Diagnostic and therapeutic strategies following spinal cord and brachial plexus injuries

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av medicine doktorsexamen framläggs till offentligt försvar i Sal N320, Naturvetarhuset, fredagen den 9 december, kl. 13:00.
Avhandlingen kommer att försvaras på engelska

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Abstract

Traumatic injuries to the spinal cord and brachial plexus induce a significant inflammatory response in the nervous tissue with progressive degeneration of neurons and glial cells, and cause considerable physical and mental suffering in affected patients. This thesis investigates the effects of the antioxidants N-acetyl-cysteine (NAC) and acetyl-L-carnitine (ALC) on the survival of motoneurons in the brainstem and spinal cord, the expression of pro-apoptotic and pro-inflammatory cell markers, axonal sprouting and glial cell reactions after spinal hemisection in adult rats. In addition, a novel MRI protocol has been developed to analyse the extent of neuronal degeneration in the spinal cord.

Rubrospinal neurons and tibial motoneurons were pre-labelled with the fluorescent tracer Fast Blue one week before cervical C3 or lumbar L5 spinal cord hemisection. The intrathecal treatment with the antioxidants NAC (2.4 mg/day) or ALC (0.9 mg/day) was initiated immediately after injury using Alzet 2002 osmotic mini pumps. Spinal cord injury increased the expression of apoptotic cell markers BAX and caspase 3, induced significant degeneration of rubrospinal neurons and spinal motoneurons with associated decrease in immunoreactivity for microtubule-associated protein-2 (MAP2) in dendritic branches, synaptophysin in presynaptic boutons and neurofilaments in nerve fibers. Immunostaining for the astroglial marker glial fibrillary acidic protein and microglial markers OX42 and ED1 was markedly increased. Treatment with NAC and ALC attenuated levels of BAX, caspase 3, OX42 and ED1 expression after 2 weeks postoperatively. After 4-8 weeks of continuous intrathecal treatment, NAC and ALC rescued approximately half of the rubrospinal neurons and spinal motoneurons destined to die, promoted axonal sprouting, restored the density of MAP2 and synaptophysin immunoreactivity and reduced the microglial reaction. However, antioxidant therapy did not affect the reactive astrocytes in the trauma zone. The inflammation modulating properties of ALC were also studied using cultures of human microglial cells. ALC increased the microglial production of interleukin IL-6 and BDNF, thereby possibly mediating the anti-inflammatory and pro-regenerative effects shown in vivo.

To study degeneration in the spinal cord following pre-ganglionic and post-ganglionic brachial plexus injuries, adult rat models of ventral root avulsion and peripheral nerve injury were used. A novel MRI protocol was employed and the images were compared to morphological changes found in histological preparations. Ventral root avulsion caused degeneration of dendritic branches and axonal terminals in the spinal cord, followed by significant shrinkage of the ventral horn. Extensive astroglial and microglial reactions were detected in the histological preparations. Peripheral nerve injury reduced the density of dendritic branches but did not cause shrinkage of the ventral horn. Quantitative analysis of MRI images demonstrated changes in the ventral horn following ventral root avulsion only, thus validating the developed MRI technique as a possible tool for the differentiation of pre-ganglionic and post-ganglionic nerve injuries.

Keywords: Spinal cord injury, brachial plexus injury, acetyl-L-carnitine, N-acetyl-cysteine, MRI, motoneurons

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