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Gene therapy for pain

A new player in gene therapy for pain?

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In a recent report that has garnered notice by the popular press, Beutler and co-workers[1] present evidence that intrathecal inoculation of an adeno-associated virus (AAV)-based vector of serotype 8 carrying a sequence coding for prepro-beta-endorphin reduces mechanical allodynia in the spinal nerve ligation model of neuropathic pain.

Chronic pain, particularly neuropathic pain arising from damage to peripheral nerves, is a serious problem that is often refractory to the best available conventional therapies.[2] Advances over the past decades have provided substantial insight into the anatomy, physiology and molecular biology of acute pain perception (nociception) and many of the alterations responsible for the transition to chronic pain states.[3,4] But because a limited repertoire of ion channels, neurotransmitters and neurotransmitter receptors are employed in pain and nonpain pathways in the nervous system, it has been difficult to identify small molecules that selectively target pain-related pathways. Intrathecal delivery of conventional analgesic agents (for example, morphine) has been used for some time to enhance the pain-relieving potency of drugs by physically directing the drug in highest concentration to the spinal cord. Here, the first synapse in the pain pathway between nociceptive neurons terminals of the dorsal root ganglion (DRG) and second order neurons in the spinal cord provide an attractive target to modulate pain neurotransmission.

The use of gene transfer, in place of drug delivery to achieve the continuous release of short-lived bioactive peptides in or near the spinal dorsal horn underlies the most common strategies for gene therapy of pain. There are two principal models. The first involves intrathecal injection of vectors derived from adenovirus, AAV or lipid encapsulated plasmids. Both have demonstrated robust antiallodynic and antihyperalgesic effects, with prolonged effects shown after two injections of a plasmid coding interleukin-10.[5] The cells transduced by vectors injected into the cerebrospinal fluid are known to include resident meningeal cells lining the intrathecal space as well as neurons and glia in spinal parenchyma. In the second approach, neurons of the DRG are transduced by injection of herpes simplex virus-based vectors into the skin. These naturally neurotropic vectors are carried by retrograde axonal transport from the skin to the neuronal perikaryon of the DRG. Here they effect production of inhibitory neurotransmitters[6] or anti-inflammatory peptides[7] to reduce pain in several different chronic pain[8] models.

The current report describes a modified method that incorporates features from each of these approaches. In recent years, several novel serotypes including AAV serotypes 7, 8 and 9 and more than 100 other AAV variants have been isolated as DNA sequences from human or primate tissues,[9] with several of these variants showing distinct tissue tropisms. In the current report, Beutler and colleagues demonstrate that intrathecal injection of a serotype 8 AAV containing a green fluorescent protein reporter transgene results in transduction into DRG neurons. The DRG lies physically at the end of root sleeves, which are continuous with the intrathecal space and, thus, bathed by cerebrospinal fluid. But infection of DRG neurons by serotype 8 AAV is apparently unique; serotype 2 AAV, for example, does not infect DRG neurons when administered by the same route. The magnitude of the antiallodynic effect of serotype 8 AAV vector containing the prepro-beta-endorphin gene appears to be comparable to that achieved by other gene transfer methods, and the duration of pain relief is longer than that achieved by a single injection of other vectors intrathecally. The authors of the report write enthusiastically about the potential of serotype 8 AAV to serve as a suitable platform for gene therapy for pain in patients and the data presented do indeed demonstrate features that may be desirable for the treatment of chronic pain. At a minimum, serotype 8 AAV should provide an interesting tool for animal studies investigating DRG mechanisms in chronic pain, but important issues are also raised that need to be explored further: (1) what is the rostro-caudal extent of transgene expression in the DRG following intrathecal injection? (2) Which regions of the brain (reported to have genome levels 10^{-4} of that in the DRG) are transduced? (3) What is the effect on brain infection if the vector is injected at thoracic or higher levels of the spinal cord? (4) Are other organs outside the nervous system, such as the liver, pancreas and muscle (all efficiently transduced by serotype 8 AAV) infected following intrathecal injection of serotype 8 AAV? (5) Is a single injection of AAV vector into cerebrospinal fluid more or less toxic than two injections of plasmid vector into the same site?

Meanwhile, earlier this year, the FDA approved an investigational new drug application for a phase 1 human trial of a nonreplicating herpes simplex virus vector expressing enkephalin, injected into the skin, for treatment of pain. On another front, preclinical studies of a plasmid expressing IL-10 delivered by intrathecal injection are moving forward. Ultimately, the human trials will inform us whether any of these approaches can be advanced from rodents to people. If we are fortunate, in the not-too-distant future, gene therapy may provide one or more novel options for physicians who struggle to treat patients suffering from intractable pain.

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