

Pain

The Clinical Challenge

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Despite tremendous improvement in the understanding of neurobiological pain mechanisms, pain management, particularly the treatment of chronic pain, remains a largely unmet need. Millions of patients suffer from persistent pain that is incompletely relieved by analgesics.

Adverse effects of analgesics and comorbidity often limit the options for pain treatment. Conditions associated with chronic pain are common among elderly people, who have an increased risk of potentially harmful side effects, such as cardiotoxicity caused by tricyclic antidepressants. Experimental pain research is required to identify drug targets with reduced toxicity and reveal mechanisms of action that explain the side effects of analgesics.

Two recent studies illustrate the need for a translational approach to pain research. Insufficient inhibition of nociceptive input is a key factor in inflammatory and neuropathic pain. The major inhibitory transmitter in the spinal cord is γ -aminobutyric acid (GABA). Treatment with GABA receptor agonists should therefore be a viable strategy for alleviating pain. However, use of GABA receptor agonists is hampered by a loss of muscle tone, sedation and the provocation of epileptic seizures. Knabl et al. (2008) generated transgenic mice with point mutations in distinct GABA_A receptor subunits to determine which subunits mediate the analgesic effect of ligands at the benzodiazepine site of the receptor, and which subunits are responsible for common side effects of benzodiazepines such as motor impairment, sedation and the development of tolerance. They identified α_2 and α_3 subunits as specific targets for analgesia and demonstrated that L-838,417, a selective agonist at α_2 and α_3 receptor subunits and

antagonist at the α_1 subunit, reduces inflammatory and neuropathic pain. Mice treated with L-838,417 did not exhibit signs of sedation or tolerance and performed well in a rotarod test. Selective targeting of the GABA_A receptor subunits α_2 and α_3 has the potential of improving the analgesic specificity of benzodiazepine-site ligands.

Neurotrophic factors are essential for neuronal survival, differentiation and axon guidance during development. In the mature nervous system, they serve as signaling molecules that regulate synaptic function and stimulus response properties of neurons, and are involved in the communication between neurons and non-neuronal cells. Nerve growth factor (NGF) is specifically required for the development of nociceptors. In the adult organism, activation of tyrosine kinase receptor A (TRKA) by NGF triggers signaling pathways that contribute to nociceptor sensitization, including an increase in the responsiveness of transient receptor potential channel V1 (TRPV1). NGF also induces an enhanced expression of ion channels, neuropeptides and brain-derived neurotrophic factor (BDNF) (Pezet & McMahon, 2006). Tanezumab is a humanized monoclonal antibody that neutralizes NGF. In a recent phase 2 research trial, its analgesic efficacy for inflammatory pain was tested in 450 patients with osteoarthritis of the knee (Lane et al., 2010). Subjects receiving tanezumab had less pain while walking, experienced less joint stiffness and showed improved physical function in tasks that required movement of the knee. However, in a different phase 3 study, several subjects receiving tanezumab developed bone necrosis that required total joint replacement. This prompted the Food and Drug Administration (FDA) to suspend further clinical testing of the drug. Was the inhibition of NGF signaling responsible for the necrosis of bone tissue? One possible explanation would be that tanezumab not only blocked excess pain caused by osteoarthritis but also protective (nociceptive) pain, so that subjects treated with tanezumab put too much load on their

damaged knees. Joint degeneration is observed in patients with peripheral neuropathy who have a deficit in nociceptive and proprioceptive input. And congenital mutations in the NGF receptor TRKA prevent the development of nociceptors, leading to complete pain insensitivity and, as a consequence, repeated injuries of joints and soft tissue.

An ideal analgesic would remove clinical pain while preserving the protection provided by nociceptive pain. It would be directed at molecular targets with sufficient specificity to prevent intolerable or harmful side effects. A thorough understanding of the complex biological changes that are responsible for clinical pain is crucial for the development of better analgesics. Experimental pain research should inspire new treatment strategies. Likewise, important lessons are to be learned from clinical experience before we will be able to tackle chronic pain.

References

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