

Opioid Research: Past and Future

Rita J. Valentino and Nora D. Volkow
National Institute on Drug Abuse
National Institutes of Health
Bethesda, MD 20892

Corresponding author: Rita J. Valentino, Ph.D.
Director, Division of Neuroscience and Behavior
National Institute on Drug Abuse
National Institutes of Health
Bethesda, MD 20892
valentinorj@nida.nih.gov

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Corresponding author: Rita J. Valentino, Ph.D.
Director, Division of Neuroscience and Behavior
National Institute on Drug Abuse
National Institutes of Health
Bethesda, MD 20892
301-443-1887
valentinorj@nida.nih.gov

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Abbreviations: International Narcotics Research Conference (INRC); opioid use disorders (OUD)

Abstract

The International Narcotics Research Conference (INRC) has a rich history of uniting the most creative minds across the fields of chemistry, pharmacology, physiology, and behavior in the study of opioids. The Conference has been a forum for sharing knowledge, discussing controversies, introducing innovative research, and announcing landmark discoveries. In this perspective for the Special Issue commemorating the 50th anniversary of the Conference we briefly highlight how INRC has guided the evolution of opioid research and how new tools, models and approaches are facilitating our ability to achieve the goals of preventing and treating opioid use disorder.

Significance Statement

This perspective highlights the important role that the International Narcotics Research Conference has played in the evolution of opioid research and emphasizes how technological advances are facilitating research towards the goals of preventing and treating opioid use disorder.

This issue commemorates the 50th anniversary of the International Narcotics Research Conference (INRC) and reflects on the science that has served as the foundation of our current knowledge of the opioid field and looks forward towards the research that drives its future evolution. Early INRC meetings were dominated by research on the chemistry and pharmacology of compounds that mimicked or antagonized the effects of morphine *in vivo* and in *in vitro* assays such as the guinea pig ileum. This research led to the identification, localization and eventual cloning of opioid receptors. These were landmark studies, not only for the opioid field, but for neuropharmacology and neuroscience in general because they were among the earliest receptors identified in brain and helped usher the era of brain neurotransmitter receptor signaling. The characterization of opioid receptors was soon followed by the discovery of the endogenous peptides that bind to the receptors. Notably, the isolation of a morphine-like compound from brain was initially announced by Hans Kosterlitz at the 1974 INRC meeting. The recognition of the multiple endogenous opioid systems and their pharmacological and functional characterization that followed was pioneered by devotees of the Conference. The informal workshop style format of the INRC meeting has consistently served as fertile ground for arising controversies, transformative concepts, and the initiation of new generations of opioid researchers. These researchers have advanced our knowledge of the role of the endogenous opioid system in physiology and brain function and its implications for understanding pain and opioid addiction.

Meanwhile this past two decades have evinced the most severe epidemic of opioid misuse in the United States of which its most dramatic manifestation has been the increasing numbers of fatalities from opioid overdoses estimated at 450,000 deaths from 1999-2018 (CDC, 2020). Though the opioid crisis was triggered by the liberal and excessive prescription of opioid analgesics and their subsequent diversion, it subsequently metamorphosed into expanded use of heroin followed by that of more potent synthetic opioids such as fentanyl. This crisis has created an urgency in opioid research to understand the mechanisms underlying pain, opioid tolerance and physical dependence, opioid-induced changes in cognitive and affective function that underlie opioid use disorders (OUD), genetic and socioenvironmental bases for individual differences in vulnerability to OUD and to elucidate the neurobiology of endogenous opioid systems at multiple levels of analyses.

