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Post-Injury Administration of an NK1 Receptor Antagonist Ameliorates the Neuroinflammatory Response in a Rodent Model of Traumatic Brain Injury

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Introduction: It is now realised that inflammation plays a key role in many CNS pathologies. In the CNS neuroinflammation can be mediated via glial cells, but can also be associated with compromised blood-brain barrier (BBB) function that can follow acute insults, such as a traumatic injury (TBI). Using an animal model of TBI, we have demonstrated that selective NK1 antagonists are able to restore BBB function following injury *(Donkin et al., 2009).*The aim of the present study was to use a rodent model of TBI to assess whether post-injury administration of an NK1 receptor antagonist can ameliorate the neuroinflammatory response associated with injury. Raised serum IL-6 levels are recognised as a biomarker of neuroinflammation associated with TBI, particularly where intracranial pressure is raised (*Hergenroeder et al., 2010*). In this study we assessed the effect of post-injury administration of an NK1 antagonist on serum IL-6 levels, as well as on the levels of IL-1β, IL-6 and TNFα mRNA expression in the cerebral cortex.

Methods: Adult male Sprague-Dawley rats (350-450gms) were used in this study (n=20). Animals were anesthetized with isoflurane, and subject to either a sham injury (n=10) or a severe TBI (n=10). Severe TBI was induced using the impact-acceleration model of diffuse axonal injury as previously described (*Foda,& Marmarou,1994*). Animals in the injury and sham-injury groups were randomly assigned to receive either post-injury treatment with an NK1 antagonist (N-acetyl tryptophan; 2.4mg/kg) or drug vehicle (n=5/group). Animals were killed by decapitation 6 hours after injury, and serum samples collected. Brains were excised, and cortical tissues were snap-frozen in liquid N_2.

Serum levels of IL-6 were determined by ELISA using a rat-specific monoclonal antibody. Total mRNA was extracted from cortical tissue samples and purified. TaqMan gene expression assays for IL-6, IL-1β and TNF-α were used, and quantitation relative to rpl32 expression was achieved by the comparative CT method. Statistical significance was determined using a one-way analysis of variance (ANOVA).

Results: In sham-injured animals, serum IL-6 levels were 103.7 ± 14.7pg/ml. Animals subject to TBI and treatment with drug vehicle showed a significant rise in IL-6 levels (289.3 ± 75.9pg/ml; $p < 0.01$). However, in animals treated with an NK1 antagonist 30mins after injury, there was no significant rise in serum IL-6 levels (127.6 ± 11.7pg/ml). RT-PCR revealed a significant increase in the mRNA levels of the inflammatory mediators IL-6, IL-1β and TNF-α, with a 134-fold, 32-fold and 45-fold increase respectively ($p < 0.01$). In animals treated with the NK1 antagonist following injury, there was no significant increase in the mRNA levels of any of these inflammatory mediators.

Conclusions: The results of this study indicate that post-injury administration of an NK1 antagonist may ameliorate the neuroinflammatory response following TBI, presumably through its restoration of BBB integrity.

Donkin et al., J Cereb Blood Flow Metab. ***29****:1388-98, 2009.*

Hergenroeder et al. Journal of Neuroinflammation ***7****:19, 2010.*

Foda,& Marmarou, Neurosurg.80: 301-13, 1994.