Published in final edited form as:

Drug Alcohol Depend. 2010 May 1; 108(3): 153–155. doi:10.1016/j.drugalcdep.2010.03.001.

Introduction to the College on Problems of Drug Dependence Special Issue: Contemporary Advances in Opioid Neuropharmacology

Sharon L. Walsh¹, Ellen M. Unterwald², and Sari Izenwasser³

¹University of Kentucky, Department of Behavioral Science, Center on Drug and Alcohol Research, Lexington, KY 40513 USA

²Temple University School of Medicine, Department of Pharmacology & Center for Substance Abuse Research, 3420 North Broad Street, Philadelphia, PA 19140 USA

³University of Miami Miller School of Medicine, Department of Psychiatry & Behavioral Sciences, 1600 NW 10th Ave, Rm. 4113A (D-80), Miami, FL 33136 USA

Abstract

Opioid receptors are critical therapeutic targets for medications development relevant to the treatment of drug dependence and pain. With recent advances in molecular neurobiology, it has become evident that the functional activity of opioid receptors, as ligand-regulated protein complexes, is modulated by multifarious intracellular and extracellular events, that there is genetic variation in coding for receptors, and that the activity of endogenous opioid systems may underlie actions common to other addictive disorders. This supplemental issue of *Drug and Alcohol Dependence*, arising from an invited symposium at the 71st Annual Meeting of the College on Problems of Drug Dependence, provides a series of contemporary reviews focused on recent advances in opioid neuropharmacology. Each speaker provides herein an invited comprehensive review of the state of knowledge on a specific topic in opioid neuropharmacology. Evans and colleagues describe the multi-faceted control of the opioid G-protein coupled receptor as a dynamic “sensor” complex and identify novel targets for drug development. Von Zastrow focuses on opioid receptor-mediated events regulated by endocytosis and membrane trafficking through the endocytic pathway and differential responses to opioid agonists. Blendy and colleague provide a review of human association studies on the functional relevance of the *mu* opioid receptor variant, A118G, and presents data from the A112G knock-in model, an analogous mouse variant to A118G. Finally, Maldonado and colleagues provide a broader systems review from genetic, pharmacologic and behavioral studies implicating the endogenous opioid systems as a substrate for the mediation of substance use disorders spanning pharmacological classes.

Keywords

opioid; pharmacology; molecular biology; receptor; genetics; analgesia; abuse

We are pleased to introduce this special issue of *Drug and Alcohol Dependence* that provides a series of contemporary review articles focused on recent advances in opioid

© 2010 Elsevier Ireland Ltd. All rights reserved.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

neuropharmacology contributed by recognized experts in the field. This collection of peer-reviewed papers arose from the Presidential Symposium presented as a keynote event at the 71st Annual Meeting of the College on Problems on Drug Dependence (CPDD) held in Reno, Nevada in June, 2009. Four speakers, Dr. Christopher Evans of the University of California Los Angeles, Dr. Mark von Zastrow of the University of California San Francisco, Dr. Julie Blendy of the University of Pennsylvania and Dr. Rafael Maldonado of the Universitat Pompeu Fabra, Spain participated in the symposium, and Dr. Nora Volkow, Director of the National Institute on Drug Abuse, served as the Discussant. Following the review papers, a commentary is provided by Dr. Mary Jeanne Kreek of the Rockefeller Institute (Kreek, 2010).

The CPDD, a present-day membership organization, evolved from a much earlier advisory committee organization (Committee on Drug Addiction and Narcotics and later the Committee on Problems of Drug Dependence) that dates its first official meeting to 1947 (Eddy, 1973). In fact, the ancestry of CPDD can be extended further to the Committee on Drug Addiction established in the 1920's in response to public pressure regarding the opium addiction problem in the United States by the Bureau of Social Hygiene, along with support from the National Research Council. By 1929, the Committee on Drug Addiction was charged with, among other things, the task of "replacement of all present use of addiction alkaloids by substitutes having no addiction properties" (Eddy, 1973). Specifically, the Committee would develop and seek funding to support a three-pronged research approach: 1) a chemistry program to design new opioid compounds, 2) a pharmacology program in which these compounds could be evaluated in non-human *in vitro* and *in vivo* studies, and 3) a clinical testing program in which compounds could be evaluated in humans for analgesia and addiction liability (later largely conducted through the United States Public Health Service at the Lexington Narcotic Prison Farm (Campbell et al., 2008)). CPDD carried on this mission for many decades, and, with time, the organizational character, management and breadth of scientific inquiry expanded (May and Jacobson, 1989). Today, CPDD is a growing and vibrant membership organization, whose members continue to provide expert advice to public health and government regulatory bodies and which serves as a forum for presentation of new scientific findings in the broader field of drug addiction.

