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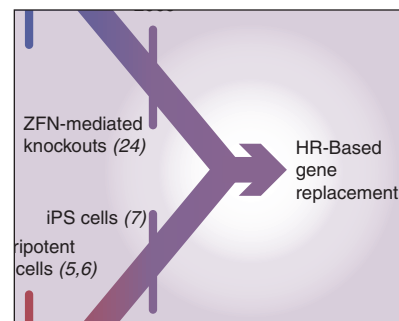
pharmacological perspectives from biology, chemistry and genomics

VIEWPOINTS

226 Targeted Genomic Knockouts in the Year of the Rat

In the last decade, use of the rat as a genetic model has gained significance. Unfortunately, the great advances that have been achieved through the genetic manipulation of mice have not been achieved through attempts to manipulate the rat genome. However, Geurts and colleagues have recently made an important contribution to the genetic toolbox as applied to the rat system. Using zinc-finger nuclease (ZFN) technology, they successfully targeted the rat genome, creating gene knockouts. The reported efficiency of the procedure in producing targeted alleles is surprisingly high. This technology will likely become the gold standard for targeted gene disruption in the rat and will undoubtedly revolutionize rat genetic research. The question remains whether the ZFN technology will also expedite the development of targeted gene replacement (“knock-in”) rat models.

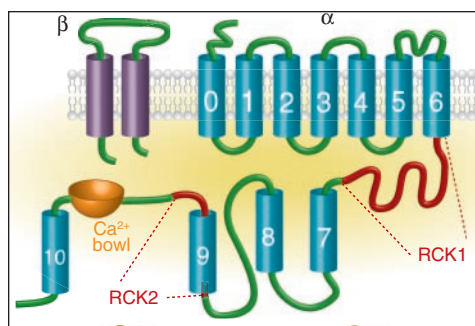
Bart M. G. Smits and Michael N. Gould



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Mutant rats in the lab?

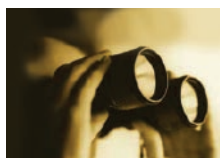
230 Channeling New Targets: The BK Channel in Aging and Cardiovascular Disease

The high-conductance, Ca^{2+} -activated K^+ (BK) channel in vascular smooth muscle cells (VSMCs) exerts a vasodilator influence that buffers vascular tone. There is strong evidence that abnormalities in the number or activity level of the BK channels can trigger vasoconstriction, disrupt blood flow to critical organs and elevate blood pressure. Indeed, a loss of BK channels has been detected in conditions associated with accentuated vascular tone, including aging, metabolic syndrome, diabetes, and some forms of hypertension. In these conditions, the homeostatic efforts of the vasculature to retain normal vascular tone may be compromised by a reduced number of BK channels and by a loss of the endothelium-derived vasodilator factors that promote channel opening. Owing to its recognized role in mediating vasodilation, the BK channel is regarded as a therapeutic target for the treatment of aging and age-related cardiovascular diseases that are associated with abnormal vascular tone.



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Making BK OK in disease states

Li Pang and Nancy J. Rusch

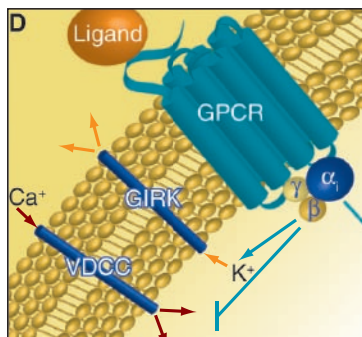


REVIEWS

234 GPCRs Join the Fight against Chronic Pain

Of all clinically marketed drugs, greater than thirty percent are modulators of G protein-coupled receptors (GPCRs). Nearly 400 GPCRs (i.e., excluding odorant and light receptors) are encoded within the human genome, but only a small fraction of these seven-transmembrane proteins have been identified as drug targets. Chronic pain affects more than one-third of the population, representing a substantial societal burden in use of health care resources and lost productivity. Furthermore, currently available treatments are often inadequate, underscoring the significant need for better therapeutic strategies. The expansion of the identified human GPCR repertoire, coupled with recent insights into the function and structure of GPCRs, offers new opportunities for the development of novel analgesic therapeutics.

Laura S. Stone and Derek C. Molliver

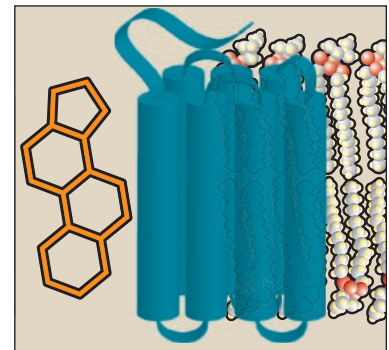


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G protein-coupled pain

252 Membrane Lipids: Integral to Protein Regulation

Neurotransmitter transporter function can be influenced by a variety of physiological factors, such as temperature, membrane voltage, pH, ion gradients, endogenous ligands, and accessory proteins. Several successful drugs that target transporter proteins, such as the selective reuptake inhibitors, have also been developed. One mechanism for regulating membrane protein function that has only started to make the list has been the impact of lipid environment. Over the last few decades, lipids, the unsung heroes of regulation have begun to emerge as critical modulators of membrane protein function through their direct actions on proteins, through their influence on the lipid milieu and through their roles in signaling pathways.

Christopher B. Divito and Susan G. Amara



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Lipids rule