New tools and approaches for studying neurons, circuits and brain function have revealed a high degree of complexity and diversity within endogenous opioid systems. For example, it is now recognized that the opioid peptides undergo further proteolytic and post-translational processing to yield numerous peptides that can potentially function through either opioid or non-opioid receptors (Fricker et al., 2020; Gomes et al., 2020). We know little about the factors that regulate this processing or their release and this is a rich avenue to exploit. Opioid receptor pharmacology has been greatly advanced by tools that facilitate our ability to visualize the structural dynamics of receptors when bound with specific ligands or when in an active vs. inactive state. Using computational tools, large libraries of compounds can now be screened to identify those

that can manipulate receptor activity in desired ways, including allosteric modulators (Manglik, 2020). Over the last few years the concept of ligand-biased receptor signaling and that of receptor heteromerization have expanded and provided new paths for therapeutic research (Rankovic et al., 2016) (Fujita et al., 2014). Recent evidence has revealed opioid receptor signaling beyond the plasma membrane and shown that it can be spatially biased, occurring in different cellular compartments depending on the ligand bound (Weingberg et al., 2019; Jullie et al., 2020). Whether this happens *in vivo* and the functional consequences have yet to be determined but differential signaling in various cellular compartments could play a role in differential tolerance or enduring effects of ligands and is an avenue for future investigation.

The cloning of opioid receptors was critical for the development of genetic tools used in opioid research including mice with deletions of opioid receptor-related proteins, mice with genetic modifications to mimic human receptor variations, Cre-dependent mice that allow for visualization of opioid receptors or manipulation of cells that express opioid receptors in discrete brain regions. These tools combine to advance our understanding of the role of opioid systems in physiological functions or of specific receptors in opioid actions. We are entering an era of single cell 'omics' that allows for the profiling and mapping of individual cells with respect to their transcriptome, proteome or epigenome. With this approach, one can elucidate how chronic opioid use regulates gene networks of specific cells, informing us about potential mechanisms underlying the enduring consequences of opioid use. A power of this approach is that it is unbiased and so can generate novel hypotheses. This approach has only recently been used in opioid

research. For example, one study revealed that morphine exposure has the most robust transcriptional effects on non-neuronal cells in the nucleus accumbens (Avey et al., 2018). An alternative unbiased genetic approach, “forward genetics” identified a novel receptor that negatively regulates μ -opioid receptor signaling (Wang et al., 2019). This highlights the concept that endogenous systems exist that oppose opioids and offer new targets for manipulating opioid effects.

Opto- and chemo-genetic tools have revolutionized our ability to chart the circuits that drive behavior (Bruchas and Roth, 2016). These approaches have shifted our view of the ventral tegmental area from solely a reward-related nucleus to one with neural clusters having distinct projections and influences that integrate to shape motivation (Morales and Margolis, 2017; Heymann et al., 2020). They were instrumental in revealing a role for the dynorphin-kappa opioid system in pain-related negative affect (Massaly et al., 2019). The technology continues to evolve with improved opsins and chemogenetic probes, greater spatiotemporal resolution and the ability to multiplex, providing a finer control of manipulation and increased sensitivity and specificity. Many of the more recently developed optogenetic and chemogenetic tools emerged from the NIH BRAIN Initiative, an effort to generate and disseminate tools and technologies for the neuroscience community to accelerate knowledge about how the brain functions on different spatiotemporal scales. Other exciting tools that are being generated from this initiative include optical sensors to accurately measure neurochemicals at synapses and tools for precision pharmacology that allow for delivery of specific pharmacophores to receptors on genetically specified cells (Bruchas and Roth, 2016; Shields et al., 2017).

Although our knowledge about actions of opioids on brain cells and circuits has rapidly advanced, it is well-recognized that OUD is complex, involving psychosocial factors, stressor and environmental experiences, developmental and sex/gender determinants and that it is tied into existing co-morbidities. Additionally, it rarely occurs in isolation but is accompanied by the use of other illicit substances. Modeling these factors in research settings is a challenge that must be met to develop strategies for prevention and treatment. Current research is beginning to address these challenges, for example, through more ethologically relevant behavior models such as those that use alternative reinforcers including social reinforcers, performing experiments in both sexes and at different developmental stages and identifying overlaps in the circuitry and substrates of OUD and mental disorders. There is an important role for big data science that can integrate information about diverse variables and endpoints obtained through multiple levels of analyses to provide with quantitative information with which to assess relationships between them. As vast amounts of data become increasingly available, this approach will yield answers that are not attainable by other means.

