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Targeting Trends

Reporting the latest news in Molecular Surgery

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Newsletter Highlights

Denise Higgins, Editor

ADVANCED TARGETING SYSTEMS

Targeted Toxins in Pain

Summary of contribution to "Recontres en toxinologie, 2005" by

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The use of targeted toxins in neuroscience research has evolved over the past twenty-plus years from original suicide transport lesions using ricin to highly selective neuron type-specific lesions made with immunotoxins, such as anti-dopamine beta hyroxylase-saporin (anti-DBH-SAP, Cat. #IT-03), and neuropeptide-toxin conjugates, such as substance P-saporin (SP-SAP, Cat. #IT-07).

Application of these agents to experiments in the neurobiology of pain began about ten years ago with the development of anti-DBH-SAP which selectively destroys adrenergic and noradrenergic neurons, and SP-SAP which destroys neurons that express neurokinin-1 receptor (NK-1r; Figure 1). Anti-DBH-SAP has been used to show the importance of central noradrenergic neurons in withdrawal from chronic opiate administration and in descending regulation of nociception. Intrathecal injection of SP-SAP produces robust decreases in operant responses to noxious thermal stimuli over a wide range of temperatures with preserved innate reflex nocifensive responses to noxious thermal and mechanical stimuli.[1,2] SP-SAP also profoundly decreases operant hyperalgesia and nocifensive hyperreflexia in a variety of animal models, including topical mustard oil or capsaicin, spinal nerve ligation, carrageenan- and Freund's adjuvant-induced inflammation.[3,4] SP-SAP reduces responding in the formalin model of persistent pain (phase II). A targeted toxin using a more stable analog of substance P (SSP-SAP, Cat. #IT-11) produces similar effects at lower doses with better specificity.[5]

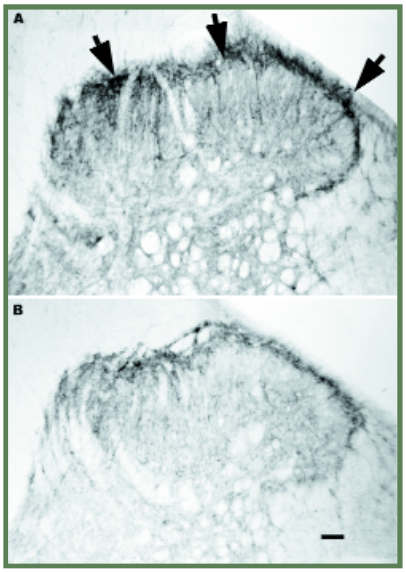

Figure 1.
Effects of intrathecal SP-SAP on NK-1r-expressing rat dorsal horn neurons.
A) Normal immunoperoxidase staining for NK-1r after vehicle injection (arrows).
B) Decreased NK-1r staining after intrathecal administration of SP-SAP (175 ng).
Magnification bar in B indicates 100 µm. Counts of NK-1r-expressing neurons in deeper laminae revealed that cell loss was limited to the superficial laminae (I and II).

A similar construct, dermorphin-SAP (Cat. #IT-12), eliminates mu opiate receptor-expressing neurons from the medulla or the substantia gelatinosa of the spinal cord.[6] Medullary dermorphin-SAP injections produce changes in descending regulation of nociception resulting in decreased hyperalgesia and allodynia in a sciatic nerve constriction injury model of neuropathic pain.[7-9] The successes of SP-SAP, SSP-SAP, and dermorphin-SAP suggest a general strategy for targeting neurons expressing specific G-protein coupled receptors. SP-SAP, and perhaps other neuropeptide-toxin conjugates, may have potential in the treatment of chronic intractable pain (see companion article on Page 2).

(continued on page 6)