Intrathecal Infusion of Decorin to Sub-acute Contusion Spinal Cord Injury Promotes Robust Functional Recovery

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Introduction

Decorin is a small leucine-rich repeat protein that has been shown to have anti-inflammatory and anti-fibrotic properties. Direct infusion of decorin into rodent cerebral cortex or spinal cord injuries can suppress fibrotic scarring and the expression of multiple axon growth inhibitory chondroitin sulphate proteoglycans (CSPGs) and semaphorin 3A(1-3). In addition, decorin can"desensitize" neurons to the inhibitory effects of both CSPGs and myelin associated molecules(4) in vitro. In the present study we have tested the ability of decorin to promote recovery in a clinically relevant sub-acute (12 days post injury) rodent cervical spinal cord contusion injury model.

Methods

Adult female SD rats received unilateral contusion injuries at the C4/C5 spinal level (Fig. 1). At 12 days after injury matched sets of SCI rats received either intrathecal infusion of hr-decorin core protein in saline for 8 days, intrathecal infusion of saline vehicle or a catheter alone. Functional recovery was assessed at 1 to 6 weeks post treatment-with horizontal ladder and CatWalk gait analyses. BDA tracing and subsequent serial section histological analysis of corticospinal tract collateral sprouting into adjacent gray matter at the C6 spinal level was conducted for Decorin treated vs control SCI rats at 9 weeks post treatment. Serial section histological analysis was also conducted to determine decorin mediated changes in immuno-density of synapsin-1, (a synaptic vesicle transport protein and reliable indicator of synaptic acitivity) within lamina IX motor neuron pools below sites of injury.

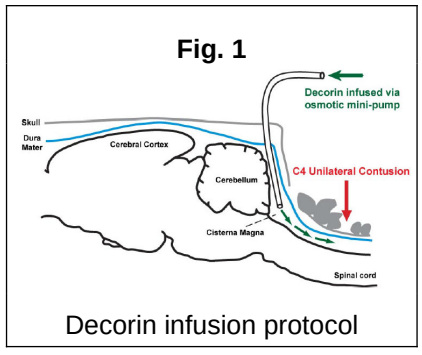

Fig 1: *Unilateral contusion injuries were conducted at the C4 /C5 spinal level. At 12 days post-injury, decorin was delivered via a trans-cerebellar approach to the cisterna magna.*

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Results

Robust functional recovery was observed in decorin treated rats in both tests compared to control spinal cord injured rats that failed to show significant improvements (Figs. 2, 6).

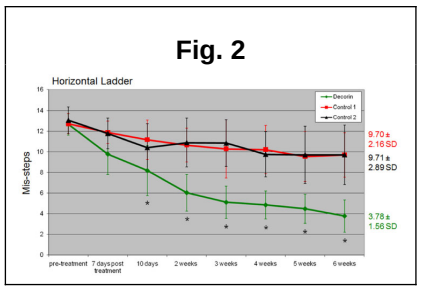
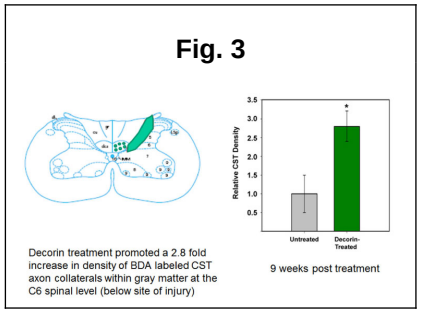


Fig. 2: *Horizontal Ladder scores for Decorin vs control 1(saline) and control 2 (untreated) SCI rats. Note the significant reductions in numbers of mis-steps for decorin treated vs control rats.*

Histological analysis of decorin treated cords revealed fold increases in densities of corticospinal tract collaterals (Figs. 3 and 4) and synaptic plasticity (Fig. 5) within spinal gray matter below sites of injury.



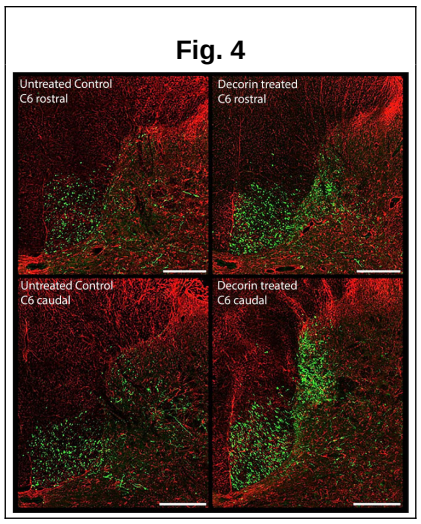


Fig. 4: *Images show BDA traced CST axon collateral sprouting into adjacent graymatter at C6 spinal level. Note the robust sprouting of CST collaterals into graymatter of decorin treated spinal cords. Red channel: GFAP; Scale bars 100 microns.*

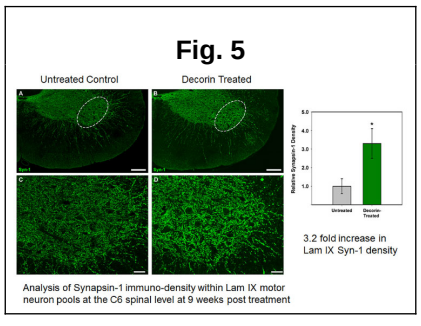


Fig. 5: Decorin treatment promotes synaptic plasticity. *Decorin treated spinal cords showed a robust 3.2 fold increase in synapsin-1 immuno-densities in motor neuron pools at the C6 spinal level below sites of injury.*

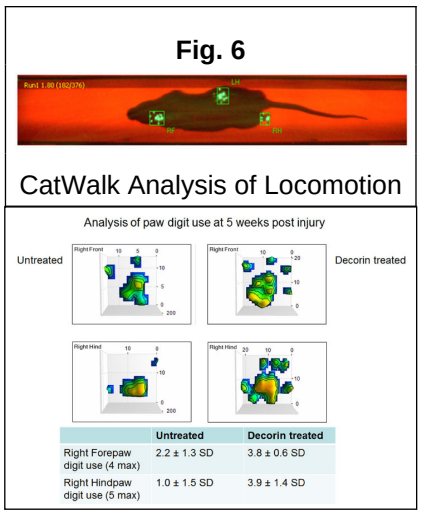


Fig. 6: *Decorin treatment promoted marked improvements in digit use in both fore and hind limbs ipsi-lateral to the side of injury at 3 weeks post- treatment compared to control untreated SCI rats.*

Conclusions

Our results demonstrate that intrathecal infusion of decorin at a clinically relevant time point of twelve days post injury can promote functional recovery and provide further support for the development of decorin as an SCI therapy.

References

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