Thus, this Presidential Symposium and the following issue of *Drug and Alcohol Dependence* is a celebration of CPDD and its founding mission to expand knowledge on the chemical, biological, pharmacological and clinical effects of opioid compounds in order to improve public health (Eddy, 1973). The idea for this Presidential Symposium arose, as do many good things in the field of science, from a conversation at a meeting with close colleagues in the field. At that time, planning was just getting underway to design a meeting to partner the annual CPDD meeting with another scientific organization whose shared interests would provide an opportunity for scientific synergy. The officers of the International Narcotic Research Conference (INRC), an organization whose mission is the advancement of science in all aspects of opioid-related research, had expressed interest and willingness to develop this joint venture for an upcoming conference. INRC, a scientific member organization with its own rich history dating back to 1969 (Archer, 1998), had periodically met as a satellite meeting of CPDD during its early years; however, it had not been since 1992 that the two organizations shared a venue. Thus, the proposed future meeting would bring together the memberships of CPDD and INRC at a single scientific conference during which both organizations would share scientific programming.

The present project was conceptualized as a symposium that would highlight work of individuals who were common contributors to INRC to stimulate cross-fertilization between the groups. The proceedings would be later expanded and published as a series of review papers. The resulting published issue would be shared, not only with CPDD members who receive *Drug and Alcohol Dependence* as part of their College membership, but would also be

distributed to members of INRC. The publication of this issue would precede and, hopefully, help to publicize the joint meeting of the CPDD and INRC planned for June 2011 in Hollywood, Florida. Prior to extending invitations for participation, a proposal was written (SLW) and submitted to Dr. Robert Balster, Editor of the journal, distributed to the Associate Editors of the journal for approval and submitted to the publishers of the journal, Elsevier. In addition, a proposal was written and submitted to Elsevier requesting financial support 1) for the speakers in the form of sponsorship of the symposium, and 2) for the publication of the issue along with extra published copies for distribution to the INRC membership and other interested parties. Approval was obtained from all parties. A timeline was developed, invitations were extended and accepted, and the reviews were requested for submission just prior to the CPDD meeting. Submissions were assigned to one of the editors of this supplement and managed in conjunction with the Editor of *Drug and Alcohol Dependence*. The guest editors were responsible for identifying peer reviewers and managing the peer review process until final acceptance. Dr. Balster did a final check and evaluation of the peer review process for each paper prior to release for publication.

The first review, by Dr. Christopher Evans and colleagues (Evans et al., 2010), provides a framework for the clinical utility of opioid compounds in the treatment of pain and highlights some of the contemporary complications arising from their use and misuse. They identify recent molecular findings on mechanisms of opioid action that suggest novel approaches for targeting drug development of new analgesic compounds that may have reduced abuse liability and/or reduced potential for development of tolerance and dependence. Evans and colleagues provide an updated view of the G-coupled receptor-protein complex in its modern form. Unlike the older and simplified view of the receptor having an activation profile similar to an on-off switch, the contemporary receptor complex is “a sophisticated sensor”- a highly complicated and integrated system consisting of interrelated signaling components whose varied responses may depend upon available proteins, ligands and the local environment. Suggested novel targets for refined opioid-directed pharmacotherapies include development of compounds that interfere with β -arrestin activity, of opioid agonists selective for receptors arising from different RNA splice variants and targeting other neurotransmitter systems with known opioid interactions.

Dr. Mark von Zastrow (von Zastrow, 2010) follows with an in-depth review on regulation of opioid receptor activity through a specific cell biological mechanism -- endocytosis and membrane trafficking through the endocytic pathway. Clinically relevant opioid drugs differ significantly in their effects on this regulatory mechanism, and there are also cell type-specific differences in regulated endocytosis that are only beginning to be understood. Data are presented from model cell systems, cultured neurons and more recent *in vivo* studies in transgenic mouse models that reveal the diversity and complexity of receptor trafficking mechanisms. These findings provide modern insight into the mechanistic underpinnings of phenomena described, but not well understood, during the early years of the field of opioid pharmacology, including receptor upregulation, downregulation and desensitization. Moreover, this review emphasizes, in part, the unique and varied cellular signaling (e.g., β -arrestins, G-protein coupled receptor kinases) that follows exposure to different opioid agonist chemical structures suggesting other targets for drug development that capitalize on differential “functional selectivity” (Urban et al., 2007) at the molecular level.

The third paper from Dr. Julie Blendy and colleague (Mague and Blendy, 2010) focuses attention on the potential clinical importance of the well characterized *mu* opioid receptor variant, A118G, that results from a relatively common single nucleotide polymorphism (SNP) in humans (Bond et al., 1998). The review provides a comprehensive analysis of human association studies conducted to date that assess a potential role of this SNP with respect to addictive disorders, including alcohol, opioids and nicotine, as well as pain sensitivity, response

to opioid analgesia and stress responses. *In vitro* results from an array of cell systems are described with the aim of clarifying the functional role of this variant with regard to biological responsiveness to endogenous and exogenous opioid exposure. Finally, recent data from studies conducted in the A112G knock-in mouse model (Mague et al., 2009), the mouse variant that is functionally equivalent to A118G, are described for both relevant biological and behavioral endpoints.

