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Special Section on 50 Years of Opioid Research — Perspective

Editorial: 50 Years of Opioid Research and the International Narcotics Research Conference

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ABSTRACT

In the past 50 years, scientists have made considerable strides toward understanding how opioids act. This special issue of *Molecular Pharmacology* celebrates these 50 years of opioid research and the role that the International Narcotics Research Conference has played in driving this research, by bringing together review and original research articles that present historical highlights, the current state of the art, and perspectives on the future of opioid research.

SIGNIFICANCE STATEMENT

Opioids have been used for thousands of years to manage pain and cause euphoria, but their use has been highly limited due to serious side effects. Deciphering the mechanisms of how opioids mediate beneficial and adverse physiological outcomes is essential for developing better treatments for pain and for opioid addiction.

Introduction

In the last 50 years, the field of opioid research has seen significant advances in our understanding of how opioid drugs act. We have identified the receptors responsible for mediating the pharmacological effects of opioids and the main signaling pathways activated by these receptors (Kieffer and Evans, 2009). We have discovered many endogenous opioid neurotransmitter peptides that activate these receptors as part of normal brain function (Emery and Akil, 2020; Fricker *et al.*, 2020) We have also developed thousands of pharmacological agents that can manipulate various aspects of opioid signaling for use in clinics and research, and we have moved closer toward learning how these drugs affect neurophysiology and behavior (Trang et al., 2015).

The last few decades, however, have also shown us the devastating consequences of opioid misuse and abuse. The development of tolerance and dependence to opioids, combined with serious adverse effects, has caused a protracted socioeconomic crisis of opioid misuse, abuse, and fatalities (Hedegaard et al., 2020). This crisis has led to intense and innovative efforts to better recognize the complexities of the opioid system and to build new strategies to manage pain and treat opioid addicts.

Over these past 50 years, the International Narcotics Research Conference (INRC) has been instrumental in shaping much of our efforts on this front. The INRC began in 1969 as a satellite session on narcotics in the triennial International Union of Basic and Clinical Pharmacology meeting. It rapidly evolved into being one of the most important platforms for researchers and clinicians working on opioid biology and medicine to come together and discuss the latest research on both the underlying biology of the opioid system and on mechanisms and therapeutic strategies for the treatment of addiction, chronic pain, and neuropsychiatric disorders.

This special issue, which brings together 15 articles, including minireviews and original research on the molecular pharmacology of opioids, celebrates INRC and the contributions made to opioid research in the last 50 years. The articles feature how our views on opioids evolved around a few important turning points in opioid research. The foreword by Dr. Valentino, Director of the Division of Neurobiology and Behavior at the National Institute on Drug Abuse, and Dr. Nora Volkow, the Director of the National Institute on Drug Abuse, summarizes the impact and immediate relevance of the work on opioids that is highlighted in this issue and the exciting potential of future work in the field (Valentino and Volkow, 2020).

The first minireview, by Dr. Brian Cox (2020), describes early studies on developing an effective analgesic that retained the desired effects of morphine but lacked the crippling adverse effects. The review covers how our views on opioids evolved at a time when the approaches and concepts were mainly focused on pharmacological characterization of opioid effects, and how those views shaped future research.

The identification of endogenous opioid peptides in the 1970s—which roughly coincided with the initial growth of the INRC as a leading entity—was an important juncture in opioid research. The minireview by Fricker et al. (2020) details the history, current views and misconceptions, and future directions in research on opioid neuropeptides. Gregoriou et al. (2020) present original research on the identification of

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the enzyme that processes enkephalin, a key opioid peptide. Using pharmacological approaches, they identify neprilysin as the main peptidase that processes enkephalin in the amygdala. They suggest that the mechanism by which opioid peptides are processed by peptidases differ in different brain regions.

The cloning of delta, mu, and kappa opioid receptors in the 1990s is another key milestone in opioid research, as it allowed the field to integrate the known pharmacological concepts with molecular aspects of receptor signaling and regulation. Birdsong and Williams (2020) focus on the mu opioid receptors to summarize how electrophysiology, combined with newer genetic methods, has advanced our grasp of the neural circuitry and signaling pathways that dictate the physiology of these receptors. They also describe how receptor phosphorylation regulates the signaling outcomes seen upon activation of these receptors.

