MAYO CLINIC

Future Directions in Pain Management: Integrating Anatomically Selective Delivery Techniques With Novel Molecularly Selective Agents

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CME Activity

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Learning Objectives: On completion of this article, you should be able to (1) recognize the health care and societal cost of chronic locoregional pain; (2) define the 2 paradigms for analgesic drug development, conventional drug discovery, and gene therapy; (3) list novel analgesic targets explored by gene therapy; and (4) discuss the role of interventional drug delivery for development of gene therapy for chronic locoregional pain.

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Abstract

Treatment for chronic, locoregional pain ranks among the most prevalent unmet medical needs. The failure of systemic analgesic drugs, such as opioids, is often due to their off-target toxicity, development of tolerance, and abuse potential. Interventional pain procedures provide target specificity but lack pharmacologically selective agents with long-term efficacy. Gene therapy vectors are a new tool for the development of molecularly selective pain therapies, which have already been proved to provide durable analgesia in preclinical models. Taken together, advances in image-guided delivery and gene therapy may lead to a new class of dual selective analgesic treatments integrating the molecular selectivity of analgesic genes with the anatomic selectivity of interventional delivery techniques.

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Chronic pain affects more than 116 million Americans and is one of the leading causes of medical appointments and disability, as reported by the Institute of Medicine in 2011.[1,2] Overall, the annual cost of chronic pain is estimated to be between $560 and $635 billion in the United States alone.[1] Although chronic pain is often viewed as a systemic disorder, the data provided by this report show that most patients experience locoregional pain, ie, pain syndromes anatomically limited to a sensory field of 1 or only a few peripheral or spinal nerves.

The Institute of Medicine identified locoregional musculoskeletal pain as the leading presentation of chronic pain in the United States. Specifically, the 2 most prevalent causes of chronic pain in the population were low back pain and knee pain, as documented by a survey performed by the National Center for Health Statistics, whereby 28.1% of adult Americans reported low back pain and 19.5% localized knee pain during the past 3 months.[1] Locoregional pain is also responsible for a substantial portion of the financial burden of chronic pain. Low back pain is estimated to cost $30 billion in direct health care expenditures and $100 to $200 billion in decreased wages and disability in the United States annually.[3,4] As for arthritic pain, annual direct health care expenses are estimated to approach $81 billion, with indirect costs reaching $189 billion annually.[5]

Similar to musculoskeletal pain, cancer pain—a subset of chronic pain that is particularly challenging to manage—also frequently presents as a locoregional syndrome. Fifteen percent of patients with cancer pain experience anatomically localized pain, such as pain originating from bone metastases or neuropathic pain from nerve compression or invasion.[6] Pain in these patients often cannot be adequately controlled by systemic analgesic treatments because the high doses needed for analgesia trigger intolerable adverse effects.[7] Although the best short-term outcomes in these patients are, therefore, frequently achieved by regional administration of local anesthetics or by selective neurolysis, neither approach is durable.[6]

THE SEARCH FOR SYSTEMIC ANALGESIC THERAPIES

The Conventional Drug Discovery Paradigm

Current analgesic therapies fail in a substantial number of patients with chronic pain.[6] This failure is most striking in cancer pain, where pain remains inadequately controlled in 50% of all patients.[8] Despite the search for novel analgesic treatments during the past few decades, currently available analgesic drugs exert their effect through very few categories of molecular targets.[9,10] Recent advances in neurobiology of nociception, however, identified a variety of candidate therapeutic targets located in the peripheral nervous system that are not used by current analgesic drugs. Important examples include ion channels expressed by primary sensory neurons, cytokines that play a critical role in the pathogenesis of neuropathic pain, and several inhibitory and excitatory neurotransmitters that modulate nociceptive signaling.

Characterization of these nociceptive mechanisms led to a search for a new generation of analgesic drugs using the techniques of conventional drug discovery (CDD); CDD, ie, the search for new small-molecule therapeutic entities, largely relies on empirical screening of candidate compounds. Two approaches are used by the pharmaceutical industry and academic laboratories involved in CDD. First, phenotype-directed screening seeks to identify chemical entities that have a desirable effect on the phenotype of a disease model without previous knowledge of their molecular mechanism of action.[11] Various assays modeling the disease phenotype on the level of a cell or an organism have been described.[12] Efficacious compounds are then examined for molecular mechanism of action using reverse biology techniques. Second, target-directed screening relies on biochemical knowledge of specific molecular targets and uses small-molecule screening strategies, typically by examining large libraries of compounds.[13] The actual biologic effect of thus discovered compounds is then tested in vivo in disease models. Although there has been a substantial effort to facilitate CDD by using high-throughput assays and by implementing genomic data, the discovery of new small-molecule drugs is declining in all medical fields. In fact, pharmaceutical industry data show that