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Nerve Injury Induced Pain and Modulation by Spinal Cord Stimulation

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Abstract

Chronic neuropathic pain caused by injury to or disease in the nervous system is relatively common and results in major suffering, poor quality of life and incapacity. Such pain is a therapeutic challenge because a considerable portion of the patients fails to benefit from pharmacotherapy. Therefore, there is a need for alternative treatment modalities. Spinal cord stimulation (SCS) has proven to be effective in the management of some forms of neuropathic pain.

The experimental studies constituting this thesis address various aspects of neuropathic pain of peripheral origin and the mode of action of SCS. Neuropathic pain is generally associated with abnormal responsiveness of the somatosensory system sometimes presenting as increased sensitivity to mechanical stimuli. Animal experimental models supposedly representing neuropathic pain, especially evoked pain, typically exhibit signs of neuropathy in the form of local cutaneous hypersensitivity.

In the present thesis a model of neuropathy (rat) according to Seltzer et. al. (1990) was used. In behavioral tests the withdrawal thresholds in response to von Frey filaments, cold spray and radiant heat were assessed. Possibly attenuating effects of SCS on hypersensitivity were examined in the awake and freely moving animal.

Immunohistochemistry, Western Blot, ELISA, microdialysis and HPLC were employed for the analysis of some transmitters and receptors related to neuropathic pain and/or SCS effects. Various agonists/antagonists were administered intrathecally for the evaluation of the significance of the corresponding spinal receptors in mechanisms underlying SCS effects. Activation of the glutamatergic NMDA receptor in the spinal dorsal horn (DH) is essential for central sensitization and plays an important role in the generation and maintenance of neuropathic pain. Quantification of dorsal horn NMDA receptor subunit expression was based on comparisons between the DHs ipsi- and contralateral to the nerve lesion. The phosphorylation of the NR1 subunit of the NMDA receptor was significantly increased in the ipsilateral DH in hypersensitive, but not in non-hypersensitive nerve injured rats. The non-phosphorylated NR1, NR2A, NR2B, NR2C or the NR2D subtypes were unaffected by the nerve injury as compared to controls.

A dysfunctional spinal GABAergic system is considered to be an important feature of neuropathic pain and this might imply also a reduced synthesis of GABA. The DH levels of the GABA synthesizing enzymes, glutamic acid decarboxylase (GAD) 65 and 67, were analyzed after nerve injury and following application of SCS. The expression of both enzymes appeared to be increased in SCS responding rats subjected to SCS immediately prior to tissue collection as compared to responders without stimulation. In non-responding rats subjected to SCS, a similar increase in GAD67 was also present. Without stimulation, nerve injury per se was not associated with any changes in enzyme expressions regardless of whether or not hypersensitivity was present.

On the basis of preceding observation that clonidine may enhance the SCS effect, experiments with microdialysis of the DH of nerve injured rats and quantitative assessment of extracellular acetylcholine (ACh) release were performed. The basal ACh release was significantly lower in nerve injured than in normal rats. In SCS responding, but not in SCS non-responding rats, application of SCS produced an increased release of ACh. In behavioral experiments, the muscarinic M_4 receptor was identified as the principle one being involved in cholinergic SCS mechanisms. The nicotinic receptor appeared to be of no significance in this study.

There is evidence that the SCS effect is partly exerted via a spinal-supraspinal-spinal loop and most probably comprises descending serotonergic pathways. When SCS was applied in nerve injured rats immediately prior to sacrifice, the 5-HT content in the dorsal quadrant of the spinal cord ipsilateral to the injury was increased in SCS responding rats. There was in these rats also a high density of 5-HT immunoreactive terminals in the DH superficial laminae (I-II) as demonstrated immunohistochemically. The potency to attenuate mechanical hypersensitivity of SCS could be significantly enhanced by a low dose of intrathecal serotonin, and this effect was partially blocked by a $GABA_B$, but not by a muscarinic M_4, receptor antagonist.

There are conflicting results regarding the predictive value of certain neurological symptoms, e.g. cutaneous sensory abnormalities, for the outcome of SCS treatment. In animal models of neuropathic “pain”, the incidence, extent and severity of hypersensitivity is quite variable. A series of rats exhibiting signs of neuropathy were subdivided in groups according to the severity of mechanical hypersensitivity and then subjected to SCS. It appeared that SCS produces a faster and more effective attenuation of hypersensitivity in rats with mild as compared to those with more severe sensory disturbance.

In conclusion, the current studies have shown that in the DH of a rodent model of neuropathy, the expression of non-phosphorylated NMDA receptor subtypes as well as of GABA synthesizing enzymes is not affected by a nerve injury, irrespective of the presence of neuropathic signs. SCS appears to produce a moderate augmentation of the GABA synthesizing enzymes. There is evidence indicating that SCS may activate several pain modulatory systems, and here it has been shown that both cholinergic and serotonergic mechanisms are involved in the SCS effect. The latter may relate to a stimulation-induced restoration of a dysfunctional descending inhibitory and/or facilitatory supraspinal endogenous control. The different SCS mechanisms may operate independently, in parallel or in concert. Finally, the relationship between the outcome of SCS and degree of hypersensitivity demonstrated in an animal model may have clinical implications.

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