., heroin), which are exogenous opioids. Rarely is there any discussion of what happens when those molecules interact with the body. Moreover, there is even less consideration of the innate opioids naturally produced by the body—the native system engaged by exogenous opioids. It is impossible to explain or understand one without the other; yet, attempts to do so happen all too often. Failing to consider the dynamic nature of opioids, "inside and out," so to speak, can have alarming consequences at the regulatory, policy, societal, and community levels, all of which can lead to devastating consequences at the individual level. Consider misguided regulation that results from a misunderstanding of the science of opioid use disorder or drug policy based more on subjective moral reasoning than scientific reasoning, e.g., the blockade or outlawing harm reduction programs. Consider community investment in prevention and intervention programs that "should" work based on a misunderstanding of the underpinnings of opioids and opioid use disorder. As the data above indicate, any obstacles to effective intervention can cost lives.

At the same time, there are health conditions, from eating disorders, to breast cancer, to depression, to obesity, in which opioids play a role, but are often not considered—either in clinical treatment or clinical research. There are places in the system of healthcare services in which endogenous opioids play a role through placebo (and nocebo) effects, but to which are rarely if ever attended. Debates about the rising increase in Cesarean sections and increasing reliance on induction of labor in childbirth abound, yet rarely are the important roles of endogenous opioids mentioned. Managing pain, especially chronic pain, is a common corollary discussion of the "opioid crisis," yet the discussion of what actually happens in the body of someone with chronic pain being managed with exogenous opioids is nearly absent. In sum, the discussion of endogenous opioids is a boat we are missing across many territories.

This book is aimed at starting the conversations we should be having about opioids. We have conceptualized the range of this book to be from basic science to clinical applications, realizing that there cannot be one without the other. The

research literature on the basic science of opioids—their structure, their metabolism, their physiological transactions—is fascinating in its own right; it is even more compelling when considered in the context of human interactions and clinical interventions. Throughout the chapters of this book, our contributors have interwoven discussions of these basic components of endogenous opioids in their respective topics.

Neither opioids nor opioid research is new in any sense. Opioids were discovered, and quickly put to use, millennia ago. We have had an understanding of the effects of opioids for centuries, which has shaped human history in fascinating ways. Indeed, across several eras and generations of human progenitors, opioids have contributed to cross-cultural relationships, the establishment of intercontinental trade routes, warfare, revolutions in pain management, and, more recently, public health crises and epidemics.

What is new is our nuanced understanding of why and how opioids yield their effects vis-à-vis endogenous opioid activity. The historical emphasis on exogenous opioids and opiates has led to an almost complete neglect of endogenous opioids. This neglect is problematic in that, by ignoring what is happening in the brain and body, efforts to reduce the adverse effects of exogenous opioids (whether at the public health, legislative, public policy, or intervention levels) have been ill-informed and myopic. Opioids are a two-sided coin, and both sides must be given equal weight. However, the relationship between these two sides is of paramount importance, as it portends an opportunity for translational science. The distinct bias in media, entertainment, and even in research toward exogeny overlooks the dynamic roles that opioids play in human lives. Those roles have a broad range: from how we respond biologically to falling in love, to how we respond physiologically to falling down; from how we develop substance use disorders, to how we could optimize treatments; from how we manage depression through engaging in exercise, to how we engage with others in helpful ways; from the pain we experience from fear, to fear we experience from pain. Endogenous opioids are ubiquitous and are part of what makes humans human. We believe that the chapters within this volume reflect long-missing pieces of the dialogue about opioids.

## *Why the Road Turns: Reasons the Research Focus Has Changed Over Time*

There are understandable reasons that research on endogenous opioids has languished, and that potentially productive lines of research have turned to other targets. Most notably, endogenous opioids are difficult to study with reliability and precision. While improved technology has made headway in this direction, the rapid catabolism of endogenous opioid molecules has historically made them difficult to locate and image. They are perhaps the “yeti” of neurophysiology, albeit with far more empirical evidence for their existence. Scientific investigations of endogenous

opioids require technological capability, resources, and persistence, all of which may prove difficult to allocate during an era in which funders often emphasize short-term return on investments. Thus, scientific efforts have turned to other biological targets that are ostensibly lower hanging fruit.

