

Neurobiology of the Opioid Epidemic: Basic and Translational Perspectives

Rita J. Valentino, Walter Koroshetz, and Nora D. Volkow

Opioid misuse and addiction have taken a massive toll on society, including lives lost, socioeconomic disruption, financial costs, and a burden on the health care system. This has accelerated exponentially in the last few years with the introduction of highly potent opioids. Intertwined with the opioid crisis is another crisis that is centered on pain, which affects a significant proportion of the population, and strategies for pain treatment. Together, these public health crises have sparked much basic and translational research in the areas of opioid pharmacology, the neuroscience of reward, affect, decision-making and self-regulation, the genetics of vulnerability, and the neurobiology of pain. For this special issue of *Biological Psychiatry* we called on experts in pharmacology, neuroscience, and translational medicine to review the current knowledge of how opioids produce their therapeutic and adverse effects and to provide future direction for optimizing the treatment of pain and the prevention and treatment of opioid misuse and addiction.

The reviews by Manglik (1) and Grim *et al.* (2) detail new knowledge about the structural dynamics of opioid receptors and how they interface with complex cellular signaling cascades that ultimately determine the balance of therapeutic and adverse effects. The review by Manglik (1) shows how advances led to the characterization of opioid receptors bound to agonists in a way that engages signaling, revealing chemical aspects of receptor structure that influence signaling bias and sites for allosteric modification. The power of computational approaches for high-throughput drug discovery is highlighted in this review, and the review provides examples of promising new analgesic compounds that are arising from this approach. The review by Grim *et al.* (2) moves from receptors to signaling and shows how genetically modified mouse models have been used to determine how opioid receptor coupling or regulation by kinases influence functions including analgesia, respiratory depression, and the development of tolerance and physical dependence. Their findings underscore the complexity of opioid receptor signaling but also suggest the possibility that the manipulation of this signaling can help us develop drugs that have therapeutic potential and that lack adverse effects.

In order to prevent and treat opioid use disorder it is necessary to elucidate the mechanisms that lead from agonist receptor binding and signaling to persistent changes in the brain that allow opioids to hijack circuits that regulate drive, affect, and cognition. Notably, there is substantial individual variability in the propensity to develop addiction that is related to the interaction of genetics with developmental and environmental factors. Browne *et al.* (3) discuss how

opioids remodel genetic programs through histone modifications and regulation by noncoding RNA. They discuss the future promise of manipulating epigenetic mechanisms and the importance of identifying not just single genes but entire gene networks that are affected by drug use. Kruyer *et al.* (4) take us from genes to synapses, emphasizing the glutamatergic synapse and its plasticity that has been implicated in addiction. They detail the complexity of this tetrapartite synapse consisting of presynaptic and postsynaptic elements, astrocytes that surround synapses, and the perisynaptic extracellular matrix, and they discuss how opioid use can produce enduring changes in these different compartments that translate to long-term changes in neurotransmission.

A recurring theme of this special issue is the role of negative affect in relapse and in maintaining compulsive opioid use. Circuits mediating the negative emotional dimension in addiction are also engaged by pain and in mood disorders. This overlapping circuitry can account for comorbidity of pain, depression, suicidality, and opioid misuse. The review by Koob (5) suggests that compulsive opioid use is maintained by a dysfunction in ventral striatal reward systems that use dopamine and endogenous opioids as neurotransmitters and extended amygdala stress-related systems that use corticotropin-releasing factor, dynorphin, hypocretin, and other stress-related molecules. Sensitization to the stress dysfunction that develops during phases of drug use followed by periods of abstinence reinforces continuation of the cycle. Welsch *et al.* (6) focus on the negative affect associated with protracted abstinence and review the value of animal models in discovering some of the circuitry involved and the critical brain regions and neuromediators. In addition to those discussed in the Koob review (5), Welsch *et al.* (6) highlight the importance of the medial habenula and the dorsal raphe serotonin system in aversion associated with abstinence, as well as projections from the paraventricular thalamic nucleus to the nucleus accumbens. A future challenge is to elucidate how these circuits work together to maintain drug-taking behavior and what can be targeted within the circuits to optimally break the cycle of addiction. The review by Serafini *et al.* (7) blends evidence from human imaging studies (functional magnetic resonance imaging and positron emission tomography) and preclinical studies to highlight the role of mesolimbic dopamine circuitry in the comorbidity between pain, depression, and substance use disorders.

