molecular interventions
pharmacological perspectives from biology, chemistry and genomics

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DEPARTMENTS

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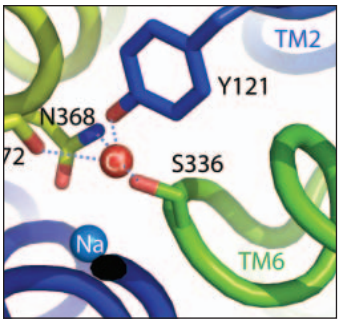
VIEWPOINTS

306 Of Bacterial Bondage: Bacterial Transporter Structure Can Help Define How Ions and Drugs Modulate Neurotransmitter Transporters



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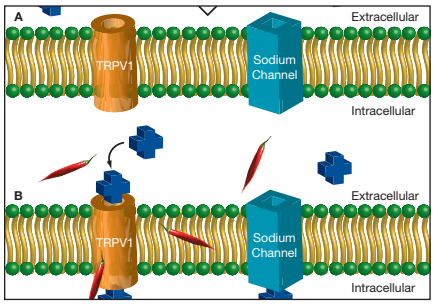
Transporters: Plundering the LeuT for neurotramsmitter transport

The neurotransmitter transporters belonging to the solute carrier 6 (SLC6) family, including the γ-aminobutyric acid (GAT), norepinephrine (NET), serotonin (SERT) and dopamine (DAT) transporters are extremely important drug targets of great clinical relevance. These Na^+, Cl^--dependent transporters primarily function following neurotransmission to reset neuronal signaling by transporting neurotransmitter out of the synapse and back into the pre-synaptic neuron. Recent studies have tracked down an elusive binding site for Cl^- that facilitates neurotransmitter transport using structural differences evident with bacterial family members (e.g., the *Aquifex aeolicus* leucine transporter $LeuT_{Aa}$) that lack Cl^- dependence. Additionally, the crystal structures of antidepressant-bound $LeuT_{Aa}$ reveals a surprising mode of drug interaction that may have relevance for medication development. The study of sequence and structural divergence between $LeuT_{Aa}$ and human SLC6 family transporters can thus inform us as to how and why neurotransmitter transporters evolved a reliance on extracellular Cl^- to propel the transport cycle; what residue changes and helical rearrangements give rise to recognition of different substrates; and how drugs such as antidepressants, cocaine, and amphetamines halt (or reverse) the transport process.

L. Keith Henry, Jens Meiler, and Randy D. Blakely

310 Improving Local Anesthetics: Blocking Pain, Permitting Normal Sensation



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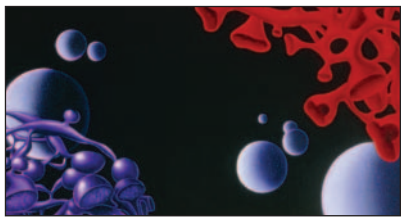
Selective inhibition of C-fiber neurons

Drug interactions and drug specificity are core themes for the pharmacologist. The paper discussed in this *Viewpoint* exploits the former to attain the latter. How can one improve local anesthetics so that they block pain but permit normal sensation? QX-314 is a charged derivative of lidocaine without anesthetic activity because it cannot diffuse across the cell membrane to access the neuronal voltage-dependent sodium channel. Capsaicin is a selective activator of the TRPV1 channel, the localization of which is restricted to sensory C-fiber neurons involved in nociception. Because the large pore size of the activated TRPV1 allows passage of large cations such as QX-314, combined treatment with capsaicin and QX-314 puts QX-314 uniquely into that subclass of neurons mediating pain, thereby achieving sensational specificity.

Peter M. Blumberg

REVIEWS



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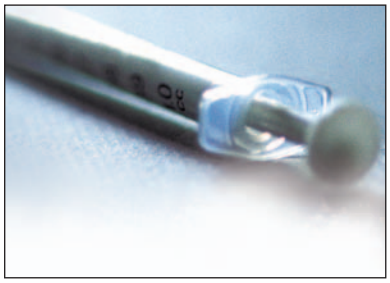
Lost in posttranslation



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Proof-of-concept at the earliest stage

The Food and Drug Administration (FDA) recently introduced the Exploratory Investigational New Drug Guidance to expedite the clinical evaluation of new therapeutic and imaging agents. Early clinical studies performed under the auspices of this guidance, so-called "Phase 0" trials, have been initiated at the National Cancer Institute to integrate qualified pharmacodynamic biomarker assays into first-in-human cancer clinical trials. The goal of this integration is to establish proof of concept at the earliest stage of drug development. Phase 0 trials do not offer any possibility of patient benefit; instead, intensive, real-time pharmacodynamic and pharmacokinetic analyses of tumor samples and/or surrogate tissues inform subsequent trials. Phase 0 studies do not replace formal Phase I drug safety testing and require a substantial investment of resources; however, they promise more rational selection of agents for further, large-scale development as well as the identification of potential therapeutic failures early in the development process.

Robert Kinders, Ralph E. Parchment, Jay Ji, Shivaani Kummar, Anthony J. Murgo, Martin Gutierrez, Jerry Collins, Larry Rubinstein, Oxana Pickeral, Seth M. Steinberg, Sherry Yang, Melinda Hollingshead, Alice Chen, Lee Helman, Robert Wiltrout, Mel Simpson, Joseph E. Tomaszewski, and James H. Doroshow

Cell responses to stress: A view from the ER.
Photo Credit: Francis Leroy, Biocosmos / Photo Researchers, Inc.