

Fumaric Acid Esters Attenuate Secondary Degeneration and Promote Functional Recovery Following Experimental Spinal Cord Injury

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Spinal cord injury (SCI) is defined as an acute traumatic lesion of neural elements in the spinal canal (spinal cord and cauda equina), resulting in a change, either temporary or permanent, in normal motor, sensory, or autonomic function. SCI usually begins with a sudden, traumatic blow to the spine that causes local segmental damage to the spinal cord, which is called primary injury. The primary damage to tissue is followed by a second phase of tissue degeneration, the 'secondary injury', that can occur over weeks or even months. In secondary injury, acute inflammation can develop into a chronic process if feedback mechanisms fail to inhibit amplification of the inflammatory response.

Fumaric acid esters (FAEs) display immunomodulatory properties and significantly reduced relapse and disability progression in patients with relapsing-remitting multiple sclerosis. The mechanism of action is not yet completely understood, but recent study has been demonstrated that treatment with FAEs significantly reduces leukocyte infiltration in experimental autoimmune encephalomyelitis and also activates the Nrf2 antioxidant response pathway, the primary cellular defence against the cytotoxic effects of oxidative stress.

The aim of the present study was to evaluate the potential beneficial effects of dimethyl fumarate (DMF) and monomethyl fumarate (MMF) in a mouse model of traumatic SCI.

Mice were anaesthetized using ketamine and xylazine (2.6 and 0.16 mg/kg body weight respectively) administered intraperitoneally. A longitudinal incision was made on the midline of the back, exposing the para-vertebral muscles. The spinal cord was exposed via a four-level T5-T8 laminectomy and SCI was produced by extradural compression for 1 min of the spinal cord using an aneurysm clip with a closing force of 24 g. DMF and MMF (both at 30 mg/kg) were orally administered to the mice 1 and 6 h after SCI, and for locomotor activity studies once daily thereafter for 10 d.

Motor function (Basso Mouse Scale) was evaluated after injury and we observed that mice treated with DMF exhibited a significantly more rapid and sustained recovery of motor function. FAEs significantly reduced the severity of inflammation by a modulation of proinflammatory cytokines and apoptosis factors, and increased neurotrophic factor as well as BDNF, GDNF and NT-3 that characterized the secondary effects of SCI. The effects of DMF were superior to those of MMF on several parameters. These results showed marked protective effects of DMF in an animal model of SCI, significantly enhancing recovery of motor function, possibly by reducing the secondary inflammation and tissue injury that characterize this model. In summary, DMF may constitute a promising target for future SCI therapies.