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# molecular interventions

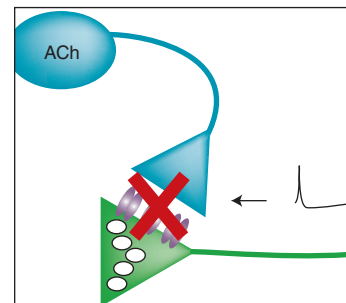
pharmacological perspectives from biology, chemistry and genomics

## VIEWPOINTS

### 304 **Addiction at the Crossroads: Interactions of Nicotinic and Opioid Receptors**

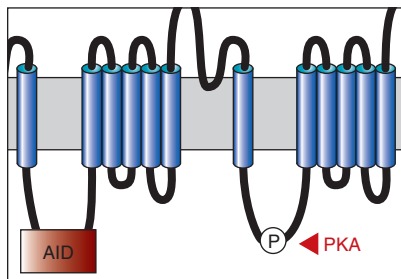
Many addictive drugs, including nicotine, increase the expression of opioid receptors and endogenous opioid peptides. How nicotinic receptors mediate this change in opioid signaling and its functional significance in the etiology of nicotine addiction remain unknown. Opioid and nicotinic receptor biology in the context of behaviors associated with drug dependence is discussed. Indeed, findings on the interactions between these receptor systems and recent studies on human behavior lead to the interesting suggestion that variants in the opioid receptor structure might predict the success of smoking cessation treatment.

Daniel S. McGehee



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New insights may provide  
new hope

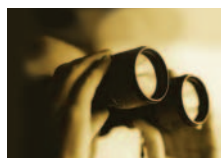
### 311 **New Strategies to Circumvent Hypertension**



page 311  
Blocking hypertension by inhibiting  
Ca<sup>2+</sup> channel expression

Voltage-gated Ca<sup>2+</sup> channels in vascular smooth muscle cells (VSMCs) are multi-protein complexes that mediate arterial contraction and gene expression. Although their subunit composition is unknown, increased expression of these channels is thought to contribute to the elevated vascular tone that is a hallmark finding in hypertension. Two strategies for blunting Ca<sup>2+</sup> channel expression have been achieved experimentally that rely on interrupting channel assembly and trafficking. The vision underlying these novel approaches to treat hypertension infers that a direct attack on the pathophysiology of the disease by reducing the over-abundance of Ca<sup>2+</sup> channels may have therapeutic advantages for lowering blood pressure.

Swapnil Sonkusare, Mony Fraer, James D. Marsh, Nancy J. Rusch

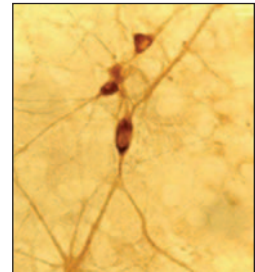


## REVIEWS

### 315 Excessive Neuronal Calcium: Reports of Its Harmfulness May Be Exaggerated

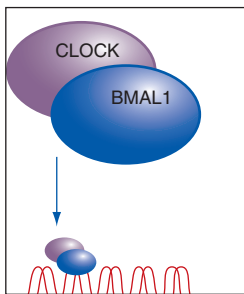
Sustained calcium ( $\text{Ca}^{2+}$ ) influx, as mediated by glutamate receptors, leads to elevated stimulation of a variety of signaling pathways that can impair neuronal respiration and eventually kill neurons. Indeed, glutamate-dependent increases in  $\text{Ca}^{2+}$  are thought to represent a common underpinning of neuronal cell death associated with neurodegenerative diseases such as epilepsy, hypoxia-ischemia, hypoglycemia, Alzheimer Disease, and schizophrenia. Recent evidence, however, indicates that under numerous conditions calcium can prevent neurons from dying. Experimental models of epilepsy and of ischemia show that protection of neurons appears to depend upon the age of the animal, the amount and route of calcium elevation, timing of initial insults, and brain regions involved. This review discusses findings on the protective signaling role of calcium under a wide range of pathological conditions.

Linda K. Friedman



page 315  
Excessive calcium:  
Not so bad after all?

### 330 The Prokineticins: Ubiquitous and Versatile



page 330  
Peptide busybodies

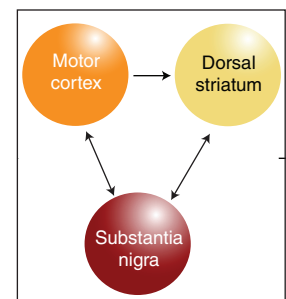
Snake venoms and skin secretions from frogs are rich sources of biologically active regulatory peptides. Two such peptides—MIT1, from a snake venom, and Bv8, from a frog secretion—have led to the discovery of mammalian analogs that regulate a broad range of physiological activities. The prokineticins are a pair of regulatory peptides that control circadian output from the brain in adults as well as development of the embryonic brain. Correspondingly, two G protein-coupled receptors have been identified that interact with the two prokineticins to support diverse routes of physiological signaling. Intriguingly, the various transcriptional machineries that are recruited for the expression of the prokineticins may themselves help to determine the peptides' ultimate physiological role. In addition to their fascinating biology, the prokineticins may offer insights into the pharmacological regulation of diverse processes, such as sleep, digestion, and reproduction.

Qun-Yong Zhou

### 339 Brainy Animal Models of Addiction

Construed as a pathology of motivation and learning, addiction challenges behavioral pharmacologists to explain some of the most complex facets of human behavior. It is therefore remarkable that animal models have been employed with great success in elucidating behavioral components of addiction as well as the neurocircuitry that underlies addictive behaviors. Pharmacological manipulation of animal models, genetic technologies, neuroimaging, and clinical evaluations are being synthesized into a very meaningful, albeit incomplete, picture of addiction as an adaptation of neural activities in the brain. An understanding of brain neurocircuitry and its manipulation by pharmacological agents offers promise for the treatment of addiction.

Peter W. Kalivas, Jamie Peters, and Lori Knackstedt



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Learning addiction