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Central neuropathic pain in mouse models of spinal cord injury: effects of sensorimotor activity

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Central neuropathic pain is a common and excruciating consequence of traumatic spinal cord injury. Up to 60 % of all patients with spinal cord injury suffer from debilitating positive and negative signs of neuropathic pain below the level of injury. Effective means for treating this type of pain are limited and alternative treatment strategies are urgently needed.

The mechanisms underlying the evolution and persistence of neuropathic conditions following spinal cord injury are only partially understood. Sprouting and robust arborization of primary nociceptive afferents into deeper laminae of the dorsal horn (III - V) seem to contribute to the development of central neuropathic pain. Targeting the dynamic changes of primary nociceptive afferents in the lumbar level of the spinal cord and the consequent misconnectivity might be a promising approach to alleviate below-level neuropathic pain. In rodent studies physical activity has been demonstrated to bear enormous potential for modulating neuroplasticity in the injured spinal cord and emerging evidence supports sensorimotor activation as beneficial approach for treating neuropathic pain in both animals and humans. The causal relationship between sensorimotor activity and plasticity at the level of structure, connectivity and representation of pain, however, remains largely unexplored in spinal cord injury. Thus, a thoracic (T11) spinal cord contusion model of below-level pain was established in female C57BL/6 mice to better characterize the behavioral and morphological correlates of central neuropathic pain in spinal cord injury. Furthermore, the influence of early-onset sensorimotor activity on pain behavior and pain associated changes of incoming nociceptive fibers was tested.

The extensive behavioral characterization revealed positive and negative signs of neuropathic pain similar to spinal cord injury pain in humans. Injured mice developed mechanical allodynia, but presented hyporesponsiveness to noxious mechanical stimulation. Furthermore, animals with spinal cord injury exhibited significant hypersensitivity to heat stimuli but developed remarkable cold hyposensitivity. Both spontaneous pain-related behavior and the behavior in a newly developed place escape/avoidance paradigm demonstrated an emotional-

affective component of below-level pain in this spinal cord injury model and involvement of supraspinal levels of the neuraxis. Therefore, the established mouse model lays a solid foundation for future preclinical studies of spinal cord injury neuropathic pain. In particular, it allows for genetic manipulations.

Importantly, this work demonstrates that sensorimotor activity ameliorates signs of below-level pain. Moderate treadmill training significantly reduced mechanical allodynia and spontaneous pain-related as well as escape/avoidance behavior. Abnormalities in temperature sensation and lost mechanosensory function, however, were not influenced by physical activity. Of note, the development of neuropathic pain was paralleled by increased calcitonin gene-related peptide labeling density in deeper laminae (III – IV) of the spinal dorsal horn. Importantly, sensorimotor activity reduced calcitonin gene-related peptide labeling density by about 50 %, partially reducing the injury-induced increases. Analysis of isolectin B4 labeled non-peptidergic sensory fibers revealed no differences between experimental groups.

The findings strongly suggest a relationship between calcitonin gene-related peptide labeled fiber density in deep layers of the dorsal horn and mechanical allodynia that are both reduced by locomotor training. The mechanisms underlying the increased density of calcitonin gene-related peptide positive fibers remain to be explored, but are likely due to injury-induced sprouting of afferent nociceptive fibers leading to central sensitization. To conclusively clarify this issue transgenic animals expressing reporter genes in specific sensory neuron subpopulations are needed. How sensorimotor activation modulates the injury-induced fiber changes is still unknown. Changes of neurotrophic factors might be involved but causal evidence is still lacking. To comprehensively explore the modality-specific effect of sensorimotor activity, the essential components of the successful training paradigm need to be identified by varying the training start, quantity, intensity and duration. Thermo-specific training paradigms might be used as rehabilitative means for thermal hypersensitivity in spinal cord injury.

In conclusion, this work provides a useful mouse model of below-level pain and demonstrates that sensorimotor activity resolves neuropathic pain in a modality-specific manner by modulating aberrant plasticity of nociceptive fibers in the spinal dorsal horn. Therefore, sensorimotor activity is a promising non-pharmacological intervention to treat central neuropathic pain in spinal cord injury.