Effects of chronic intrathecal infusion of BDNF on interneuronal activity in a large animal model of spinal cord injury[1]

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In the present study, we examined the correlations between the recovery of stepping obtained with intrathecal Brain Derived Neurotrophic Factor (BDNF) delivery via mini-pump to the lumbar spinal cord and the firing of the lumbar spinal interneurons in a feline model of Spinal Cord Injury (SCI).

Studies conducted on feline models of complete SCI at the thoracic level demonstrated a gradual recovery of hind limb stepping after undergoing intensive treadmill training. Similarly, delivery of neurotrophins such as Brain Derived Neurotrophic Factor (BDNF) or Neurotrophin-3 (NT-3) to the injury site via cellular transplant [1, 2] or to the lumbar cisterna via implantable mini-pump (non-published results) has been shown to independently promote recovery of locomotor behavior in the absence of locomotor training. We have previously shown that a substantial proportion of interneurons located at the L3-L7 spinal level are significantly tuned to the locomotor step cycle and power spectral analysis revealed greater multiunit power in midlumbar segments L3-L5 during air-stepping [3]. Studies on rats also showed that chronic BDNF expression increases interneurons excitability, leading to an improved hindlimb locomotion [4].

In-vivo recordings of spinal extracellular signals were conducted using two 64 channels microelectrode arrays inserted at the dorsal root entry zone of the L3-L7 lumbar segments of cats spinalized at the T11-T12 level five weeks before recordings. Activity of interneurons located between 0-3000µm depths were acquired during air-stepping trials induced by perineal stimulation. Recordings were conducted in six spinal animals, three received Brain Derived Neurotrophic Factor (BDNF, 50 ng/day) for 5 weeks after injury, and three received saline solution and served as controls.

We observed longer bouts of air-stepping walking activity, often spontaneous, i.e. not initiated by perineal stimulation, in the BDNF treated group, and consider this spontaneous locomotor behavior as a sign of a potential BDNF-induced increase in lumbar interneuronal activity. As of today, neuronal activity analysis has been completed for one treated and one control cat that both exhibited good air-stepping activity. Connection strength was evaluated using a point process generalized linear model approach (PP-GLM) to assess the strength of the connections between spike trains. Results show similar number of active interneurons in the control animal and similar connection strength between interneurons. Analysis of the remaining cats is ongoing, and we did observe poorer walking ability in the other control cats, which will hopefully support our hypothesis that BDNF-induced changes in interneuronal activity are likely involved in recovery of stepping ability after SCI.

1. Research reported in this abstract was supported by the National Institute of Health under Award Number NS055976

References:

1. Boyce, V.S., et al., Neurotrophic Factors Promote and Enhance Locomotor Recovery in Untrained Spinalized Cats. Journal of Neurophysiology, 2007. 98(4): p. 1988.
2. Krupka, A.J., Transplant of neurotrophin-producing autologous fibroblast promote recovery of treadmill stepping in the acute, sub-acute, and chronic spinal cat. Journal of Neurotrauma, 2016.
3. McMahon, C., Lumbar Spinal Interneuron Activity as it Relates to Rhythmic Motor Output in the Adult, Spinal, Air-Stepping Cat, in Department of Neurobiology and Anatomy. 2014, Drexel University
4. Boyce, V.S., et al., Differential effects of brain-derived neurotrophic factor and neurotrophin-3 on hindlimb function in paraplegic rats. The European Journal of Neuroscience, 2012. 35(2): p. 221-232.