The 50 years of research that has emerged from the INRC is a major chapter in the larger volume of research on understanding the brain. It has also given us the most effective tools we have to address and prevent mortality from the opioid epidemic; these are medications to treat OUD (methadone, buprenorphine and naltrexone) and to reverse opioid overdoses (naloxone). In the future this knowledge will serve as the

basis from which we can translate into better treatments for pain and for interventions to prevent and treat OUD.

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References

- Avey D, Sankararaman S, Yim AKY, Barve R, Milbrandt J, Mitra RD (2018) Single-Cell RNA-Seq Uncovers a Robust Transcriptional Response to Morphine by Glia. *Cell Rep* 24:3619-3629 e3614.
- Bruchas MR, Roth BL (2016) New Technologies for Elucidating Opioid Receptor Function. *Trends Pharmacol Sci* 37:279-289.
- CDC (2020) Opioid data analysis and resources. In. <https://www.cdc.gov/drugoverdose/data/analysis.html>
- Fricker LD, Margolis E, Gomes I, Devi LA (2020) Five decades of research on opioid peptides: Current knowledge and unanswered questions. *Mol Pharmacol*. PMID: 32487735 DOI: [10.1124/mol.120.119388](https://doi.org/10.1124/mol.120.119388)
- Fujita W, Gomes I, Devi LA (2014) Revolution in GPCR signalling: opioid receptor heteromers as novel therapeutic targets: IUPHAR review 10. *Br J Pharmacol* 171:4155-4176.
- Gomes I, Sierra S, Lueptow L, Gupta A, Gouty S, Margolis EB, Cox BM, Devi LA (2020) Biased signaling by endogenous opioid peptides. *Proc Natl Acad Sci U S A* 117:11820-11828.
- Heymann G, Jo YS, Reichard KL, McFarland N, Chavkin C, Palmiter RD, Soden ME, Zweifel LS (2020) Synergy of Distinct Dopamine Projection Populations in Behavioral Reinforcement. *Neuron* 105:909-920 e905.

- Jullie D, Gondin AB, Von Zastrow ME, Canals M (2020) Opioid pharmacology under the microscope. *Mol Pharmacol*. PMID: 32198210 DOI:10.1124/mol.119.119321
- Manglik A (2020) Molecular Basis of Opioid Action: From Structures to New Leads. *Biol Psychiatry* 87:6-14.
- Massaly N, Copits BA, Wilson-Poe AR, Hipolito L, Markovic T, Yoon HJ, Liu S, Walicki MC, Bhatti DL, Sirohi S, Klaas A, Walker BM, Neve R, Cahill CM, Shoghi KI, Gereau RWt, McCall JG, Al-Hasani R, Bruchas MR, Moron JA (2019) Pain-Induced Negative Affect Is Mediated via Recruitment of The Nucleus Accumbens Kappa Opioid System. *Neuron* 102:564-573 e566.
- Morales M, Margolis EB (2017) Ventral tegmental area: cellular heterogeneity, connectivity and behaviour. *Nat Rev Neurosci* 18:73-85.
- Rankovic Z, Brust TF, Bohn LM (2016) Biased agonism: An emerging paradigm in GPCR drug discovery. *Bioorg Med Chem Lett* 26:241-250.
- Shields BC, Kahuno E, Kim C, Apostolides PF, Brown J, Lindo S, Mensh BD, Dudman JT, Lavis LD, Tadross MR (2017) Deconstructing behavioral neuropharmacology with cellular specificity. *Science* 356:42.
- Wang D, Stoveken HM, Zucca S, Dao M, Orlandi C, Song C, Masuho I, Johnston C, Opperman KJ, Giles AC, Gill MS, Lundquist EA, Grill B, Martemyanov KA (2019) Genetic behavioral screen identifies an orphan anti-opioid system. *Science* 365:1267-1273.
- Weinberg ZY, Crilly SE, Puthenveedu MA (2019) Spatial encoding of GPCR signaling in the nervous system. *Curr Opin Cell Biol* 57:83-89.