Fortunately, research on endogenous opioids has persisted. However, examination of the recent history of endogenous opioid research reveals that studies of this system have been distributed across subgenres of science, and that findings were largely "siloed" for decades. Nonetheless, there is clear evidence of an interest in endogenous opioid research across disciplines. Such evidence derives from the range of journals and scientific disciplines represented in the endogenous opioid literature as a whole. The datasets in different disciplines are disparate and disconnected, which is a disservice to the applied value that integrating these lines of research would have. This book is aimed at breaking down those siloes, and each of our authors has contributed to this mission by integrating literature reviews, or presenting translational science approaches, within their respective chapters.

## *A Synthesis of Parallel Paths*

This volume represents an effort to develop a cross-disciplinary lens on a transsystemic phenomenon. Our chapter contributors extend scientific branches to the edges of what is known about endogenous opioids, while at times proposing innovative next steps to advance our knowledge base. We have conceptualized this work as a synthesis of parallel paths. Each line of research is distinct in focus, methodology, and applicability. However, all share a common purpose—advancement of the human condition through an understanding of endogenous opioids. In the last two centuries, opioids have traversed from causes of warfare to sources of human welfare. This is an encouraging metamorphosis indeed.

No single field has produced all the data on endogenous opioids; all the data there are come from nearly all of biological science. In science, there is strength in unity: strength to replicate findings, strength to translate findings into applications, and strength to test translational applications of basic science. From its inception, this volume has been aimed at strengthening this field of research to make the thousands of papers that have been published on the endogenous opioid system as meaningful and impactful as possible. One volume cannot accomplish all the unification that is needed, but we saw importance in taking this necessary step toward doing so.

## *Organization and Structure of the Volume*

*Endogenous Opioids: From Basic Science to Biopsychosocial Applications* spans three broad themes, which are interwoven throughout the book: the roles of endogenous opioids in health-related functioning; the roles of endogenous opioids in

pathology; and clinical applications and interventions of endogenous opioid science. Across the themes within this book, the authors provide thorough syntheses of research demonstrating the many ways in which endogenous opioids serve as vehicles for preservation of health. Our volume launches with a flagship chapter on neurobiology by Tache and colleagues, providing an extensive exploration of the molecular structure of endogenous opioid peptides, and their multitude of receptor types. The chapter by Barenz and colleagues outlines the role that endogenous opioids have in facilitating pleasant emotional states, which are critical to human functioning and health. Rusu describes a creative model that places endogenous opioids at the heart of altruistic behaviors associated with volunteering. Capitalizing on cardiovascular research, Dr. Cristina Sirbu describes the cardioprotective effects of endogenous opioids. Dr. Alan Goldfarb and colleagues make an empirically sound case for the involvement of endogenous opioids, and especially endorphins, in hypoalgesia associated with physical exercise. The chapter by Felicione and colleagues explores the role of endogenous opioids in pain and fear conditioning. Spanning the full range of pleasure to pain, Marjan Khajehei galvanizes a new lens on reproductive health in her review of the involvement of endorphins in childbirth and sexual functioning.

Some chapters address endogenous opioids with a more pathocentric focus, with chapters identifying opioid-related mechanisms involved in pathology. Dr. Lindsay Acree makes an impactful contribution to this discussion by describing the molecular intricacies of opioid use disorder. Sessle's chapter on craniofacial pain places endogenous opioids on the proverbial hook and in the hotseat for evaluation of their contributions. Chapters by Flores, Stephano, and Albu turn the lens on endogenous opioids as prime biological suspects in disordered eating.

Our book also shines a hopeful light on the contributions endogenous opioids make to alleviating suffering. The contribution by Pettrey and colleagues updates our current knowledge base about the endogenous opioids as a mechanism through which exercise may alleviate depression. A far-reaching explanation of placebo and nocebo effects is presented in the chapter by Kerr and Gregg, elucidating the ways in which these well-established effects could be harnessed. Dr. David Nguyen's chapter poses thoughtful questions about how the body's own defenses can be weaponized against breast cancer and proposes several novel experiments that would clearly advance our ability to capitalize on these processes to save lives. The chapter by Hancock and colleagues bookends Dr. Nguyen's chapter, offering a model of endogenous opioids' contribution to recovery from breast cancer, and diving deeply into a different yet complementary dimension of the breast cancer literature. Finally, Dr. Karin Westlund-High and her team describe their preclinical research examining enkephalin as an intervention for temporomandibular joint pain, with encouraging preliminary findings.

For now, we turn to the journey ahead, and we begin down the winding road through research past, present, and planned.

