Low Dose Ampakine Stimulates Diaphragm Activity and Increases Tidal Volume following Cervical Spinal Cord Injury in Non-Anesthetized Freely Behaving Rats

Sabhya Rana1,2,3, Michael D. Sunshine1,2,3, David D. Fuller1,2,3
1Department of Physical Therapy, 2 McKnight Brain Institute, 3 Breathing Research and Therapeutics Center
University of Florida, Gainesville, Florida

A. Introduction
The majority of spinal cord injuries (SCI) occur in the cervical region. These injuries result in respiratory impairment, including the inability to clear airways. Strategies to improve respiratory muscle activation in SCI patients, either alone or in conjunction with respiratory rehabilitation, are needed. AMPA receptors mediate excitatory drive from descending brainstem respiratory centers to phrenic motor neurons. Acute treatment with an ampakine (positive allosteric modulator of AMPA receptor) can increase inspiratory phrenic output in rat models of incomplete cervical SCI when studied under anesthesia.1 The next step in translational pathway is testing efficacy of ampakines in awake rodents with SCI.

Hypothesis: Intravenous (i.v.) delivery of low dose, low impact ampakines increases diaphragm electromyographic (EMG) activity and increase breathing after C2 spinal hemisection (C2Hx) in freely moving awake rats.

B. Methods

C. C2Hx Reduces Diaphragm Activity

D. Ampakines Increase Tidal Volume

E. Effect of Ampakines on Eupneic Breathing

F. Effect of Ampakines on Challenged Breathing

G. Effect of Ampakine pre-treatment + hypoxia

H. Conclusions

- C2Hx injury impairs ipsilateral diaphragm EMG activity and decreases tidal volume.
- Low dose, low impact ampakine treatment can increase diaphragm muscle activity and ventilation after C2Hx

- No adverse off-target effects were apparent
- Ampakines in conjunction with a single bout of hypoxia can evoke motor facilitation in awake rats
- The divergent response to CX717 vs. CX1739 at 4 vs. 14 days post-injury merits further study

- 3 groups (CX717, CX1739, HPCD) n = 8 each group
- Whole body plethysmography and diaphragm EMG conducted at pre-injury, 4 and 14 days post hemisection
- 5mg/kg dose (CX717, CX1739)

Representative traces of tidal volume at 4 days post C2Hx. HPCD infusion has no effect on tidal volume, whereas ampakine (CX1739) increases tidal volume post infusion. Summary data provided in subsequent panels for 4 and 14 days post C2Hx.

References: