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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 SCI when studied *under anesthesia*.¹ The next step in translational pathway is testing efficacy of ampakines in awake rodents with SCI.

AMPA receptors on PhMNs

Phrenic motor neuron (PhMN)

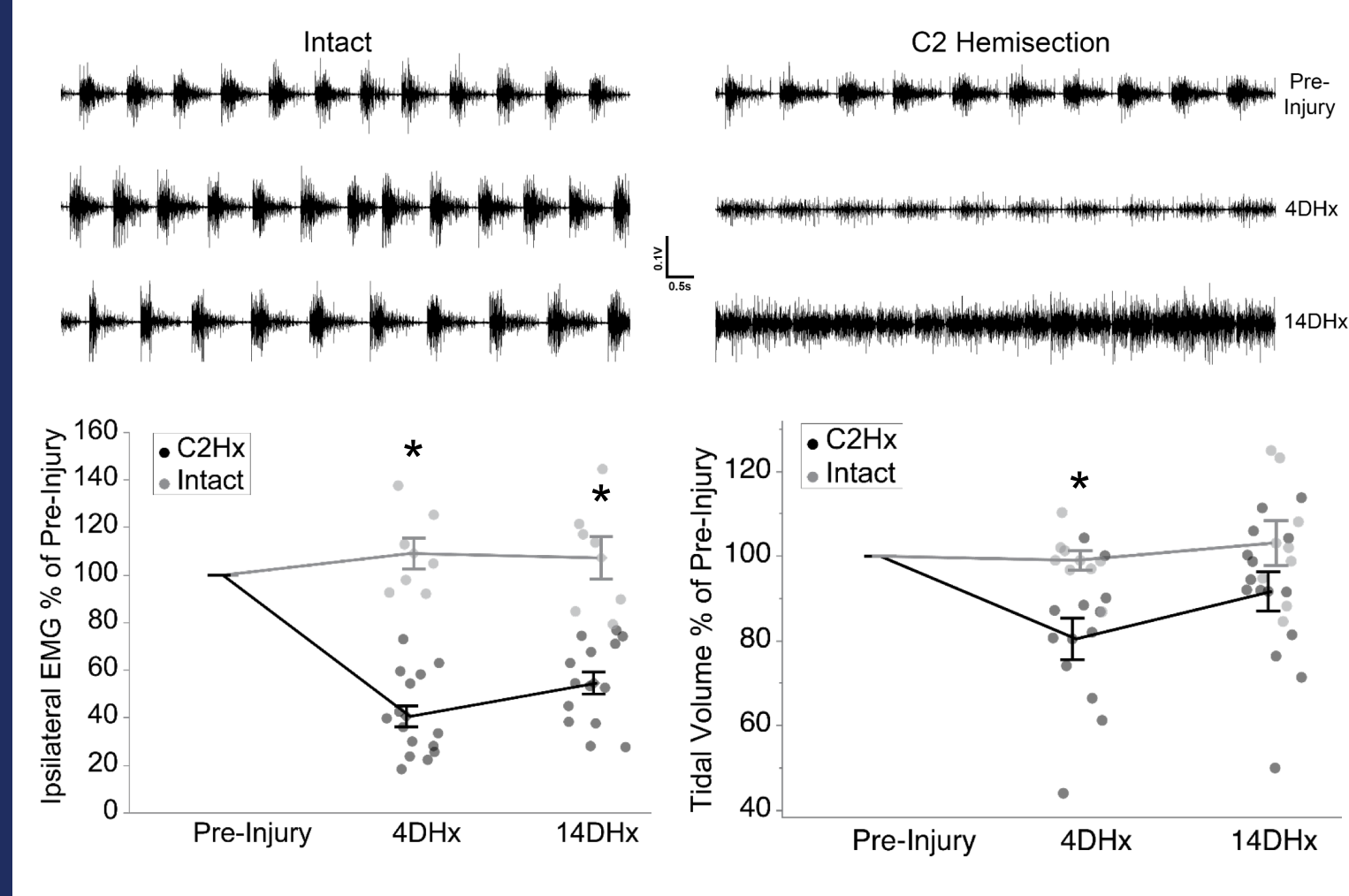
Phrenic nerve innervating diaphragm muscle

