RILUZOLE PROVIDES NEUROPROTECTION AND ATTENUATES ISCHEMIA REPERFUSION INJURY FOLLOWING SURGICAL DECOMPRESSION IN EXPERIMETNAL CERVICAL SPONDYLOTIC MYELOPATHY

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Introduction

Cervical spondylotic myelopathy (CSM), which is caused by progressive compression of the cervical cord due to spondylosis, is the most common cause of spinal cord impairment worldwide. While decompression demonstrates efficacy, the physiological consequences of decompression have yet to be studied. Here, we used a preclinical rat CSM model to characterize the physiological changes in spinal cord after decompression and to examine the synergistic effects of decompression and riluzole.

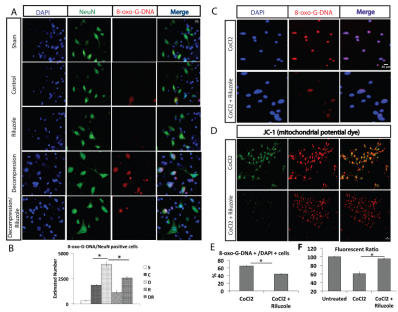
Methods

Spinal cord blood flow (SCBF) before and after decompression in CSM animals was assessed using FAIR MRI Oxidative damage and the forelimb and forepaw function were evaluated before and after decompression. Then, we developed a novel experimental paradigm to examine the effects of combinatorial strategy consists of decompression and riluzole. Gait analysis was performed weekly using a computerized kinematic assessment (CatWalk). Immunohistochemistry was used for detection of apoptosis, astrogliosis, motoneuronal survival and axonal integrity. ANOVAs was used for statistical analysis.

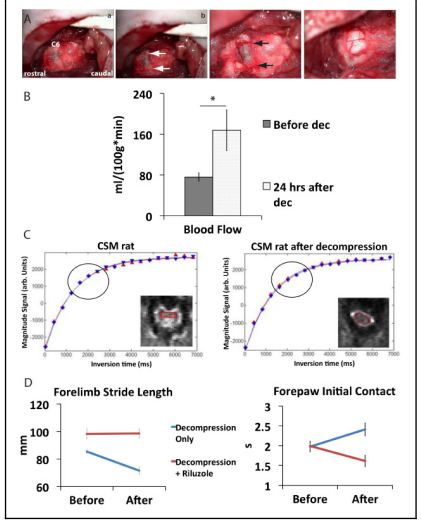
Results

We demonstrated increased SCBF, clinical decline and oxidative damage soon after decompression indicating ischemia-reperfusion injury (IRI).

In vivo and in vitro studies confirmed that decompression-mediated IRI could be prevented by riluzole administration.

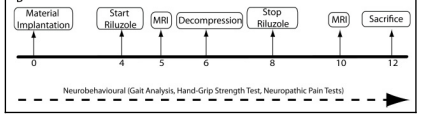


Increased SCBF following surgical decompression is associated with early neurobehavioural decline.



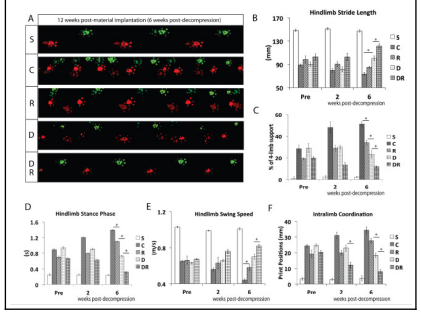
Experimental design for evaluating the effects of the combinatorial strategy consisting of surgical decompression and riluzole administration in CSM

Experimental Groups	Cervical Spinal Cord Decompression	Riluzole Administration
Sham (S)	-	-
Control (C)	-	-
Riluzole (R)	-	+
Decompression (D)	+	-
Decompression/Riluzole (DR)	+	+

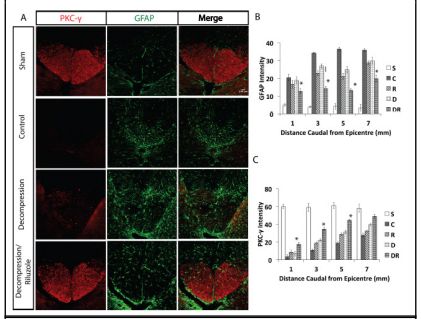


Moreover, combinatorial strategy markedly improves hand and gait function and attenuates below-level neuropathic pain compared to decompression alone. Finally, combined strategy reduces axonal damage, cellular apoptosis and motoneuronal injury in the cervical area and suppressing microglial activation in lumbar dorsal horns.

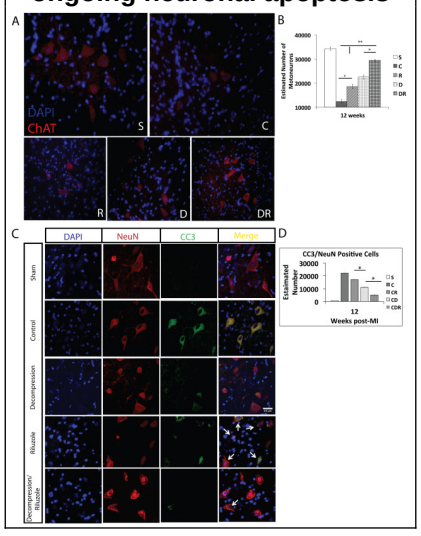
Combined decompression-riluzole treatment almost restores the normal rhythmic gait pattern.



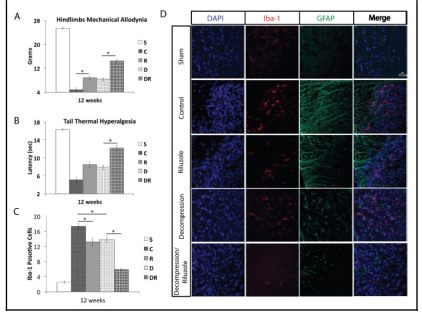
Combinatorial treatment decreases astrogliosis and promotes axonal preservation in the area of the main CST



Combinatorial treatment preserved the motoneuronal population in the anterior horn of the grey matter and markedly decreased the ongoing neuronal apoptosis



Combinatorial treatment alleviates the below level neuropathic pain by almost eliminating microglia activation and astrocytosis in the lumbar dorsal horns



Conclusions

Here we identify the development of a physiological injury in the cervical spinal cord induced by the mainstay of current treatment of CSM. This study paved the way for CSM Protect clinical trial, which examines the synergy of decompression and riluzole in human CSM.

References

1. Karadimas SK, Moon ES, Satkunendrarajah K, Kallitsis JK, Gatzounis G, Fehlings MG. A Novel Experimental Model of Cervical Spondylotic Myelopathy (CSM) to Facilitate Translational Research. Neurobiology of Disease, 2013 Mar 4;54C:43-58.
2. Karadimas SK, Erwin WM, Ely CG, Dettori JR, Fehlings MG. The Pathophysiology and Natural History of Cervical Spondylotic Myelopathy. Spine (Phila Pa 1976). Spine (Phila Pa 1976). 2013 Oct 15;38(22 Suppl 1):S21-36.