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Abstract

Neuroprotective Therapies in Spinal Cord Injury, the First and Necessary Step towards the Cure †

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A trauma to the spinal cord involves the massive injury to the white matter and initiates a severe, destructive and extraordinarily protracted inflammation characterized by heavy infiltration by CD68+/CD163-, inflammatory macrophages. Post-traumatic destruction of the spinal cord by phagocytic macrophages along with a marked elevation of pro-inflammatory cytokines, including IFN-γ, IL-1α, IL-1β, IL-6 and of chemokines indicates the need for anti-inflammatory therapies to inhibit and eliminate these damaging processes and to result in neuroprotection. In a rat model of the balloon crush over the mid-thoracic spinal cord from the 3Fogarty catheter placed epidurally a deep area of necrosis and hemorrhage resulting from the trauma is converted into a cavity of injury (COI) filled by necrotic debris and hemorrhage and filling up with excess edema fluid. The COI is defined by progressively severe astrogliosis forming a wall whose thickness grows with a progressive lowering of the numbers of phagocytic macrophages beyond 16 weeks post-SCI. An area of necrosis that is superficial with disruption of a wide area of the surface of the spinal cord, it becomes invaded by granulomatous inflammation from the sub-arachnoid space including macrophages, fibroblasts and blood vessels. The expansion of this type of inflammation, called arachnoiditis, is counteracted by a progressively severe astrogliosis and in time it is often separated from the spinal cord by liquid-containing cystic spaces not unlike the COI. A macrophage count in the COI test has been developed to measure the severity of inflammation and also, to measure the anti-inflammatory effect of a candidate treatment. It involves counting phagocytic macrophages in a standardized fashion at the margin of the COI in consecutive sections of the spinal cord stained with luxol fast blue and haematoxylin and eosin (LFB+H&E). This new analytic method allowed for detection of a powerful anti-inflammatory effect of dexamethasone and two Myxomavirus-derived proteins, Serp-1, with anti-thrombotic/anti-thrombolytic action, and M-T7, a chemokine inhibitor. Each of these 3 agents were administered by a continuous subdural infusion in the vicinity of the SCI for one week and resulted in lowering of the numbers of macrophages by 50-80% with remarkable slowing down of the phagocytosis of myelin-rich necrotic debris and hemorrhages in the COI, indicating the need for much longer administration to eliminate the debris by drug-reduced phagocytosis. While administration of dexamethasone has proven to result in severe toxicity leading to shock, both viral proteins were well tolerated. Continuous subdural administration of Serp-1 for 8 weeks resulted in elimination of phagocytic macrophages from the COI. This is the first pre-clinical study demonstrating that an anti-inflammatory treatment can effectively shorten the inflammatory disease and result in neuroprotection. The inhibition and elimination of severe, destructive inflammation post-SCI is the first and necessary step in a multistep therapy leading to the cure of severe spinal cord trauma. Once inflammation is eliminated, implantation of a bridge into the COI that will support axonal regeneration in neuroregenerative therapies can be contemplated.

Keywords: spinal cord; neuroregenerative therapies