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# The Foundational Science of Endogenous Opioids and Their Receptors


**Simona Tache, Patrick L. Kerr, and Cristian Sirbu**

**Abstract** The function of endogenous opioids spans from initiating behaviors that are critical for survival, to responding to rapidly changing environmental conditions. A network of interconnected systems throughout the body characterizes the endogenous opioid system (EOS). EOS receptors for beta-endorphin, enkephalin, dynorphin, and endomorphin underpin the diverse functions of the EOS across biological systems. This chapter presents a succinct yet comprehensive summary of the structure of the EOS, EOS receptors, and their relationship to other biological systems.

**Keywords** Endogenous opioids · Systems · Peptides · Beta endorphins · Dynorphins · Enkephalin

## Introduction

Opioids were in use long before they were understood, and opioid receptors were being engaged by exogenous opioids far prior to their identification and description in scientific literature. Like many other facets of human history, the history of opioids predates the history of science. For millennia, human societies used morphine (derived from poppy plants, or mixed in tinctures of paregoric, theriaca, and others) to treat ailments such as pain or diarrhea, as well as to induce pleasure. It would take

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hundreds of years, and the development of the scientific method, before the molecule responsible for these ostensibly miraculous effects would be isolated in the early nineteenth century through work by Friedrich Sertuner (Krishnamurthi & Rao, 2016) and by Derosne (1803). Belying the most nascent conceptualization of this discovery, Derosne (1803) originally referred to morphine as "the salt of opium." Another century would pass before the molecular structure of morphine was characterized in the early 1920s by the Nobel laureate chemist Robert Robinson and his research group (Cahn & Robinson, 1926).

A full account of the history of endogenous opioids research is beyond the scope of this chapter, but is summarized in Fig. 1 by Benyhe et al. (2015). Endogenous opioids were first discovered in the mid-1970s, when opioid receptors were discovered and located within the central nervous system and the peripheral tissue. As depicted by Benyhe et al. (2015), progress in identifying and then understanding endogenous opioids, their receptors, their functions, and their structure, has been gradual. This scientific work has been punctuated by occasional breakthroughs and

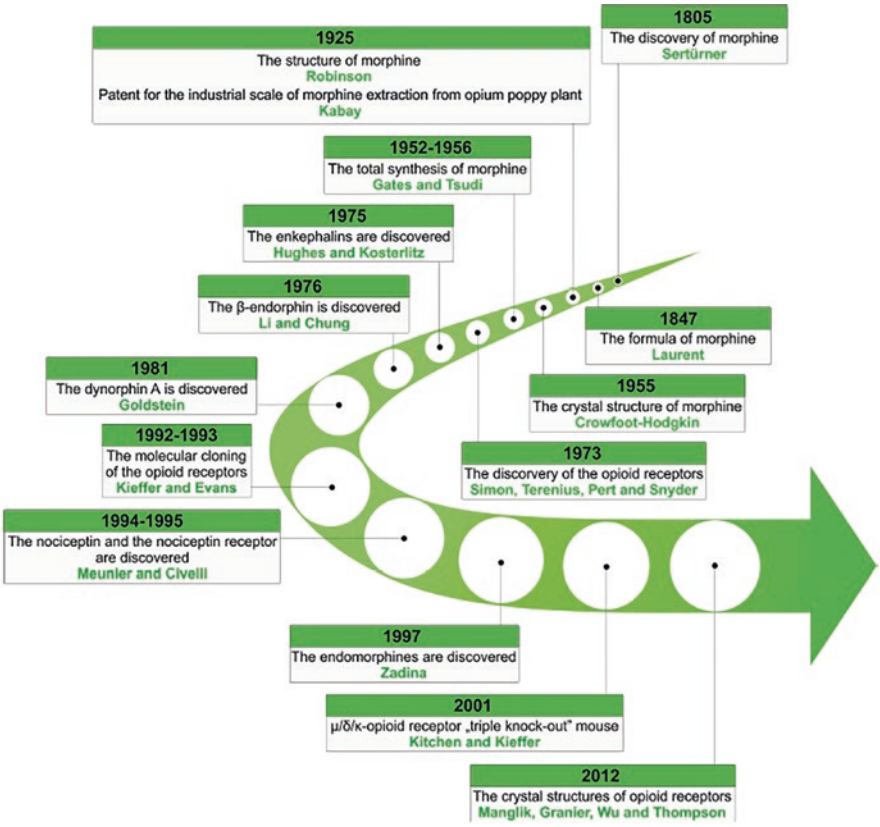


Figure 1. Milestones in morphine and opioid research.

