

DEPARTMENTS

268 Reflections

Something Old...Something Blue
Stanley Scheindlin

274 Significant Deciles

ASPET celebrates its centennial anniversary

276 Nascent Transcripts

Emerging concepts from the literature

303 Beyond the Bench

Holiday Round-Up 2008
John Nelson

305 Net Results

Sites of Interest on the World Wide Web

308 On Deck

Upcoming meetings

312 Outliers

mi cartoon

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molecular interventions

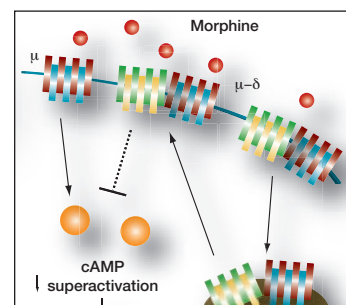
pharmacological perspectives from biology, chemistry and genomics

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 μ (MOR) and δ (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



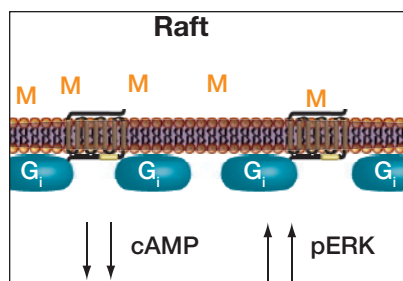
page 277
Heterodimers at the cell surface may hold the key

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 μ 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



page 281

Navigating the sea of signals to find the right port



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/>).

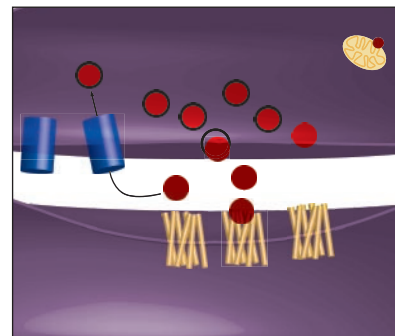


REVIEWS

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.

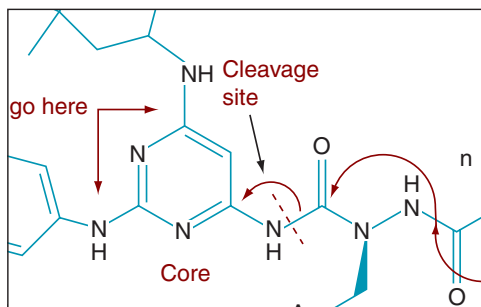
Richard Nass, Kalpana M. Merchant, and Timothy Ryan



page 284
Parkinson's drugs: go green!

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

page 294
Radioprotective agents