Because activation of a given opioid receptor can initiate diverse and specific signaling pathways, a relatively recent approach that has been pursued is to test whether we could selectively activate the pathways that cause beneficial effects without activating the ones that cause adverse effects. The main thrust of these efforts has been on identifying opioid agonists that can "bias" signaling outcomes to G protein–mediated pathways and away from other signaling pathways (Conibear and Kelly, 2019). Gillis et al. (2020) outline important considerations to keep in mind when using operational models to determine bias and argue that agonist-dependent differences in intrinsic efficacy of effector coupling, as opposed to true bias, could be the main driver of beneficial physiologic outcomes. In this context, Barnett et al. (2020) show that different agonists cause the kappa opioid receptor to couple to distinct inhibitory G proteins with different efficacies. One possibility that could explain bias is that agonists allow receptors to sample distinct sets of conformational spaces that correlate with specific effectors and signaling pathways. Kapoor et al. (2020) use molecular dynamics simulations to predict the conformational dynamics of the mu opioid receptor bound to methadone in comparison with morphine and a G protein–biased ligand, as useful tools to navigate these conformational spaces.

Recent advances in optical imaging and biosensors are now providing new insights into the diversity of opioid signaling from a cell biologic perspective. Jullié et al. (2020) describe optical imaging approaches that have allowed us to address the importance of receptor dynamics in activating specific signaling pathways that could in turn dictate specific aspects of opioid physiology. One such pathway could be the platelet-derived growth factor receptor beta signaling pathway, which Puig et al. (2020) show contributes to the development of spinal opioid tolerance. Some of these pathways could be disrupted by adaptive changes that follow chronic drug exposure, as indicated by Leff et al. (2020), who show that kinase-dependent desensitization of the mu opioid receptor is disrupted in animals that have been treated chronically with morphine.

In addition to the traditionally ascribed roles of the mu opioid receptor in pain and euphoria, the broader opioid system is being increasingly recognized as playing critical roles in many other physiologic and disease processes. Parker et al. (2020) review the role of delta opioid receptors in headache and migraine and of kappa opioid receptors in mediating the affective component of pain. They also review the utility of the nociception receptor system, a more recent addition to the opioid family, in understanding the link between opioids and motivation. Eacret et al. (2020) focus on the relationship between sleep and opioids and outline the mechanisms underlying the reciprocal feed-forward interaction between these sleep disruption and opioid use. Interestingly, some synthetic opioids might also act outside of opioid receptors, as shown by Tschirhart and Zhang (2020) in their study that describes how metabolic changes can potentiate the inhibition of specific potassium channels by fentanyl.

The cloning of receptors also brought into focus the question of how this handful of receptors can generate the great diversity of pharmacological and clinical effects of opioids seen in the population. Although variations in downstream signaling components and regulatory factors might be part of the answer, polymorphisms and alternative splicing of opioid receptor genes themselves could contribute to variations seen in opioid responses between individuals. Zhang et al. (2020) present intriguing data that truncated splice variants of the mu opioid receptor could regulate the sensitivity of cells to opioids by acting as a chaperone and increasing expression of the full-length receptor. In this context, Parker et al. (2020) also discuss emerging views on how the gut microbiome, which could vary extensively between individuals and could contribute to specificity of opioid related behaviors at an organismal level.

Together, the articles in this issue highlight key historical, current, and future perspectives of the molecular pharmacology of opioids. The wealth of data generated over the last 50 years has advanced our understanding of how this fascinating system functions in our brains and has set the stage for future work on the many new and exciting aspects of opioid biology that are still being uncovered.

This special issue is a result of the collective effort of members of the INRC community, who contributed in many different ways toward publication of the issue. I would especially like to thank Dr. Martin Michel for handling the minireviews and for providing essential advice, and the editorial community of *Molecular Pharmacology* for their substantial help and guidance, without which this issue would not have been possible.

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