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

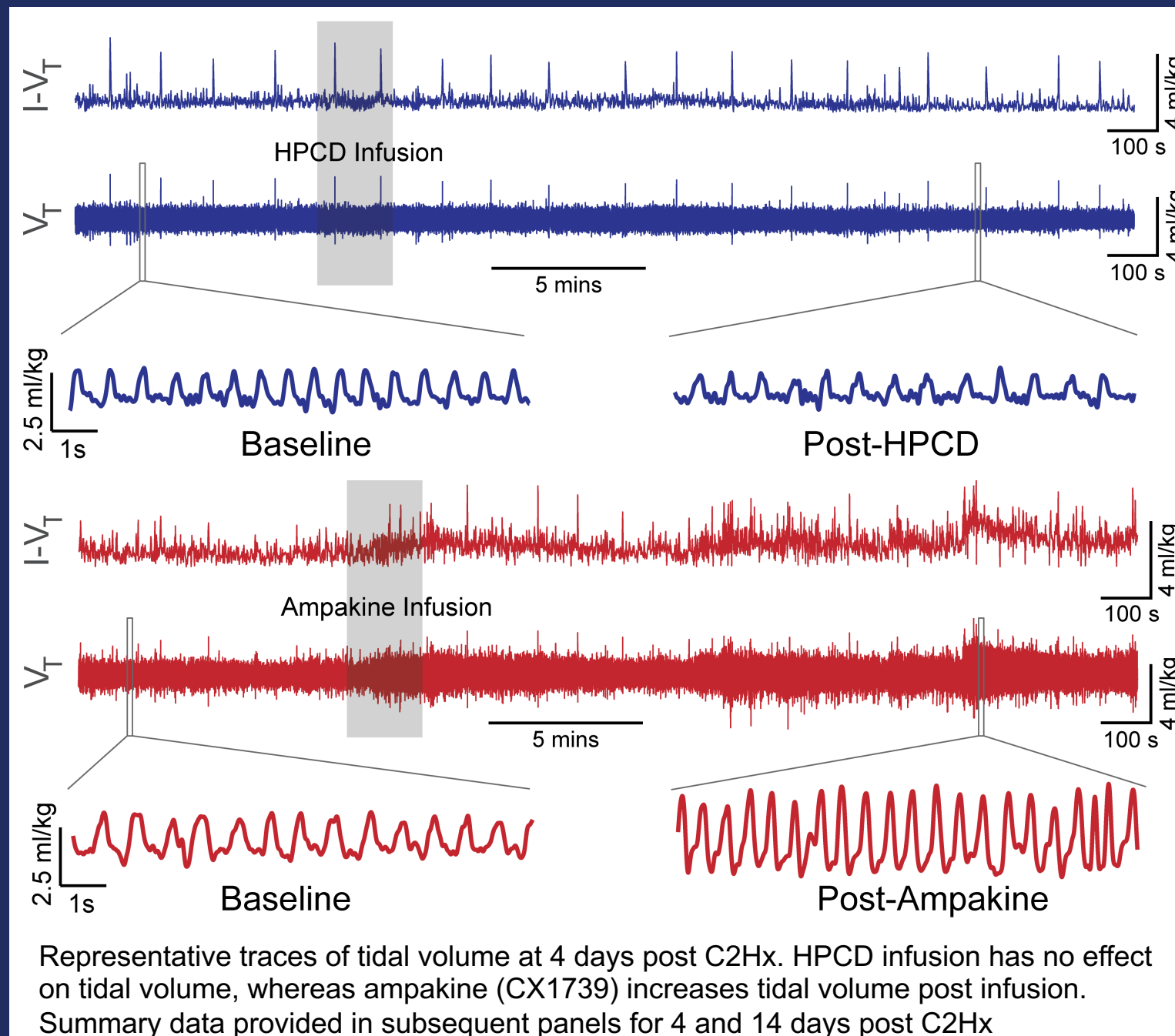
B. Methods

- 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)

