NGF and Pain

Wilma Friedman

Chronic pain is a condition suffered by many thousands of individuals and met with inadequate available treatments. The two classes of treatments currently in use, nonsteroidal anti-inflammatory drugs (NSAIDs) and opioid drugs, are not always effective for different types of pain, and can have deleterious side effects. Novel strategies are currently being developed based on the effect of NGF on nociceptive neurons (Hefti et al., 2006; Pezet & McMahon, 2006).

There are many indications that NGF plays a role in pain processing. Increased production of NGF is associated with injury and the levels are maintained in situations of chronic pain and blocking NGF strongly attenuates pain under these conditions. Deficiencies in NGF production are associated with a reduction in pain, and congenital insensitivity to pain has been associated with mutations in the NGF, TrkA and their downstream signaling genes. Focused administration of NGF evokes a robust and prolonged hyperalgesic response in animals. In clinical trials that administered NGF therapeutically to treat peripheral neuropathies, one of the critical side effects was severe hyperalgesia, even in healthy control subjects.

NGF promotes the survival and function of the nociceptive subpopulation of sensory neurons within the DRG during development, and many of these neurons continue to express TrkA and are functionally responsive to NGF throughout life. NGF treatment of sensory neurons elicits release of substance P and CGRP, two neuropeptides that are involved in pain neurotransmission. Additionally, NGF induces the synthesis and release of BDNF from the nociceptive neurons, which acts as a modulator of central nociceptive neurons in the spinal cord. NGF can also modulate the activity of a variety of ion channels involved in nociception, in particular the transient receptor potential vanilloid receptor 1 (TRPV1) channel. NGF increases

expression of TRPV1 mRNA, facilitates insertion of these channels in the membrane resulting in a greater density of channels, and can lead to phosphorylation and greater activity of the channel, causing increased sensitivity to capsaicin. Thus, NGF regulates many aspects of nociceptive function in adulthood (Pezet & McMahon, 2006).

A strategy to block NGF either by sequestering the factor itself or blocking its binding to TrkA has proven to be efficacious in ameliorating pain in several animal models. Treatment with anti-NGF agents has diminished or reversed hyperalgesia in chronic inflammatory conditions in which the two established pain treatments, NSAIDs and opiates, either have limited efficacy or adverse side effects.

Strategies for modulating NGF in the treatment of pain

Strategies for reducing NGF levels to treat pain have taken several forms, but the goal is to inhibit the binding of NGF to TrkA on the nociceptive neurons by using either competitive antagonists, or antibodies to NGF or to the binding domain of TrkA (Watson et al., 2008).

1. TrkA-Fc, the ligand binding domain of TrkA bound to the Fc portion of human IgG, yields a soluble molecule that binds NGF with high affinity and sequesters the ligand to prevent binding to TrkA on nociceptive neurons. Infusion of this TrkA-Fc prevented the pain response in animal models of inflammation.

2. Anti-NGF antibodies have been efficacious in reducing pain in a variety of animal models, including peripheral nerve injury, partial spinal cord transection and bone pain associated with fracture or an animal model of cancer. The humanized version of some of these antibodies are in clinical trials for treatment of various types of inflammatory and chronic pain (Cattaneo, 2010).

3. TrkAd5 is a small portion of TrkA that contains the NGF-binding domain and can be

produced as a small soluble protein that sequesters NGF with high affinity. Several models of inflammation have demonstrated the efficacy of this therapeutic agent in preventing hyperalgesia.

These approaches focus on sequestering NGF to prevent binding to TrkA. Additional approaches focus on blocking the receptor, either with antibodies or antagonists. A monoclonal antibody to TrkA (MNAC13) has been developed that blocks the NGF binding site on the receptor (Ugolini et al., 2007). All the antibody approaches have drawbacks associated with the size of the molecule potentially limiting its availability, as well as the possibility of generating an immune response. The development of small molecule antagonists is an alternative approach to prevent the binding of NGF to TrkA. All of the strategies discussed have been tested in animal models and show efficacy in reducing hyperalgesia in multiple paradigms of inflammatory and neuropathic pain. Several of these approaches are currently in clinical development for therapeutic use (see also Pain in Chap. 54).

References

Cattaneo, 2010 A. Cattaneo, Tanezumab, a recombinant humanized mAb against nerve growth factor for the treatment of acute and chronic pain. Current Opinion in Molecular Therapeutics. 12 (2010) 94–106.

Hefti et al., 2006 F.F. Hefti, A. Rosenthal, P.A. Walicke, S. Wyatt, G. Vergara, D.L. Shelton, Novel class of pain drugs based on antagonism of NGF. Trends in Pharmacological Sciences. 27 (2) (2006) 85–91.

Pezet and McMahon, 2006 S. Pezet, S.B. McMahon, Neurotrophins: Mediators and modulators of pain. Annual Review of Neuroscience. 29 (2006) 507–538.

Ugolini et al., 2007 G. Ugolini, S. Marinelli, S. Covaceuszach, A. Cattaneo, F. Pavone, The

function neutralizing anti-TrkA antibody MNAC13 reduces inflammatory and neuropathic pain. Proceedings of the National Academy of Sciences of the United States of America. 104 (8) (2007) 2985–2990.

Watson et al., 2008 J.J. Watson, S.J. Allen, D. Dawbarn, Targeting nerve growth factor in pain: What is the therapeutic potential?. BioDrugs: Clinical Immunotherapeutics, Biopharmaceuticals and Gene Therapy. 22 (6) (2008) 349–359.