Finally, Dr. Maldonado and colleagues (Trigo et al., 2010) focus on the endogenous opioid system as a common neurobiological substrate for addictive disorders. A review of findings on adaptive system responses, including mRNA and protein expression, neurotrophic factors and neurotransmission, occurring after both acute and chronic exposure to drugs of abuse is reviewed. The remaining framework reviews the extant preclinical evidence, arising from pharmacological and microinfusion studies in wild-type and knock-out species, of the role of the midbrain endogenous opioid systems, including the *mu*, *kappa* and *delta* opioid receptor systems, in mediating or modulating the addictive potential of drugs from a spectrum of pharmacological classes including opioids, alcohol, nicotine, psychostimulants and cannabinoids.

In closing, we are pleased with the papers in this issue and believe that, together, they will serve as a valuable resource to readers because they provide a broad and updated review of progress in the field of opioid neuropharmacology. Since the advent of CPDD, the advances in our understanding of the biological and pharmacological underpinnings of opioid receptor-mediated events relevant to analgesia, tolerance and drug dependence, reflected herein, are simply remarkable. Despite these great advances, morphine and morphine-like drugs remain the most efficacious analgesics available for clinical use. The current epidemic of prescription opioid abuse and dependence in the United States (Compton and Volkow, 2006) is a reminder that much work remains in order to reduce the public health risks of opioid use. We have not yet accomplished the goal of separating the analgesic efficacy of these compounds from the abuse liability but continue to pursue this goal through inventive medicinal chemistry and creative formulation approaches. It is our hope that, with greater understanding of the molecular pharmacology of opioid-mediated events and relevance of genetic variation, novel neurobiological targets and design approaches will lead to improved analgesic development.

References

- Archer, S. The early history of the INRC (1969-1975). [accessed date February 15, 2010]. 1998 on <http://www.inrcworld.org/history.htm>
- Bond C, LaForge KS, Tian M, Melia D, Zhang S, Borg L, Gong J, Schluger J, Strong JA, Leal SM, Tischfield JA, Kreek MJ, Yu L. Single-nucleotide polymorphism in the human mu opioid receptor gene alters beta-endorphin binding and activity: Possible implications for opiate addiction. *Proc Nat Acad Sci* 1998;95:9608–9613. [PubMed: 9689128]
- Campbell, ND.; Olsen, JP.; Walden, L. *The Narcotic Farm The Rise and Fall of America's First Prison for Drug Addicts*. Abrams Books; New York: 2008.
- Compton WM, Volkow ND. Major increases in opioid analgesic abuse in the United States: Concerns and strategies. *Drug Alcohol Depend* 2006;81:103–107. [PubMed: 16023304]
- Eddy, NB. *The National Research Council Involvement in the Opiate Problem*. National Academy of Sciences; Washington, D.C.: 1973.
- Evans CJ, Walwyn WM, Miotto KA. Opioid pharmaceuticals and addiction; The issues, and research directions seeking solutions. *Drug Alcohol Depend*. 2010 in press, this issue.
- Kreek MJ. Commentary: Overview and historical perspective of four papers presented on research related to the endogenous opioid system. *Drug and Alcohol Depend*. 2010 in press, this issue.
- Mague SD, Blendy JA. OPRM1 SNP (A118G): Involvement in disease development, treatment response, and animal models. *Drug Alcohol Depend*. 2010 in press.

- Mague SD, Isiegas C, Huang P, Liu-Chen L-Y, Lerman C, Blendy JA. Mouse model of OPRM1 (A118G) polymorphism has sex-specific effects on drug-mediated behaviors. *Proc Nat Acad Sci* 2009;106:10847–108852. [PubMed: 19528658]
- May EL, Jacobson AE. The Committee on Problems of Drug Dependence: A Legacy of the National Academy of Sciences. A historical account. *Drug Alcohol Depend* 1989;23:183–218. [PubMed: 2666074]
- Trigo JM, Martin-Garcia E, Robledo P, Maldonado R. The endogenous opioid system: a common substrate in drug addiction. *Drug Alcohol Depend*. 2010 B. in press, this issue.
- Urban JD, Clarke WP, von Zastrow M, Nichols DE, Kobilka B, Weinstein H, Javitch JA, Roth BL, Christopoulos A, Sexton PM, Miller KJ, Spedding M, Mailman RB. Functional selectivity and classical concepts of quantitative pharmacology. *J Pharmacol Exp Ther* 2007;320:1–13. [PubMed: 16803859]
- von Zastrow M. Regulation of opioid receptors by endocytic membrane traffic: Mechanisms and translational implications. *Drug Alcohol Depend*. 2010 in press, this issue.