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Molecular Interventions (ISSN 1534-0384) is published by the American Society for Pharmacology and Experimental Therapeutics, 9650 Rockville Pike, Bethesda, MD 20814-3995. Published bimonthly in February, April, June, August, October, and December. Annual subscription rates: U.S.: $240 for institutions; and $78 for individuals. Outside the U.S.: $261 for institutions and $99 for individuals. The subscription price to ASPET members ($30) is included in membership dues. Single issue: $44. Subscriptions include access to the online version of MI at molinterv.org (ISSN 1543-2548). Indexed or abstracted by Biochemistry & Biophysics Citation Index, EMBASE/Excerpta Medica, Index to Scientific Reviews, ISI Alerting Services, ISI Web of Science, PubMed/ Medline, and Science Citation Index-Expanded.

Advertising (FASEB AdNet): 301-634-7103; adnet@faseb.org.
Editorial: 301-634-7390; mi@aspet.org
Subscriptions: 301-634-7099; staff@dues.faseb.org; ASPET: 301-634-7090; info@aspet.org.

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VIEWPOINTS

277 Targeting the Traffickers of Opioid Receptors:
A Route to Breaking Tolerance?

The development of morphine tolerance is a complicated process likely involving many different factors. Both $\mu$ (MOR) and $\delta$ (DOR) opioid receptors are known to influence morphine tolerance. Significantly, the role of both receptors appears to change during the acquisition of tolerance, and for both these receptors, regulated receptor trafficking may influence these changes. Morphine does not induce substantial endocytosis and recycling of MORs but appears to increase surface expression of DOR, which, under many conditions, is not efficiently transported to the cell surface. A recent report demonstrates that members of the family of Receptor Transporter Proteins increase surface expression of MOR-DOR heterodimers. The implications of these findings with regard to morphine tolerance are discussed.

Richard M. van Rijn and Jennifer L. Whistler

281 Life on a Raft: Exploiting Differences in Signaling for Therapeutic Benefit

Ligand functional selectivity occurs when full agonists at a single type of G protein-coupled receptor differ in their abilities to activate intracellular signaling pathways. Membrane rafts are cholesterol and sphingolipid-enriched areas of the cell membrane that tether signal protein complexes. Recent data suggests that functional selectivity of signaling through the $\mu$ opiate receptor depends on location of receptor and G proteins in raft or nonraft membrane domains. Changes in the distribution of signaling molecules in different membrane domains with age, disease, or drug history may contribute to variations in signaling and drug effects. Other results suggest that functional selectivity may account for therapeutic advantages of certain beta blockers used to treat heart failure. Functional selectivity could be exploited to develop drugs with more therapeutic value and fewer side effects.

Mark A. Simmons

The cover imagery of C. elegans and its internal dopaminergic neurons comes from a short animated movie in development at Indiana University in a collaborative effort between science (Richard Nass; see the Review on page 284 and http://pharmtox.iusm.iu.edu/ext/nass.htm) and art (Albert William; see http://informatics.iupui.edu/research/imaging/).
284 C. elegans: Going Green with Dopamine

The relevance of dopaminergic function to Parkinson’s disease has been exploited for forty years, and pharmacological supplementation of brain dopamine levels continues to be the primary goal of treatment. Novel pharmacotherapies are desperately needed to attenuate disease progression, but a primary problem of research has been the daunting challenge of monitoring the degeneration of dopamine neurons in a living organism. Enter *C. elegans*, a small nematode, complete with eight dopamine neurons, that is amenable to genetic manipulation and laboratory observation. Through transgenic addition of the green fluorescent protein to the organism’s dopamine neurons, a model system has been developed in which dopamine neurodegeneration, in vivo, can be assayed in a microtiter plate format. The induction of dopamine neuron degeneration in these organisms results in the loss of green fluorescence—and the effect of gene products and chemical agents upon such degeneration can be assessed on a high-throughput basis. The power of the model is just beginning to be tapped, and the accuracy to which the model recapitulates the human disease is surprising. Today, novel targets for therapeutic intervention—and potentially, novel drugs—promise to extend treatment beyond the brute aim of supplying degenerating neurons with dopamine.

Richard Nass, Kalpana M. Merchant, and Timothy Ryan

294 Radiation Treatment, Radiation Damage: Can Drugs Control Outcome?

The therapeutic and technological use of ionizing radiation is one of the hallmarks of twentieth-century medical progress. Additional applications of nuclear energy—and all the implications of the atomic age—will continue to mark medicine, society, and government at the global level for the foreseeable future. Increasingly, pharmacological research is entering into equations that are formulated to assess the risks and benefits of human exposure to radiation in diverse contexts: patient exposure to radiotherapeutic procedures; occupational hazards of medical, technological, and custodial personnel; and terrorist exploitation of radioactive materials. Research biologists customarily think of ionizing radiation in terms of its physical and mutational insults to DNA. The generation of aqueous radicals as a product of mitochondrial metabolic reactions, however, may be fundamental to cellular demise in tumors and healthy tissues alike. Intriguingly, pharmacological manipulation and chemical.syntheses promise the possibility of drug development that may allow for the exacerbation of tumor responses to radiation (i.e., “radiosensitization”) while sustaining the survivability of healthy tissues (i.e., “radioprotection”).

Irina Zabbarova and Anthony Kanai