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Mechanisms underlying central pain in animal models of multiple sclerosis and stroke

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Mechanisms underlying central neuropathic pain are not well understood. While central pain can be induced by all kinds of lesions or dysfunctions in the central nervous system, it is especially frequent in patients suffering from cerebrovascular lesions and patients affected by multiple sclerosis. Although a disturbance of the central somatosensory-pathways has been identified as a prerequisite for the development of central pain, the exact nature, location and pathophysiology of this lesion in central pain states induced by stroke or multiple sclerosis have not been worked out so far. Partially this is due to the lack of a robust animal model for central pain, which seriously limited the research in this field.
To elucidate the pathophysiological changes underlying central pain associated with multiple sclerosis, we reproduced a primary parameter of the multiple sclerosis pathophysiology, namely breakdown of the oligodendrocyte-myelin-axon unit, by expressing the diphtheria toxin receptor specifically in mouse oligodendrocytes using Cre/lox system and applying diphtheria toxin. Detailed behavioral analysis in mice that underwent inducible oligodendrocyte ablation revealed a distinct deviation from normosensitivity consisting of lowered mechanical and cold thresholds and unaltered heat thresholds, a pattern often observed in neuropathic pain states. This behavioral phenotype preceded overt demyelination in the spinal cord and was associated with marked and progressive axonal degeneration within the spinothalamic tract but not with an adaptive immune response. This clearly demonstrates that oligodendrocyte dysfunction-induced axonal degeneration, in the absence of obvious demyelination or neuroinflammation, is sufficient to trigger central neuropathic pain.
Additionally, we successfully generated and characterized a mouse model for cerebrovascular lesion induced central neuropathic pain that is based on a unilateral stereotactic lesion of the thalamic ventral posterolateral nucleus. Our analysis of mice that underwent targeted injury to the thalamus revealed that injury to the ventral posterolateral nucleus is sufficient to trigger a deviation from normosensitivity that is comparable to the nociceptive hypersensitivity commonly observed in patients with central neuropathic pain. Surprisingly, pharmacological inhibition of spinal and peripheral key components of the pain system failed to influence nociceptive hypersensitivity following thalamic injury. In contrast, on-going neuronal activity in the thalamic ventral posterolateral nucleus, a major projecting zone of the spinothalamic tract, emerged as an important pathophysiological mechanism.
Taken together, these findings clearly elucidate the important role of injury to the spinothalamic tract and its major projecting zone the ventral posterolateral nucleus of the thalamus in the development of diverse central neuropathic pain states. These results also support the hypothesis that lesion induced thalamic hyperexcitability plays a fundamental role in the maintenance of central neuropathic pain.