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Abstract

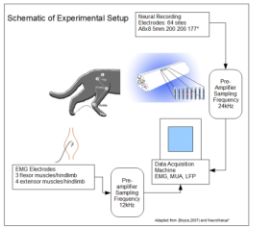
We have shown that delivery of neurotrophins to the injury site via cellular transplant or to the lumbar cisterna via implantable mini-pump promotes recovery of weight bearing stepping in cats spinalized at the thoracic level. In the present study, we examined the correlations between the recovery of stepping obtained with intrathecal BDNF delivery via mini-pump to the lumbar spinal cord and the firing of the lumbar spinal interneurons in a feline model of spinal cord injury. Our model suggests that BDNF promotes recovery by enhancing the activity of the locomotor circuit, thus compensating for the absence of descending drives. We recorded the activity of spinal interneurons of the L3-L7 lumbar segments in cats spinalized at the T11-T12 level. Recordings were conducted 5 weeks after injury in six spinal animals, three received BDNF (50 ng/day) and three received saline solution. We found locomotor activity to be superior in the BDNF treated animals, with 2/3 BDNF treated animals spontaneously locomoting for part of the session and all exhibiting locomotion bouts lasting approximately 50 secs/episode with perineal stimulation. Interneuronal connectivity was estimated using a generalized-linear-model (GLM) approach to calculate the influences between spike trains. Results show superior number of interneurons active and an increased firing frequency during the locomotor bouts in the BDNF treated animal. Connection "strengths" between interneurons in the two groups were weak, but weaker in the BDNF cats.

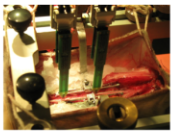
Objectives

Evaluate increase in interneuronal activity associated with stepping ability recovery following BDNF intrathecal delivery

Evaluate increase in interneuronal connectivity following BDNF intrathecal delivery

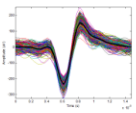
Recordings set-up



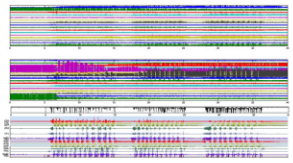


Single units identifying criteria:

1. > 300 spikes/trial
2. < 5% RPVs (2 ms)
3. > 5Hz
4. > 5 spikes/sec for walking period
5. Silence period < 1.5 sec during walking
6. SNR > 1.5



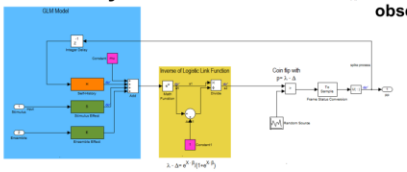
MUAs and EMGs activity during air-stepping



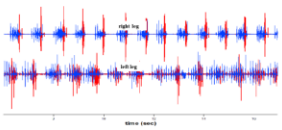
Data Analysis

Statistical Evaluation:

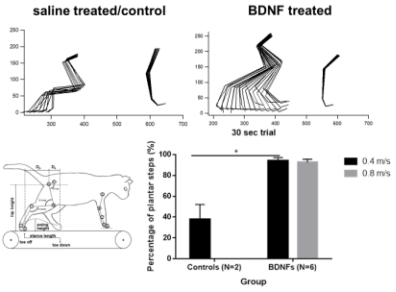
1. # units active/trial
2. Average firing frequency of units in trial
3. Connectivity (GLM coefficients)

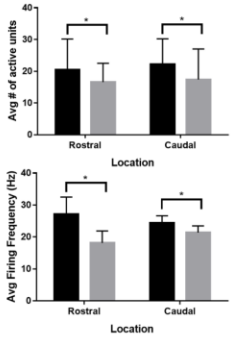


Spontaneous locomotor activity observed in 2/3 BDNF animal treated, but never in control cats

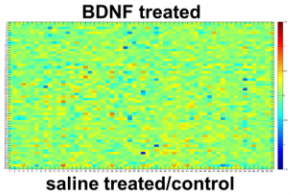


Intrathecal BDNF delivery restores stepping in untrained spinal cats

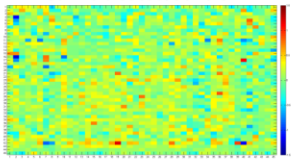


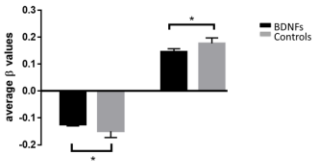


BDNF treated



saline treated/control





Conclusions

- BDNF likely induces locomotor recovery by increasing neuronal excitability as evidenced by increased # of units active during locomotor bouts and increased firing frequency for those units
- Strength of connections between recorded interneurons is weak, and weaker in BDNF treated animals