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Risk of dementia/depression and associated inflammatory mechanisms in spinal cord injury

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Spinal cord injury (SCI) research has focused on sensorimotor deficits, neuropathic pain and/or autonomic dysfunction. Although not well appreciated clinically, SCI can cause cognitive impairment including deficits in learning and memory, executive function, attention, and processing speed; it also commonly leads to depression. Although cognitive alterations have been discounted as likely reflecting undiagnosed concurrent head injury (TBI), studies clearly show that SCI patients who present without a history of TBI may develop cognitive decline and other neuropsychiatric abnormalities. Use of an anti-inflammatory drug in one recent clinical trial improved mood after SCI. Yet, little basic research has addressed potential mechanisms for cognitive or affective disorders after injury. We report that cognitive impairment in Y-maze, novel objective recognition, and step-down fear conditioning tasks were increased in moderate and severe-injury mice that also displayed depressive-like behavior as quantified in the sucrose preference, tail suspension, and forced swim tests. The potent microglial activator cysteine-cysteine chemokine ligand 21 (CCL21) was elevated in the brain sites after SCI in association with increased microglial activation. Such inflammation is associated with greater neuronal endoplasmic reticulum (ER) stress and reduction in the number of newly-generated immature neurons in the hippocampal dentate gyrus. These findings indicate that SCI causes chronic neuroinflammation that contributes to neuronal loss, impaired hippocampal neurogenesis and increased neuronal ER stress in important brain regions associated with cognitive decline and physiological depression. Accumulation of CCL21 in brain may subserve a pathophysiological role in cognitive changes and depression after SCI.

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