**Fig. 1** Milestones in morphine and opioid research. (Adapted from Benyhe et al. (2015))

discoveries. It is worth noting that morphine itself represented a significant discovery in the field of organic chemistry—it was the first alkaloid ever identified.

Together, over centuries of research, the aforementioned work has laid the foundation for this chapter. The goal of this chapter is not to explicate all of the myriad nuances, debates, and controversies of this line of scientific research; some of these are addressed in subsequent chapters in this volume. For a more thorough catalogue of such nuances, the reader is directed to the most recent series edition on opioids and behavior by Bodnar (2022), as well as to the references for the contemporary and historical work by prior researchers noted in the introduction to this book. Conversely, our aim in this chapter is to straightforwardly describe the present state of knowledge regarding the structures, functions, and interactions of endogenous opioids and their receptors.

## Basic Scientific Foundations of Endogenous Opioids

### *Foundations 1: Nomenclature, Terminology, and Typology*

At the outset of this chapter, some basic terminology must be established. First, although often erroneously used interchangeably, *opioids* and *opiates* are different. The term *opioid* (which includes the suffix –oid, meaning resembling or like) refers to any chemical (natural, semisynthetic, or fully synthetic) that engages opioid receptors in the body and brain, and which attenuates or eliminates pain signals. The related term *opiate* (with the suffix –ate meaning to act on in a specific way), refers specifically and exclusively to naturally occurring opioids, e.g., morphine, heroin, and codeine. Thus, opioids include natural, exogenous substances such as opium, morphine and codeine; synthetic and semisynthetic substances; and natural endogenous substances.

In the nearly five decades since the discovery of the first endogenous opioids in the mid-1970s, researchers have made significant progress in identifying a full range of EOS molecules and receptors. The currently known endogenous opioids include: β-endorphin, enkephalin, dynorphin, and endomorphin. An additional "orphan" peptide (nociception/Orphanin) was also identified relatively recently; because of its actions, it is sometimes conceptualized as an "antiopioid" (Cox et al., 2015). See Tables 1, 2, 3, 4 and 5.

#### Enkephalins

Enkephalins (derived from the Greek word *enkephalos,* or "brain") are smaller peptides involved in the regulation of analgesia in the body. Two types of enkephalins have been identified in the human body. These are the pentapeptides methionine [met-]enkephalin and leucine [leu-]enkephalin). Met-enkephalins are endogenous

**Table 1** Main location of opioid peptides

| Opioid peptides | Distribution |
|---|---|
| Enkephalins | Brain: hypothalamus, brain stem, periaqueductal gray<br>Spinal cord: substantia gelatinosa<br>Nerve endings in the gastrointestinal tract and carotid body<br>Retina |
| β-Endorphine | Brain: hypothalamus, thalamus, brain stem (nucleus of solitary tract)<br>Pituitary gland<br>Gastrointestinal tract<br>Lung, placenta, retina |
| Dynorphins | Brain: hypothalamus, periaqueductal gray, rostroventral medulla<br>Spinal cord: substantia gelatinosa<br>Posterior pituitary gland (Dynorphin 1–8)<br>Duodenum (Dynorphin 1–17) |
| Endomorphins | Brain: cortex, amygdale, thalamus, hypothalamus, striatum<br>Brain stem (nucleus accumbens, nucleus of solitary tract)<br>Spinal cord<br>Dorsal root ganglia<br>Histaminergic neurons |

opioid pentapeptides, a type of neurotransmitter found naturally in the brain, with molecular formula $C_{27}H_{35}N_5O_7S$. Leu-enkephalins are endogenous opioids pentapeptides, with molecular formula $C_{26}H_{17}N_5O_{7.}$ These peptides are synthesized as part of larger precursor molecules (discussed below) called proenkephalin (PENK). PENK was first identified decades ago in the adrenal medulla (Birch & Christie, 1986; Quach et al., 1984). Each PENK molecule contains four met-enkephalins, one leu-enkephalin, one octapeptide, and one heptapeptide.

In addition to CNS and PNS distribution noted in subsequent sections of this chapter, PENK expression has been found in various tissues in humans. These include heart, smooth and skeletal muscle, kidney and intestinal tissues. Enkephalins are metabolized primarily by two peptidases. The first is enkephalinase A, which splits the Gly-Phe bond. The second is enkephalinase B, which splits the Gly-Gly bond. Aminopeptidase splits the Tyr-Gly bond and contributes to their metabolism. From PENK are synthesized other potent opioid peptides, such as peptide E,F and BAM P 22,20,12, and nonopioid peptides such as synenkephalin, peptide I, and peptide B are also described (Rossier, 1993).

