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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.

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molecular interventions

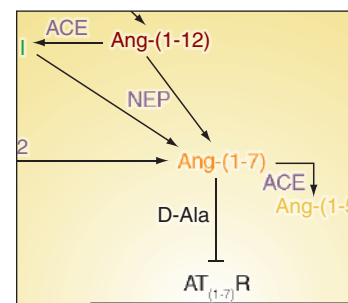
pharmacological perspectives from biology, chemistry and genomics

VIEWPOINTS

222 Improving Cardiovascular Health: New Targets in the Renin-Angiotensin System

Advances in cardiovascular pharmacological research will be necessary to treat effectively the increasingly complex patient with disorders in multiple control systems. The constituents of the renin-angiotensin system, as a result of the widespread effects of angiotensin II to increase inflammation and promote oxidative stress, remain prime targets for overall improvements in cardiovascular health in patients with co-existing metabolic, renal and cardiac dysfunction. Additional research is required to determine whether additional benefits can be achieved with tissue-selective or intracellular blockade of angiotensin II versus targeting overexpression of Ang-(1-7) and the enzymes that promote its formation. Newly identified components including renin receptors and intermediates in the processing of angiotensinogen provide potential future molecular targets that might allow improved clinical benefits.

Debra I. Diz

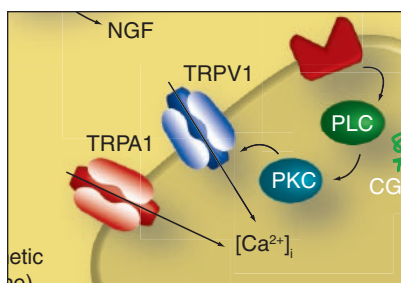


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Ang-(1-7) and the enzymes that process it

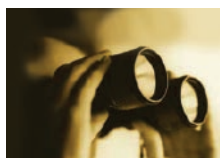
226 Slings and Arrows of Outrageous Fortune: When Anesthetics Cause Pain

General anesthetics produce a reversible loss of consciousness at low concentrations and also render patients immobile in response to surgical stimulation. Despite their widespread use for more than 150 years, the molecular mechanisms of most general anesthetics are poorly understood. Surprisingly, the sensitivity of the peripheral nociceptive neurons may be increased at clinically relevant concentrations of the same anesthetics that induce immobility. This article reviews two recent studies that propose activation of the nociceptive ion channels TRPA1 and TRPV1 as a mechanism by which certain irritant anesthetics might increase postoperative pain as well as produce airway irritation and burning pain during intravenous injection. Confirmation of the clinical relevance of this proposed mechanism through future studies might have important implications on the choice of anesthetic agents.

Helge Eilers



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TRPA1 and TRPV1 collude in pain

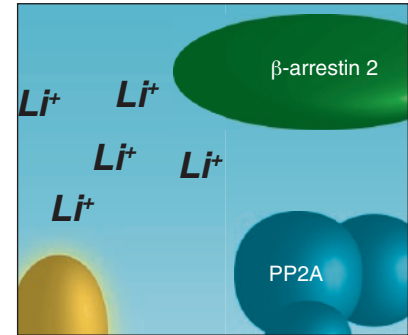


REVIEWS

230 Lithium's Disruptive Behavior: The Key to Mood-Stabilizing Drugs?

Since its approval in 1970 for the treatment of bipolar illness, lithium has become a commonly prescribed mood stabilizer, with use in depression and psychotic disorders and potential use in neurodegenerative disorders such as Alzheimer disease. The predominant explanation for lithium's actions (e.g., in FDA labeling) was for many years limited to alterations in sodium transport in excitable cells and a "shift" in catecholamine metabolism. Remarkably, specific enzyme activities were subsequently identified as targets of the simple cation, and the roles of these and other proteins in psychiatric disease were corroborated as genomic data and animal models of mood became available. New insights into catecholamine signaling, concerning the specificities of receptor subtypes and novel modalities of receptor signaling, continue to broaden our understanding of lithium's actions. In some instances, lithium may affect mood-regulating enzymes that normally utilize magnesium as a cofactor; protein-protein interactions that control neuronal receptor pathways also appear to be subject to disruption by lithium. These insights have implications not only for the development of new psychotropic medicines, but also for our understanding of mood and behavior as functions of discrete molecular interactions.

Jean-Martin Beaulieu and Marc G. Caron

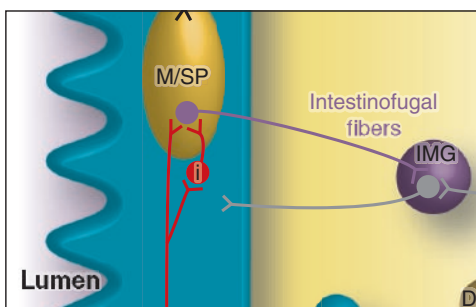


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Lithium's targets

242 Unique Features of Visceral Sensation

The majority of what is known about pain and nociceptors originates from studies of "somatic" structures (i.e., non-visceral components of the body, principally skin). Nevertheless, the most common pain produced by disease (and the most difficult to manage) is that originating from the internal organs (i.e., visceral pain), and the characteristics of visceral innervation differ significantly from other tissues. Visceral and non-visceral afferents encode different types of information, and a key difference between visceral and non-visceral sensory neurons is the degree to which their peripheral terminals are specialized. An exploration of the special aspects of visceral sensation is not only important to understand a clinically important context of pain and patient management; it also offers an opportunity for re-discovering basic terminology of pain sensation, including some taken-for-granted definitions.

David R. Robinson and G. F. Gebhart



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Gut feelings