Frontiers in Opioid Pharmacology

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FOR millennia, opioids have been a mainstay of pain treatment. Nature created opioid receptors as an eloquent means to allow us to continue to function in the face of painful illness or injury, and clinicians learned long ago how to exploit those receptors to relieve pain.

Fields of endeavor undergo cycles of languor alternating with explosive discovery. Opioid pharmacology is a field that has recently seen rapid and seminal discoveries that challenge long-held tenets and "conventional wisdom." Recent decades have seen tremendous growth in the clinical application of opioids for acute, postoperative, chronic, neuropathic, and cancer pain, as the emphasis on adequate pain treatment emerged. With the increased use of traditional opioid analgesics has come a surge in illicit use of prescription opioids, changing the way clinicians use existing opioids. New concepts appearing from the basic science of opioid pharmacology have spawned major new efforts in drug discovery, aimed at the development of opioids with greater clinical effectiveness and diminished side effects. These new opioids are now advancing through clinical trials, with their intended application for pain treatment and other therapeutic areas such as itch and depression.

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For these reasons, Anesthesiology chose to focus its 25th annual Journal Symposium at the 2017 American Society of Anesthesiologists meeting on "Frontiers in Opioid Pharmacology." Coincident with the appearance of new scientific discoveries was the escalating recognition of a public health problem of opioid overprescribing, diversion, misuse, addiction, overdose, and death, later to be labeled the "opioid epidemic."[1] This crisis today permeates every aspect of clinical opioid use: prescribing, regulation, reimbursement, and public policy, with individual, local, and national importance and consequence. Changes in institutional, payer, and governmental policies all aimed at stemming the tide of addiction, diversion, and abuse have hastily emerged. As editors of Anesthesiology, we could not have imagined how ripe the topic of opioid pharmacology would be by the time of the symposium.

The Anesthesiology Journal Symposium featured two plenary speakers, Laura M. Bohn, Ph.D., Professor of Molecular Medicine and Neuroscience at the Scripps Research Institute, and Nora Volkow, M.D., Director of the National Institute on Drug Abuse. Dr. Bohn spoke on "Refining Opioid Receptor Signaling to Improve Therapeutic Outcomes," addressing the new concept of biased signaling in opioid pharmacology and presenting for the first time a whole new suite of compounds that leverage the concept to reduce opioid side effects. Dr. Volkow spoke on "The Current Opioid Epidemic: Intersection between Pain and Addiction," highlighting the magnitude of the current prescription opioid epidemic and calling for development of new and safer pain treatments and better education of all healthcare practitioners in the treatment of both pain and addiction.

Dr. Bohn explained how pharmacology has traditionally held that any agonist binding to a receptor will elicit the full range of responses associated with activation of that receptor. Restated, traditional theory holds that all full agonists are alike, and the response they elicit is determined only by the receptor they activate. Some time ago, it was discovered that drugs that bind to G-protein–coupled receptors activate G-protein signaling and elicit one response, typically the usual response associated with receptor binding. In the case of the μ-opioid receptor, a G-protein–coupled receptor, agonist–receptor binding leads to G-protein signaling and analgesia. A newer discovery is that opioid agonists can also bind to μ-opioid receptors and activate a different pathway,

Image: A. Johnson, Vivo Visuals.

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the β-arrestin pathway, leading to unwanted effects including respiratory depression and drug tolerance.[2] Even more exciting is the discovery that various opioids can selectively confer more activity in one pathway than another, called "biased agonism" or "functional selectivity." Different opioids, including those currently used, have different "bias" factors, favoring *selective* activation of the G-protein signaling pathway or the β-arrestin pathway.[3] New opioids have been developed that are biased more toward G-protein signaling than β-arrestin signaling, offering the hope that this will translate into analgesia with less respiratory depression and less drug tolerance. One of these new biased opioid agonists is already in clinical trials and has been shown to be effective in relieving pain with potentially some modest improvement in reducing respiratory events.[4] Dr. Bohn reviewed the properties of an entire panel of new compounds with even greater bias that have been synthesized and evaluated in animals and show great promise for improving the safety of opioid analgesics.[3,5]

Dr. Volkow described how the Centers for Disease Control and Prevention reported that synthetic opioid-related fatalities increased 22% in 2016, surpassing deaths related to heroin or prescription opioids. The United States now prescribes 80% of the world's opioids. There are multiple national efforts underway to curb opioid prescribing. But where does that leave patients with acute pain? Dr. Volkow said that we need to develop better pain medications that will bind to the opioid receptor but not engage the β-arrestin pathway, as described by Dr. Bohn. Drug development, however, is a lengthy process. More immediately, we need to focus on better use of our existing pharmacologic resources and on expanding our training and education for practitioners in the healthcare system. For example, initiating buprenorphine treatment in the emergency department reduces illicit opioid use and increases the likelihood of successful engagement in addiction treatment. Extended-release naltrexone has also shown some promise for preventing opioid overdoses.[6] In clinical development are vaccines for heroin and fentanyl.[7] Dr. Volkow showed us that it is plausible that we may soon be able to treat addiction with a completely different set of tools.

The second half of the symposium featured oral presentations of the top eight abstracts relevant to the symposium topic, ranging from current and future opioid pharmacology, new and developing drugs, and strategies for optimal opioid use, across the domains of basic science, translational, clinical, and population/outcomes research. Along with announcement of the Anesthesiology Journal Symposium, we issued a call for papers related to the topic of the symposium and received dozens of submissions. In this issue of Anesthesiology, readers will find articles describing new original laboratory and clinical research, retrospective and population studies with practice and policy implications, and reviews on a number of topics related to the pharmacology and clinical use of opioid analgesics. Many of these are written by anesthesiologists that are leading clinician–scientists in our field. We invite you to read and learn more from the *Frontiers in Opioid Pharmacology*.

Competing Interests

Dr. Kharasch is the Editor-in-Chief of Anesthesiology and his institution receives salary support from the American Society of Anesthesiologists for this position. Dr. Rathmell declares no competing interests.

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