Both the mechanisms of action and the functional roles of enkephalins are diverse. Enkephalins act through both MOPs and DOPs. Through these pathways, enkephalins serve a variety of functions. These include functioning as neurotransmitters in the brain, pain regulation and modulation, cardiac and respiratory functions, immunological functions, ischemic tolerance (e.g., myocardial ischemia and/or angina), mediating the effects of alcohol**,** and altering emotional responses. Thus, the ways in which enkephalin activity affects the brain, body, behavior, emotion, and cognition goes well beyond the concept of pain that may most immediately come to mind when one thinks of endogenous opioids.

**Table 2** Opioid peptides, their precursors and location, and structures

| Opioid peptides | Precursor | Location | Structures |
|---|---|---|---|
| Met-enkephalin | Proenkephalin (PENK) | Adrenal medulla Brain | Tyr-Gly-Gly-Phe-$Met_5$ |
| Leu-enkephalin | | | Tyr-Gly-Gly-Phe-$Leu_5$ |
| Octapeptide | | | Tyr-Gly-Gly-Phe-Met-Arg-Gly-$Leu_8$ |
| Heptapeptide | | | Tyr-Gly-Gly-Phe-Met-Arg-$Phe_7$ |
| β Endorphin | Proopiomelanocortin (POMC) | Anterior and intermediate pituitary gland lobes Brain | Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Var-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Val-Lys-Asn-Ala-His-Lys-Lys-Gly-$Glu_{31}$ |
| Dynorphin 1–8 (B) | Prodynorphin (PDYN | Posterior pituitary gland Hypothalamus Duodenum Hypothalamus Gastrointestinal tract Hypothalamus Gastrointestinal tract | Tyr-Gly-Gly-Phe-Leu-Arg-Arg-$Ile_8$ |
| Dynorphin 1–17 (A) | | | Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-$Gln_{17}$ |
| α-Neoendorphin | | | Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro-$Lys_{10}$ |
| β-Neoendorphin | | | Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-$Pro_9$ |
| Endomorphins Endomorphins 1 | Unknown | Brain Upper brainstem | Tyr-Pro-Trp-Phe-$NH_2$ |
| Endomorphin 2 | | Spinal cord Lower brain stem | Tyr-Pro-Phe-Phe-$NH_2$ |

## Endorphins

Endorphins (an English neologism derived from a combination of the words "endogenous" and "morphine") are endogenous opioid polypeptides, composed of 31 amino acids. They are produced in the pituitary gland and in the hypothalamus in vertebrates during stress, strenuous exercise, pain, and orgasm-induced excitement. Four types of endorphins are produced in the human body: alpha (α), beta (β), gamma (γ), and sigma (σ). Each of these has different numbers and types of amino acids in their molecules, ranging from 16 to 31 amino acids in each molecule.

These peptides are synthesized from the precursor molecule proopiomelanocortin (POMC). POMC is a large precursor molecule found in anterior and intermediate lobes of the pituitary gland in the brain. POMC stimulates β-endorphins. β-endorphins are the most powerful endogenous opioid peptides and are found in the neurons of the CNS (hypothalamus, pituitary gland, limbic system) and PNS.

The mechanisms of action for endorphins are generally well-established (McNally & Akil, 2002). Endorphins act through opiate receptors; β endorphins have the highest affinity for $\mu_1$ opioid receptor, a slightly lower affinity for $\mu_2$ and σ opioid receptors, and a low affinity for the $\kappa_1$ opioid receptors.

**Table 3** Opioid receptors location and responses by stimulation

| Receptor | Central nervous system location | Endogenous ligands | Effects produced by stimulation |
|---|---|---|---|
| μ | Brain (laminae III and IV of the cortex, thalamus, periaqueductal gray)<br>Spinal cord (substantia gelatinosa) | Endomorphins<br>B-Endorphin<br>Dynorphins<br>Enkephalins | Supraspinal analgesia<br>Physical dependence<br>Action site of morphine<br>Respiratory depression<br>Euphoria<br>Reduced gastrointestinal motility<br>Meiosis<br>Increased secretion of growth hormone and prolactin |
| κ | Brain (hypothalamus, periaqueductal gray, claustrum)<br>Spinal cord (substantia gelatinosa) | Dynorphin A | Spinal analgesia<br>Sedation<br>Meiosis<br>Inhibition of antidiuretic hormone release and diuresis |
| δ | Brain (pontine nucleus, amygdale, olfactory bulbs, deep cortex) | Enkephalins<br>β-Endorphin<br>Dynorphins | Analgesia<br>Euphoria<br>Physical dependence |

