Paradigms in Spinal cord stimulation and pain relief: a systematic review on modulation of the central inflammatory response in neuropathic pain.

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Background: Spinal cord stimulation (SCS) is a last resort treatment for chronic neuropathic pain patients. The inflammatory balance between pro- and anti-inflammatory molecules in the spinal nociceptive network is pivotal in the development and maintenance of neuropathic pain. Unraveling the effects of different SCS-paradigms may help understand the mechanisms of SCS and improve the therapy. The aim of this systematic review is to understand the effects of different SCS-paradigms on the central inflammatory balance in the spinal cord as related to pain relief.

Methods: A systematic literature search was conducted using three databases: Medline, Embase, and PubMed. Al papers studying the effects of SCS on inflammatory or glial markers in neuropathic pain models were included. A quality assessment was performed on predetermined entities of bias.

Results: The search resulted in 374 articles of which eleven were eligible for this systematic review. In general, induction of neuropathic pain in rats results in an imbalance between pro- and anti-inflammatory molecules towards a pro-inflammatory state, as well as increased activity/expression of microglial and astroglial cells in the spinal cord dorsal horn. Conventional (con-) SCS enhances this inflammatory imbalance, increases mRNA expression of microglial markers, but results in a decrease of microglial protein marker levels. High frequency (HF-) and especially Differential Targeted Multiplexed (DTM-) SCS (also increased stimulation frequency) are able to restore this inflammatory imbalance and overexpression/activation of glial cells. Results must be interpreted with caution as the risk of bias analysis showed that the methodology of preclinical studies is often unclear.

Conclusion: In summary an imbalance in the central inflammatory balance towards a pro-inflammatory state was reported and related to increased glial cell activation in neuropathic pain animals. Con-SCS does not restore this imbalance. Use of new SCS-paradigms with increased stimulation frequency, such as HF- and DTM-SCS, might result in more optimal restoration of the central inflammatory balance and better pain relief. The preclinical findings and effect of SCS frequency needs not only to be further confirmed with future experimental studies, but may also initiate new clinical studies which are directed to optimization of SCS-treatment in chronic neuropathic pain patients.

Keywords: Spinal cord stimulation; Inflammation; Neuropathic pain