

molecular interventions

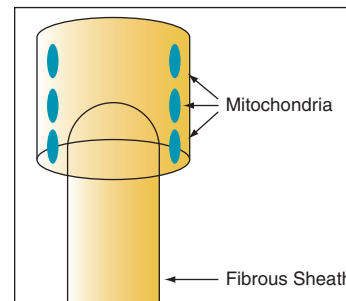
pharmacological perspectives from biology, chemistry and genomics

VIEWPOINTS

68 Male Contraceptives: New Targets, Future Breakthroughs

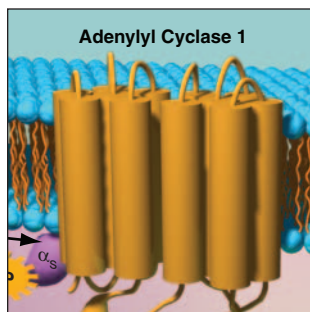
Blocking sperm motility has great appeal as a male contraceptive. A drug that targets sperm motility might have a very rapid onset of action, possibly allowing for administration immediately prior to intercourse and minimizing concerns about compliance. Promising sperm motility targets include transmembrane calcium channels, a unique adenylyl cyclase, and novel flagellar proteins. Future efforts directed towards effectively antagonizing the activities of these or other such targets will be required to completely impair sperm production, function, or both and create a usable male "pill."

John K. Amory



page 68
Blocking sperm motility and production

70 Targeting Adenylyl Cyclase in Neurotoxicity



The use of transgenic animals lacking one or multiple adenylyl cyclase (AC) isoforms has provided significant information on the roles of AC-dependent signaling in the central nervous system. A recent study provides evidence that AC type 1 (AC1) might be important in glutamate-induced neuronal toxicity. However, the absolute AC specificity revealed in this study contrasts earlier work examining other forms of neurodegeneration. Nonetheless, these observations suggest that specific AC isoforms may represent novel targets for the treatment of central nervous system disorders. It is anticipated that such findings will help catalyze new drug discovery efforts to identify small-molecule modulators of individual AC isoforms.

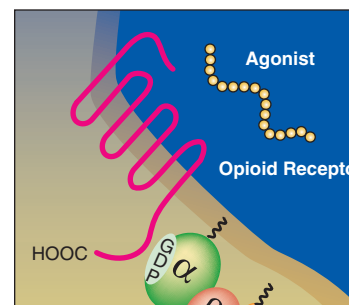
Val J. Watts

page 70
Targeting AC isoforms to ameliorate damage

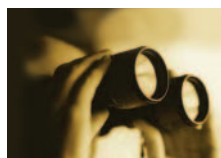
74 Polymorphisms and Propensity for Addiction

Discovery and characterization of the functional A118G mu-(μ)-opioid receptor variant led to hypotheses, now in part proven, about its role in alterations of endogenous human physiology and in responses to opioid antagonist administration. Differences in cellular expression levels, ligand binding, and signal transduction for variant receptors have been documented in vitro. Human genetic studies also indicate that individuals carrying one or two copies of the 118G allele may have increased risk for opiate and alcohol addictions and that this polymorphism may also explain some of the variability in success of opioid antagonist treatment for alcoholism. Future research will further define the role of the A118G variant in addictive diseases and their treatment, in pain perception and opioid analgesia, and for a myriad of other responses mediated by the μ -opioid receptor.

Mary Jeanne Kreek and K. Steven LaForge



page 74
A118G in addiction: An analysis of "variants"

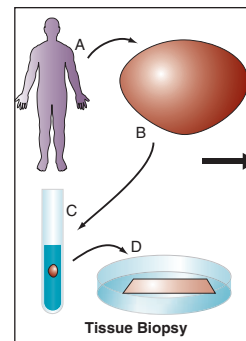


REVIEWS

79 Salamanders Do It. Let's Fall for Regenerative Medicine.

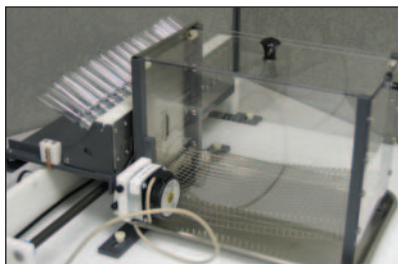
The idea of regenerative medicine has been with us for so long that the concept has been relegated to mythology (think of Prometheus) or to the wildly creative (think of Walt Disney). But the reality is that regenerative biomedicine has begun to show great promise in the laboratory and clinic, and the field may well be poised to revolutionize worldwide healthcare. Cells cultured from the failing organs of patients can be conditioned in "bio-reactors" and grown on scaffolds to take on shapes that recapitulate functional organs. "Neo-organs" constructed in this way represent fully immunocompatible resources for organ implants, and encouraging clinical results with "neobladders" and tissue-engineered vasculature are established in the literature. The demands and opportunities that regenerative medicine places on pharmacology are enormous, from experimental systems on which to test bioactive agents, to the characterization of neo-organs for use in medicine and research.

Karl-Erik Andersson and George J. Christ



page 79
Tissue-engineered organs

87 Molecular Matters of Taste



page 87
"Chewing the food of sweet and bitter fancy...."

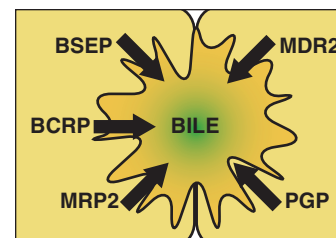
Many of the molecular components of the signal transduction pathways underlying taste have been elucidated. In taste buds, the chemosensory receptors for bitter, sweet, and umami (i.e., savory) tastes now are known to be G protein-coupled receptors, whereas salty and sour tastes result from tastant-activation of ion channels. The sense of taste has been investigated for many years using the methods of psychophysics and neurophysiology, and several excellent animal-based taste models are in use. New methods now are being developed for evaluating taste signaling in isolated taste bud and taste cells, and in cells that heterologously express taste receptors and other taste-specific signal transduction proteins.

R. Kyle Palmer

99 Discounting the Role of Inflammation in Drug Availability Could Be Harmful

Membrane transporters play an important role in determining the absorption and activity of many drugs. Intriguingly, inflammation alters the expression and activity of many drug transporters and thereby affects drug absorption and efficacy. The effects of inflammatory conditions on drug transporter regulation and a possible link between differences in drug disposition and inflammation are discussed.

Vanja Petrovic, Shirley Teng, and Micheline Piquette-Miller



page 99
Inflammatory statements: As easy as ABC (and SLC)