**Table 4** Effector systems coupled through G proteins to opioid receptors

| Receptor type | Effector |
|---|---|
| μ, δ, κ | Inhibit adenylyl cyclase and ↓cAMP |
| μ, δ | Increase $K^+$ conductance |
| Δ | Decrease $Ca^{2+}$ conductance |
| κ | Stimulate $IP_3$ |

Similar to enkephalins, endorphins have diverse roles in health and pathophysiology. First, endorphins act as neurotransmitters in CNS and PNS. Some data indicate they may function protectively to prevent obesity (see Flores & Zuniga, Chap. 18 of this volume), and diabetes, potentially via metabolic control assisting in glucose and lipid homeostasis. Considering the emotional effects of endorphins, as described by Pettrey and colleagues (chapter "Physical Exercise as an Intervention for Depression: Evidence for Efficacy and Mu-Opioid Receptors as a Mechanism of Action", this volume), endorphins may also play a role in mitigating psychiatric diseases, especially depression. As discussed by Felicione and colleagues (chapter "Pain, Fear, Anxiety, and Stress: Relations to the Endogenous Opioid System", this volume), endorphins may downregulate anxiogenic factors. In a similar vein as that observed for enkephalin, and as discussed by Acree (chapter "Endogenous and Exogenous Opioids: Role in Substance Use Disorders", this volume), endorphins may mediate the effects of alcohol and other substances. Endorphins are also involved in the release of many sex hormones, which is discussed in careful detail by Khajehei (chapter "Endorphins, Sexuality, and Reproduction", this volume). As noted early on in research on endorphins, these peptides appear to be involved in immunological functioning (Fischer & Falke, 1984; Panerai & Sacerdote, 1997).

**Table 5** Opioid receptors and their ligands

| Receptor | Endogenous ligands | Selective agonist | Exogenous ligands antagonist | Ligands agonist | Nonselective ligands antagonist |
|---|---|---|---|---|---|
| μ or previous IUPHAR name $OP_3$ IUPHAR name MOP (MOR) | Endorphins Endomorphins | DAMGO Methadone Fentanyl Dermorphin | CTOP | Levorphanol Etorphine | Naloxone Naltrexone B-funaltrexamine |
| κ or kappa previous IUDHAR name $OP_2$ current IUDHAR name KOP(KOR) | Dynorphin A | Spiradoline $U_{50,488}$ | Nor-BNI | Levorphanol Etorphine EKC | Naloxone Naltrexone |
| δ or delta previous IUPHAR: $OP_1$ name current IUPHAR name DOP(DOR) | Enkephalins | DPDPE Deltorphin DSLET | Naltrindole NTB BNTX-7 | Levorphanol Etorphine | Naloxone Naltrexone |

Adapted from Koneru et al. (2009)
*BNTX-7* benzylidenenaltroxone, *EKC* etylketocyclazosine, *NBT* benzofuran ethyl, *Nor-BNI* norbinaltrophimine, *DAMGO* [D-Ala2,MePhe4,Gly(ol)5] enkephalin, *DPDPE* [D-Pen 2,D-Pen 5] enkephalin, *DSLET* O[D-Ser2,Leu5] enkephalin -Thr 6, *CTOP* D-Phe-Cys-Tyr-D-Trp-Orn-Thr-Pen-Thr-$NH_2$, *OP* opioid receptors, *MOR* μ opioid receptors, *KOR* κ opioid receptors, *DOR* δ opioid receptors

Perhaps most well-known of all mechanisms of action and outcomes is that endorphins act as analgesic factors that modulate/regulate pain.

## Dynorphins

Dynorphins are produced in different parts of the brain, including the hypothalamus, hippocampus, midbrain, medulla, and pons. They are also found in the spinal cord. Dynorphins have 13 amino acid length protein. These peptides are synthesized from the precursor prodynorphin (PDYN). Proprotein convertase (PC 2) cleaves PDYN in active peptides: Dynorphin A and Dynorphin B. Dynorphins primarily exert their effects through the KOP receptors, and secondarily through MOP and DOP receptors.

Dynorphins act as modulators of pain responses. Research also implicates these opioid peptides in maintenance and return to homeostasis agent through appetite control, which may also account for their proposed role in weight maintenance. There is some evidence of dynorphins' role core biological processes related to basic survival, including in circadian rhythm regulation, as well as biothermal regulation.