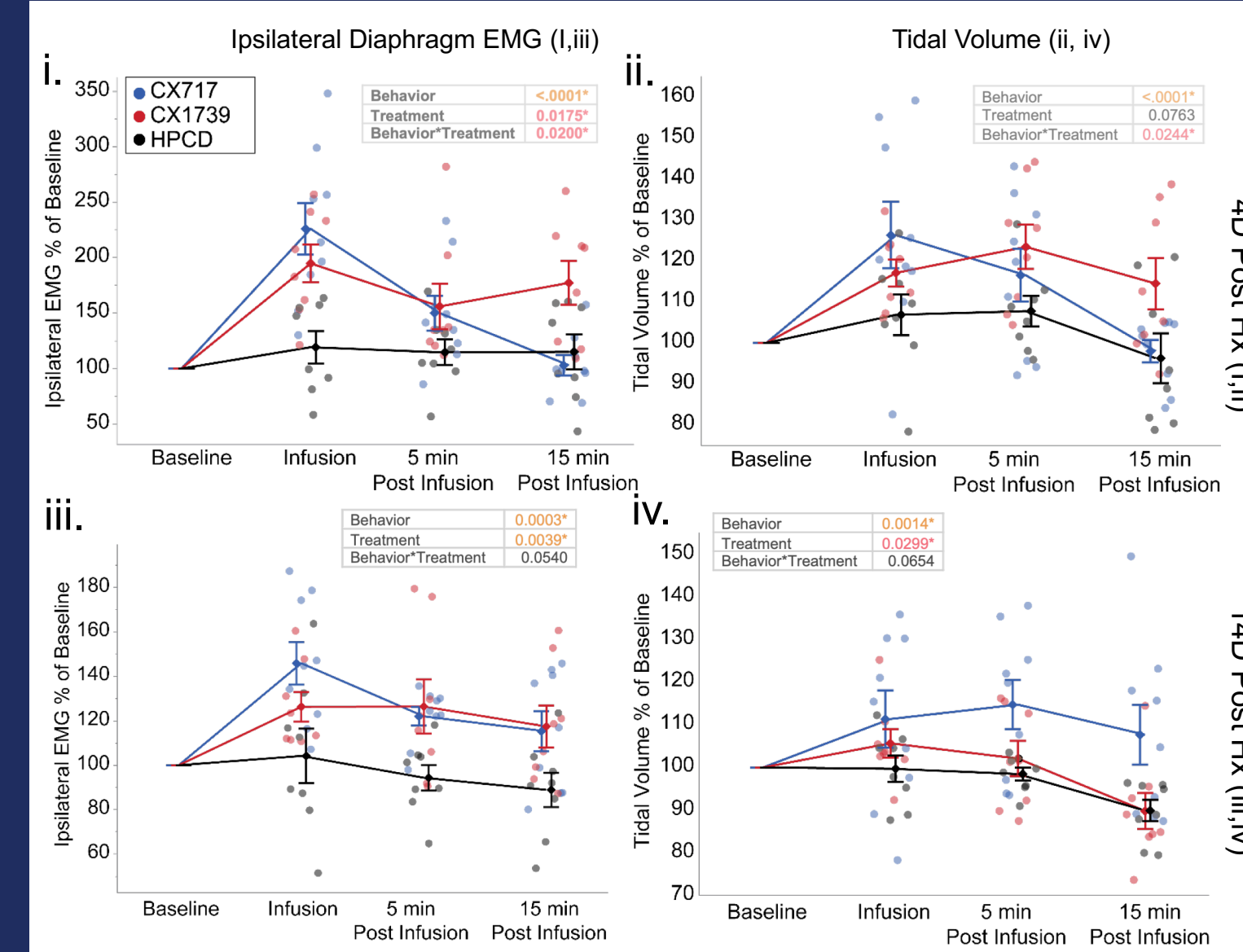
C. C2Hx Reduces Diaphragm Activity



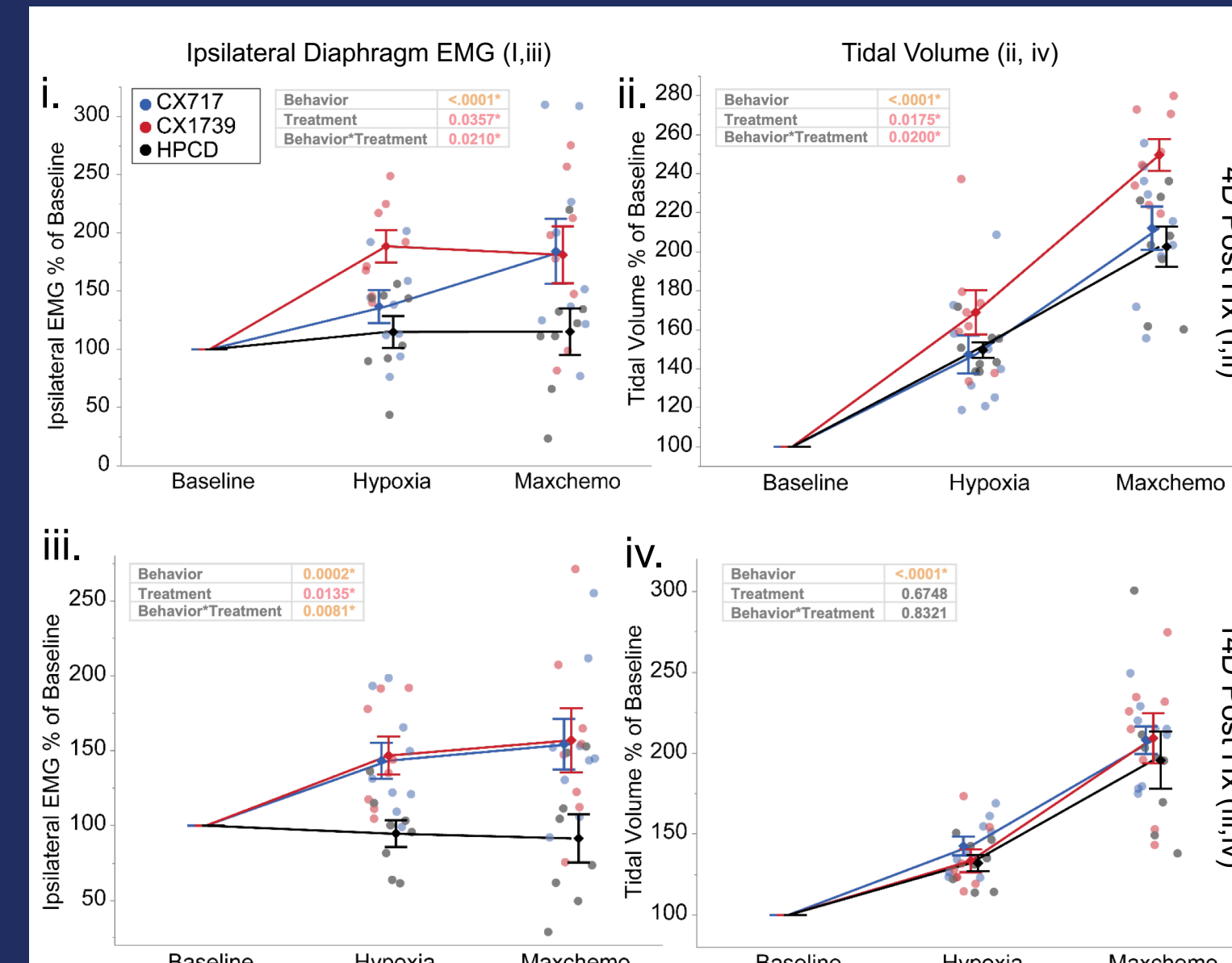
D. Ampakines Increase Tidal Volume



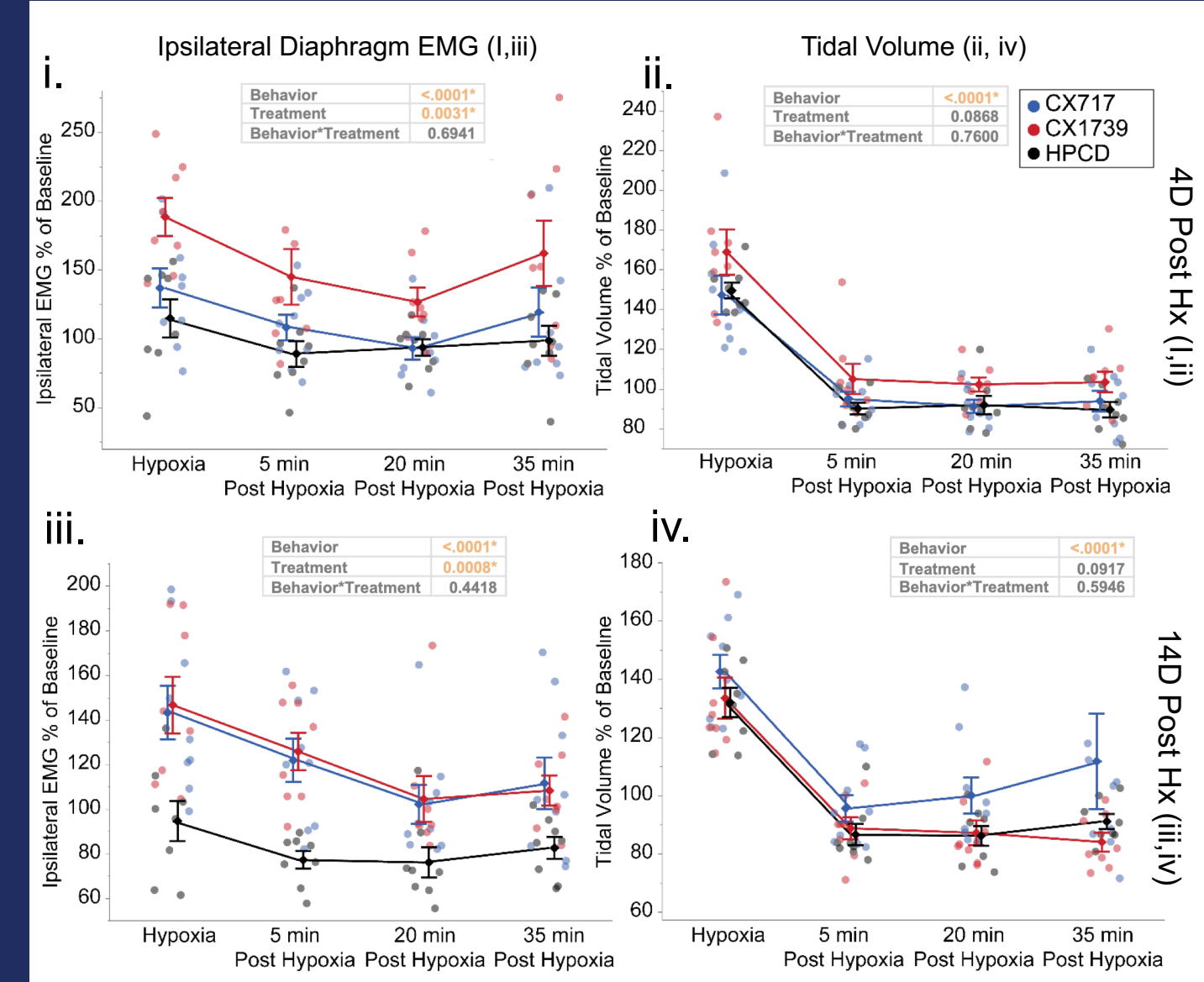
E. Effect of Ampakines on Eupneic Breathing



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

Wollman LB, Streeter KA, Fusco AF, Gonzalez-Rothi EJ, Sandhu MS, Greer JJ, Fuller DD. Ampakines stimulate phrenic motor output after cervical spinal cord injury. *Exp Neurol*. 2020 Dec;334:113465. doi: 10.1016/j.expneurol.2020.113465. Epub 2020 Sep 17. PMID: 32949571.

1R01HL139708-01A1 (DDF), 1 R01 HL153140-01 (DDF)
Thank you to Dr. Arnold Lipka from RespireRx for providing us with the ampakines.

RespireRx Pharmaceuticals Inc.