Chemogenetic Stimulation of the Lumbar Locomotor Network Enhances Motor Function Following Experimental Cervical Spinal Cord Injury: Translational Relevance for a Novel Therapeutic Strategy

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Introduction

Cervical spinal cord injury (SCI), the most common type of SCI, results in substantial motor impairment. No effective treatment options currently exist to restore motor function. The neural network responsible for locomotion resides within the lumbar region of the spinal cord. Interestingly, we discovered for first time significant neural degeneration of the lumbar locomotor network during the chronic phase of cSCI. Here, we hypothesized that early chemogenetic stimulation of the lumbar glutamatergic cells may prevent degeneration of the locomotor central pattern generator and the associated motor decline after cSCI.

Methods

Using intersectional technology we specifically expressed hM3Dq within the lumbar glutamatergic cells of mice. Following cSCI induction we administered clozapine N-oxide (CNO) intraperitonealy to activate hM3Dq. hM3Dq activation leads to depolarization, and enhanced neuronal excitability resulting in burst-like firing. Control mice with hM3Dq expression received saline. The effectiveness of stimulation was assessed using detailed gait and kinematic analysis and anatomical examination.

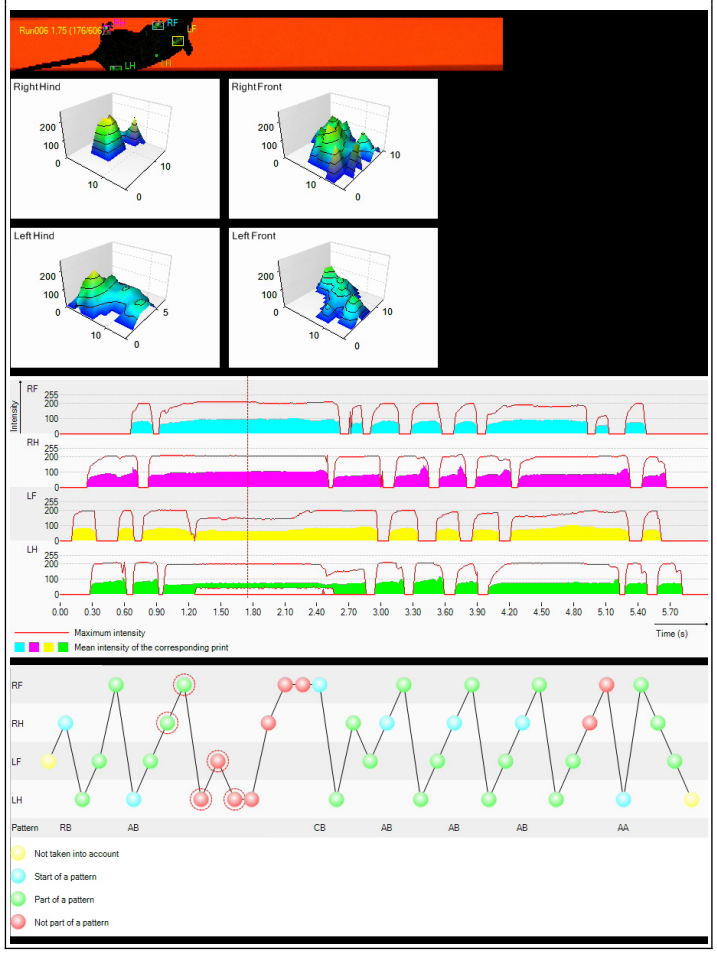
Results

At 12 weeks post cSCI, mice that underwent chemogenetic stimulation of the lumbar glutamatergic neurons demonstrated higher locomotor ability compared to controls. Specifically, chemogenetic stimulation attenuated the loss of speed, cadence and stride length during overground locomotion compared to controls. Moreover, abatement of locomotor deficits was associated with preservation of interneurons and motoneurons within the lumbar locomotor neural network compared to controls. Thus, indicating the effectiveness of stimulation therapy in preventing the degeneration of the distal locomotor network after sSCI.

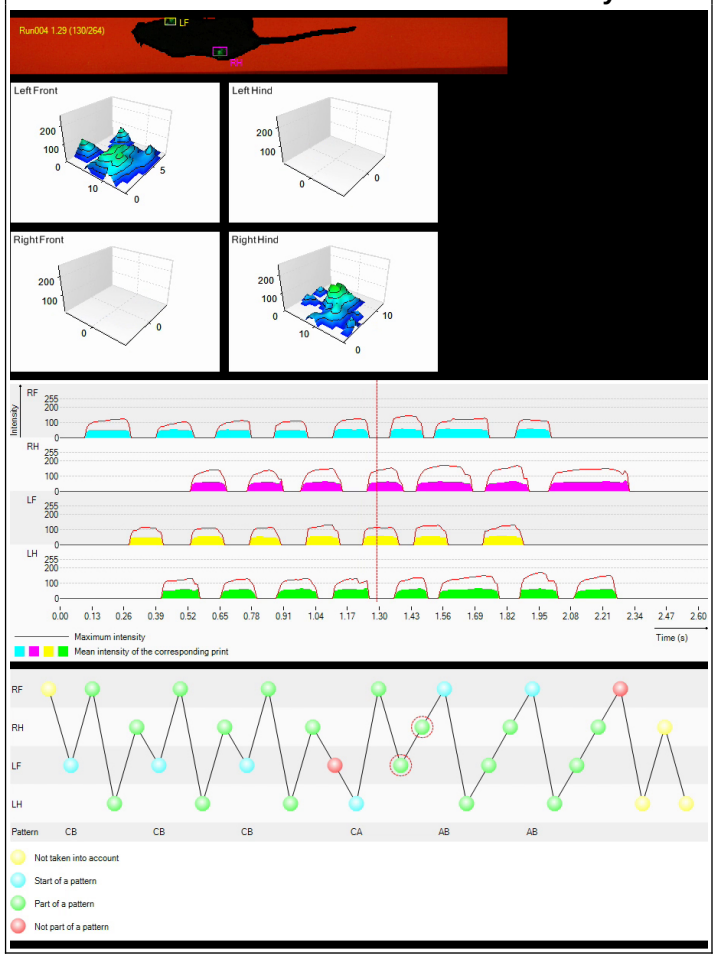
Conclusions

Early artificial replacement of the supraspinal input on lumbar glutamatergic preserves the anatomical and functional integrity of the locomotor neural network and attenuated the extent of locomotor dysfunction. Our novel and exciting work suggests that chemogenetic modulation of the lumbar locomotor network can prevent the loss of motor function following cSCI.

Control cSCI mouse



cSCI mouse with stimulated lumbar excitatory cells



Learning Objectives

Here we describe the importance of providing artificial and selective input to the electrically deprived neurons knowing that the distal locomotor network after cervical SCI is damaged.

We will inform the field for a novel effective treatment for acute and traumatic cervical spinal cord injury

References

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