## Endomorphins

Endomorphins are a relatively new addition to the family of endogenous opioids. Early work by the research group spearheaded by James Zadina and Lazslo Hackler (Hackler et al., 1997; Zadina et al., 1997) first identified and characterized these peptides. Zadina et al. (1999) state that the two new peptides (Tyr-Pro-Trp-Phe-NH2 and Tyr-Pro-Phe-Phe-NH2) were endogenous peptides that had a high and selective affinity for MOP receptors. Therefore, they were given the names endomorphin-1 and -2 (EM1 and EM2).

EM1 and EM2 are C-terminally amidated tetrapeptides, with a high affinity and specificity for MOP receptors. As noted above, the N-terminal message sequence of EM1 is defined by two Tyr and Trp. These pharmacophoric amino acid residues are necessary for recognition of MOP receptors. The N-terminal sequence for EM2 is similar to EM1, except that it includes Phe (instead of Trp, as in EM1). For both EM1 and EM2, the N-terminal sequence composition also includes a spacer (Pro), which links the pharmacophoric residues.

Endomorphins yield diverse effects, and may regulate a variety of physiological functions and associated behaviors. These include both sedative and arousal behaviors; pain perception; responses to stress, reward, arousal and vigilance; autonomic, cognitive, neuroendocrine and limbic homeostasis. Additionally, EM1 and EM2 may modulate the secretion of multiple neurotransmitters, including dopamine (e.g., Bagosi et al., 2006; Ukai & Lin, 2002a), norepinephrine (e.g., Al-Khrasani et al., 2003; Rialas et al., 1998), serotonin (e.g., Tao & Auerbach, 2002), and acetylcholine (e.g., Patel et al., 1999; Ukai & Lin, 2002b). Finally, endomorphins may modulate the release of the neurohormones oxytocin and vasopressin (Doi et al., 2001). For an extensive discussion of these roles of endomorphins, we direct readers to the excellent authoritative review by Fichna et al. (2007).

## Opioid Receptor Types and Subtypes

In addition to the discovery of the endogenous opioid ligands themselves, the discovery of receptors for these molecules reflected a significant advancement in understanding pain signaling, and disruptions in pain signaling, including chronic pain and opioid use disorder. The opioid receptors, together with the endogenous opioids, form the so-called endogenous opioid system. This system produces diverse effects and functions throughout the body (see Fig. 2) via wide distribution throughout the CNS (see Fig. 3)

The opioid receptors are characterized by a heptahelical structure, with 400 aa in μ, 372 aa in δ, and 380 aa in κ. These receptors belong to the super-family of the G-protein-coupled receptors (GPCRs). The GPCRs are located in the cell membrane and most of them are activated by molecules outside the cell to trigger signal, transduction pathways inside the cell. The binding of opioid peptides to these receptors initiates biochemical events and various effects.

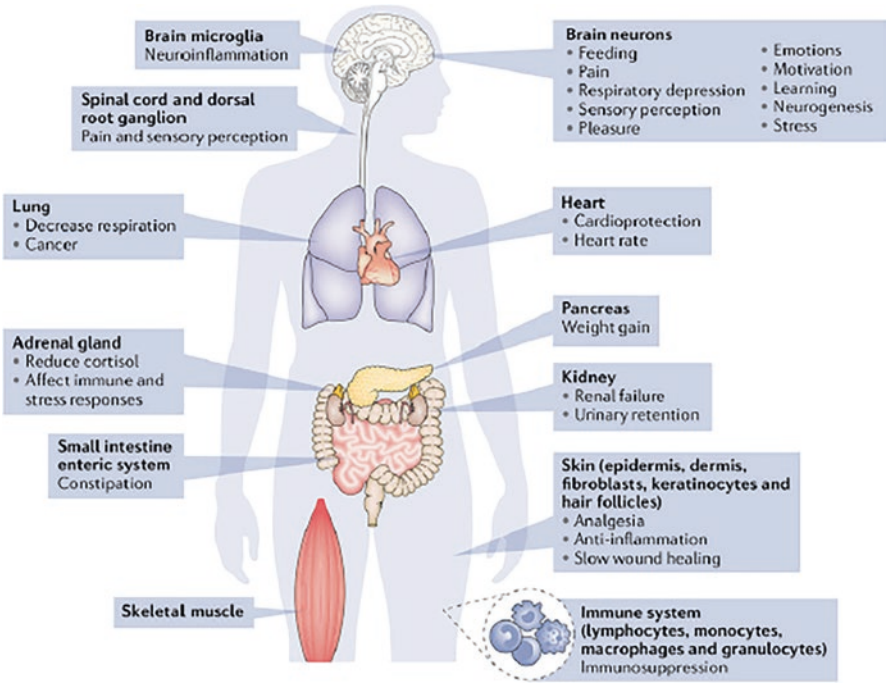


**Fig. 2** Opioid actions throughout the body. (Adapted from Kibaly et al. (2019). Used with permission)

As characterized by Simon and Gioannini (1993), methods for separation and purification of binding sites of opioid receptors consist of:

