PAIN CONTROL FROM THE BRAIN: GENE THERAPY IN THE TREATMENT OF CHRONIC PAIN

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**Aims:** Develop new methods of manipulation of the supraspinal pain control system to correct the neurobiological changes induced by chronic pain. The studies were focused on two components of the supraspinal pain control system: the dorsal reticular nucleus (DRt) and the caudal ventrolateral medulla (VLM). These two areas were elected based on the profound knowledge of their participation in pain modulation at the spinal cord level. The DRt is involved in pain facilitation whereas the VLM appears to be involved in mixed effects (facilitatory and inhibitory).

**Methods:** Transduction of neurons by HSV-1 (Herpes-Simplex Virus, type 1) or lentiviral based constructs (replication-defective forms) and evaluation of nociceptive behaviours in sustained and chronic pain models. In the case of the DRt, three studies were performed using the following constructs and pain models: 1) HSV-1 vectors overexpressing pre-proenkephalin in monoarthritic animals; 2) HSV-1 vectors overexpressing mu-opioid receptors (MOR) in a neuropathic pain model; 3) HSV-1 vectors that reduce the release of noradrenaline in a neuropathic pain model. In the VLM, we studied the effect of overexpressing pre-proenkephalin in an inflammatory pain model.

**Results:** In summary, the studies demonstrated that chronic pain affects descending modulation and that gene transfer can correct those effects in a sustained manner. The studies indicate that during chronic pain, a depression in the expression of MOR at the DRt is associated with hyperalgesic effects induced by local injection of opioids. The hyperalgesia induced by overexpression of enkephalins at the DRt can be switched to analgesia by overexpression of MOR. It is possible that the VLM does not undergo similar changes since local overexpression of enkephalins induces analgesia. A decrease of noradrenaline release at the DRt is analgesic probably because chronic pain increases the tonus of noradrenergic input to the DRt and facilitates pain modulation from this nucleus.

**Conclusion:** By allowing sustained and directed manipulation, gene transfer is an effective tool to study pain modulation from the brain. Vector constructs produced taking into account the specific changes induced by chronic pain in the brain will continue to be developed.

**Publications (full papers):**
1. Pinto M, Lima D, Tavares I. (2007). Neuronal activation at the spinal cord and


**Key words:** Receptor expression; Animal models; Gene transfer; Viral vectors.