

Pain control from the brain- gene therapy in the treatment of chronic pain

Results:

The activity of the brain in pain modulation during chronic pain is changed. In general, the net balance of descending modulation during chronic pain consists on a decrease of descending inhibitory actions and an increase of facilitatory effects. Synchronous changes in neuronal responses at the spinal cord and pain control centres in the brain were detected. Variations in the brain may account for the effects of chronic pain. To target pain control centres of the brain, we elected a gene therapy approach based on the sustained and directed effects of the technique. The overexpression of preproenkephalin using a replication-defective vector derived from Herpes Simplex type 1 (HSV-1) in a pain control area of the brain (the caudal ventrolateral medulla), decreased behavioural responses in an inflammatory pain model, the formalin test, and inhibited nociceptive responses of spinal neurons. A reversal of behavioural pain responses was also induced in a traumatic neuropathic pain model using a HSV-1 vector in which a tissue-specific promoter (tyrosine hydroxylase; TH) controlled the expression of the TH transgene inserted in an antisense sequence. Using this vector, the decrease in the release of noradrenaline in a pain facilitatory centre (the dorsal reticular nucleus) induced long-lasting antinociceptive effects, detected during 22 days. Gene therapy may be considered an excellent molecular tool to understand the effects of chronic pain installation in pain control circuits of the brain. Furthermore, based on detailed morphofunctional knowledge of pain control centres of the brain and by electing the vector type, determining the better promoter and the suitable transgene for the construct, the effects of chronic pain may be corrected using gene therapy approaches.

Published work:

Pinto M, Lima D, Tavares I (2006) Correlation of noxious evoked c-fos expression in areas of the somatosensory system during chronic pain: involvement of spino-medullary and intra-medullary connections. *Neurosci Lett.*, 409: 100-105

Tavares I, Lima D (2007) From neuronatomy to gene therapy: searching for new ways to manipulate the supraspinal endogenous pain modulatory system. *Journal of Anatomy*, 211: 261-268

Martins I, Pinto M, Wilson SP, Lima D, Tavares I (2008) Dynamic of migration of HSV-1 from a medullary pronociceptive centre: antinociception by overexpression of the preproenkephalin transgene. *Eur. J. Neurosci.*, 28: 2075-2083.

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