Deficiencies in our understanding of pain and our ability to treat it play a key role in the current opioid crisis. In this special issue, Woolf (8) provides a comprehensive review of

the nature of pain and highlights the challenges in treating pain, stressing its diversity, sex and individual differences, the lack of biomarkers, and the poor translation of human genetic and current animal models. Woolf (8) provides guidance for moving forward—for example, by using unbiased approaches to identify targets, omics profiling of cells, human neurons from stem cells, state-of-the-art approaches for investigating and manipulating pain circuits, and computational modeling.

Bell and Strang (9) provide an overview of medication treatment of opioid use disorder and discuss the efficacy, advantages, and disadvantages of methadone, buprenorphine, and naltrexone, as well as the use of “take-home naloxone” for the prevention of overdose. The review underscores the role of psychosocial aspects in recovery, the need to eliminate stigma, and the need to increase availability for successful treatment. In our commentary (10), we review the history of how preclinical neuropharmacology and behavioral pharmacology research predicted the pharmacological profile of opioids in humans as well as their subjective effects, abuse potential, and dependence liability. These basic studies led to the development of the medications in use today. We discuss how these animal models are being refined to improve translation and to ultimately aid in the discovery of new treatments for opioid use disorder.

The reviews in this special issue highlight only a selection of the ongoing basic and translational research on opioid use disorder and pain. Although the opioid crisis has been devastating, the urgency to abate it has expanded the resources available for research to understand, prevent, and treat addiction as well as emotional and physical pain.

Acknowledgments and Disclosures

The authors report no biomedical financial interests or potential conflicts of interest.

Article Information

From the National Institute on Drug Abuse (RJV, NDV) and the National Institute of Neurological Disorders and Stroke (WK), Bethesda, Maryland.

Address correspondence to Rita J. Valentino, Ph.D., National Institute on Drug Abuse, 6001 Executive Blvd, Bethesda, MD 20892; E-mail: valentinorj@nida.nih.gov.

Received Sep 4, 2019; accepted Sep 5, 2019.

References

1. Manglik A (2020): Molecular basis of opioid action: From structures to new leads. *Biol Psychiatry* 87:6–14.
2. Grim TW, Acevedo-Canabal A, Bohn LM (2020): Toward directing opioid receptor signaling to refine opioid therapeutics. *Biol Psychiatry* 87:15–21.
3. Browne CJ, Godino A, Salery M, Nestler EJ (2020): Epigenetic mechanisms of opioid addiction. *Biol Psychiatry* 87:22–33.
4. Kruyer A, Chioma VC, Kalivas PW (2020): The opioid-addicted tetrapartite synapse. *Biol Psychiatry* 87:34–43.
5. Koob GF (2020): Neurobiology of opioid addiction: Opponent process, hyperkatifeia, and negative reinforcement. *Biol Psychiatry* 87:44–53.
6. Welsch L, Bailly J, Darcq E, Kieffer BL (2020): The negative affect of protracted opioid abstinence: Progress and perspectives from rodent models. *Biol Psychiatry* 87:54–63.
7. Serafini RA, Pryce KD, Zachariou V (2020): The mesolimbic dopamine system in chronic pain and associated affective comorbidities. *Biol Psychiatry* 87:64–73.
8. Woolf CJ (2020): Capturing novel non-opioid pain targets. *Biol Psychiatry* 87:74–81.
9. Bell J, Strang J (2020): Medication treatment of opioid use disorder. *Biol Psychiatry* 87:82–88.
10. Valentino RJ, Korshetz W, Volkow ND (2020): Translating opioid pharmacology from bench to bedside, and back. *Biol Psychiatry* 87:4–5.