The Effects of Pro- and Anti-Angiogenic Factors on Spinal Cord Injury

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Introduction: Angiogenesis is an essential component of wound repair and is known to occur in response to spinal cord trauma, yet its role in neurological recovery is controversial. Angiogenesis may be beneficial in the early stages of spinal cord injury (SCI) as critical nutrients can be delivered to partially damaged tissue; however, in chronic phases of SCI it may be detrimental due to leakiness of new vessels. One way to study the association between angiogenesis and recovery is to modulate the angiogenic activity. Vascular endothelial growth factor (VEGF), a known angiogenic growth factor and potent stimulator of vessel growth, is known to be upregulated following SCI [1, 2]. Preliminary studies indicate that increased vasculature is associated with functional recovery; therefore exogenous delivery of a pro-angiogenic growth factor such as VEGF may improve healing. The purpose of these studies was to modulate angiogenic activity, via pro-angiogenic VEGF and anti-angiogenic α-VEGF, and determine the effects on lesion volume and functional recovery in experimental traumatic spinal cord injury (SCI).

Methods: A total of 28 adult male Sprague-Dawley rats, each weighing between 300 to 350 g, were used in these studies. The rats were assigned to one of three treatment groups: SCI treated with VEGF (n=9), SCI treated with α-VEGF (n=10), SCI treated with saline (n=9). All animals underwent surgery under isoflurane anesthesia in which they received a laminectomy and a moderately severe contusion at level T7. The injury was produced using an in-house-designed-and-fabricated injury device [3]. The assigned treatment was administered at the time of surgery via gelfoam placed directly on the injured spinal cord. A 11x35 mm implanted RF coil was positioned above the site of injury and was inductively coupled to an external coil for improved signal-to-noise ratio. Prior to each MR session, open-field locomotion tests based on the BBB scale [4] were performed to assess functional recovery. MRI scans were performed on days 7, 14, 28, 42, and 56 post-injury using a Bruker 7T scanner. Multi-slice T1 and T2-weighted images were acquired with TE/TR of 10.4/500 ms, and 4/1,875 ms, respectively. A total of 20 contiguous and interleaved 1 mm thick axial images with a square FOV of 2.62 cm and 256 x 256 image matrix were acquired. The T2-weighted images were inspected for lesions; regions of interest, which included areas of hyper- and hypointensities, were manually selected and lesion volumes were quantified using the vendor-supplied software. Differences in the hyper- and hypointense lesion volumes for all treatment groups were evaluated using repeated measures ANOVA; Pearson's correlation was calculated for relating the BBB behavioral score with treatments.

Results and Discussions:

In the acute phase of injury, hyperintense lesions correspond to edema and hypointense lesions correspond to hemorrhage, while in the chronic stages of injury they are associated with demyelination and necrosis, respectively. The temporal changes in the hypo- and hyperintense lesions are summarized in **Figure 1**. Statistical analysis did not indicate significant differences in the hyperintense lesion volumes between the two treatment groups and saline controls at any time point. In general, the hyperintense lesion volume was smaller in VEGF treated animals compared to α-VEGF and saline treated groups. It was also found that hypointense lesion volume did not vary significantly between groups for days 7 through 42; however, it was found that hypointense lesions were significantly larger in α-VEGF versus VEGF treated animals on Day 56. Based on these results, it appears that delivery of VEGF at the time of injury results in less necrosis by 56 days post-injury; animals treated with α-VEGF appear to have more necrosis and therefore possibly increased functional deficits. Promoting angiogenesis via administration of VEGF in the early phases of injury appears to be beneficial, possibly because critical nutrients can be delivered to tissue and prevent further damage. In order to determine the treatment effect on neurological outcome, BBB scores were compared to both hyper- and hypointense lesion volumes. No significant correlation between BBB score and lesion volumes were observed for both treatment and control groups with only one exception: there was a significant negative correlation between BBB score and hypointense lesion volume in VEGF treated animals. This indicates that, as BBB score increased (signifying improved functional recovery), hypointense lesion volume decreased in the VEGF treated animals.

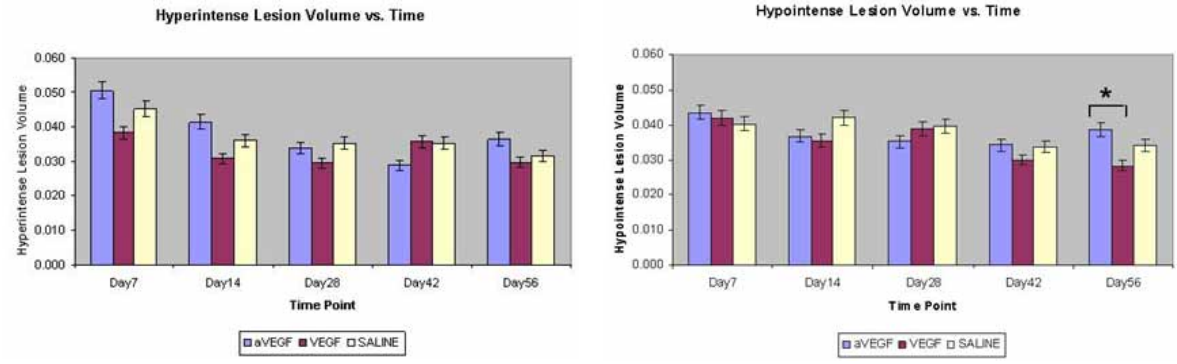

Fig 1. Plots of hyper- and hypointense lesion volume over time

Conclusions: These studies indicate that VEGF treatment early on appears to have a beneficial effect in SCI. In contrast, α-VEGF treatment in the acute phase appears to be detrimental.

References:

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