- Solubilization
- Physical separation
- Affinity cross-linking
- Partial purification
- Purification to homogeneity

The three G-protein-coupled opioid receptors are mu (μ; MOP), kappa (κ; KOP), delta (δ; DOP), and nociceptin (NOP). As discussed by Cox et al. (2015), there has been some debate about whether NOP/Orphanin is appropriate for classification in the endogenous opioid nomenclature. However, research has demonstrated that all four of these receptors share a highly similar crystalline structure (e.g., Granier et al., 2012; Manglik et al., 2012; Thompson et al., 2012; Wu et al., 2012; see Fig. 4a, b).

MOP receptors are characterized by their high affinity for morphine. Endogenous ligands for MOP receptors are Endomorphine-1 and Endomorphin-2. β-Endorphins, Enkephalins and Dynorphins bind to μ receptors but with lower affinity.

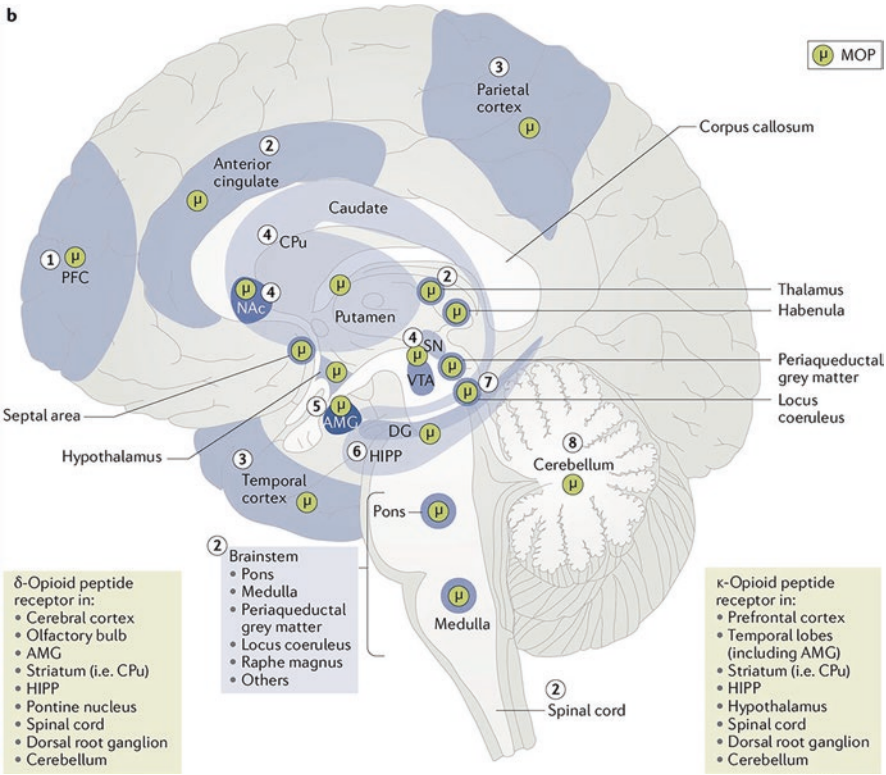


**Fig. 3** Opioid actions in brain functions. (Adapted from Kibaly et al. (2019). Used with permission)

Subtypes of MOP receptors have been identified and characterized as follows:

- $\mu_1$: with higher affinity for morphine; mediates supraspinal analgesia; selectively blocked by naloxone
- $\mu_2$: with lower affinity for morphine, mediates spinal analgesia, respiratory depression and constipation.

Regarding KOP, several laboratories have emphasized two populations of KOP receptors. These can be differentiated based on their affinity for benzeneacetamides as: $U_{50,488}$; $U_{69,583}$; and PD 117302. They are also displaceable by KOP agonists and KOP antagonists as follows:

- κ1: sensitive sites
- κ2: insensitive sites