RespireRx Pharmaceuticals Inc

OTC QB: RSPI

A Translation Approach to Drug Discovery and Development: A Case Study with AMPAkines

November 8, 2022

CAUTIONARY NOTES

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FORWARD LOOKING STATEMENTS

This presentation contains certain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended (the "Securities Act") and Section 21E of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and the Company intends that such forward-looking statements be subject to the safe harbor created thereby. These might include statements regarding the Company's future plans, targets, estimates, assumptions, financial position, business strategy and other plans and objectives for future operations, and assumptions and predictions about research and development efforts, including, but not limited to, preclinical and clinical research design, execution, timing, costs and results, future product demand, supply, manufacturing, costs, marketing and pricing factors.

In some cases, forward-looking statements may be identified by words including "assumes," "could," "ongoing," "potential," "predicts," "projects," "should," "will," "would," "anticipates," "believes," "intends," "estimates," "expects," "plans," "contemplates," "targets," "continues," "budgets," "may," or the negative of these terms or other comparable terminology, although not all forward-looking statements contain these words, and such statements may include, but are not limited to, statements regarding (i) future research plans, expenditures and results, (ii) potential collaborative arrangements, (iii) the potential utility of the Company's products candidates, (iv) reorganization plans, and (v) the need for, and availability of, additional financing. Forward-looking statements are based on information available at the time the statements are made and involve known and unknown risks, uncertainties and other factors that may cause our results, levels of activity, performance or achievements to be materially different from the information expressed or implied by the forward-looking statements in this presentation.

These factors include but are not limited to, regulatory policies or changes thereto, available cash, research and development results, issuance of patents, competition from other similar businesses, interest of third parties in collaborations with us, and market and general economic factors, and other risk factors disclosed in "Item 1A. Risk Factors" in the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2021, as filed with the SEC on April 15, 2022 (the "2021 Form 10-K").

You should read these risk factors and the other cautionary statements made in the Company's filings as being applicable to all related forward-looking statements wherever they appear in this presentation. We cannot assure you that the forward-looking statements in this presentation will prove to be accurate and therefore prospective investors, as well as potential collaborators and other potential stakeholders are encouraged not to place undue reliance on forward-looking statements. You should read this presentation completely. Other than as required by law, we undertake no obligation to update or revise these forward-looking statements, even though our situation may change in the future.

We caution investors, as well as potential collaborators and other potential stakeholders not to place undue reliance on any forward-looking statement that speaks only as of the date made and to recognize that forward-looking statements are predictions of future results, which may not occur as anticipated. Actual results could differ materially from those anticipated in the forward-looking statements and from historical results, due to the risks and uncertainties described in the 2021 Form 10-K and in this presentation, as well as others that we may consider immaterial or do not anticipate at this time. These forward-looking statements are based on assumptions regarding the Company's business and technology, which involve judgments with respect to, among other things, future scientific, economic, regulatory and competitive conditions, collaborations with third parties, and future business decisions, all of which are difficult or impossible to predict accurately and many of which are beyond the Company's control. Although we believe that the expectations reflected in our forward-looking statements are reasonable, we do not know whether our expectations will prove correct. Our expectations reflected in our forward-looking statements can be affected by inaccurate assumptions that we might make or by known or unknown risks and uncertainties, including those described in the 2021 Form 10-K and in this presentation. These risks and uncertainties are not exclusive and further information concerning us and our business, including factors that potentially could materially affect our financial results or condition, may emerge from time to time.

For more information about the risks and uncertainties the Company faces, refer to "Item 1A. Risk Factors" in our 2021 Form 10-K and other reports filed or furnished with the SEC from time-to-time. Forward-looking statements speak only as of the date they are made. The Company does not undertake and specifically declines any obligation to update any forward-looking statements or to publicly announce the results of any revisions to any statements to reflect new information or future events or developments. We advise investors, as well as potential collaborators and other potential stakeholders to consult any further disclosures we may make on related subjects in our annual reports on Form 10-K and other reports that we file with or furnish to the SEC.

CAUTIONARY NOTES (cont'd)

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Project Endeavor - Neuromodulators

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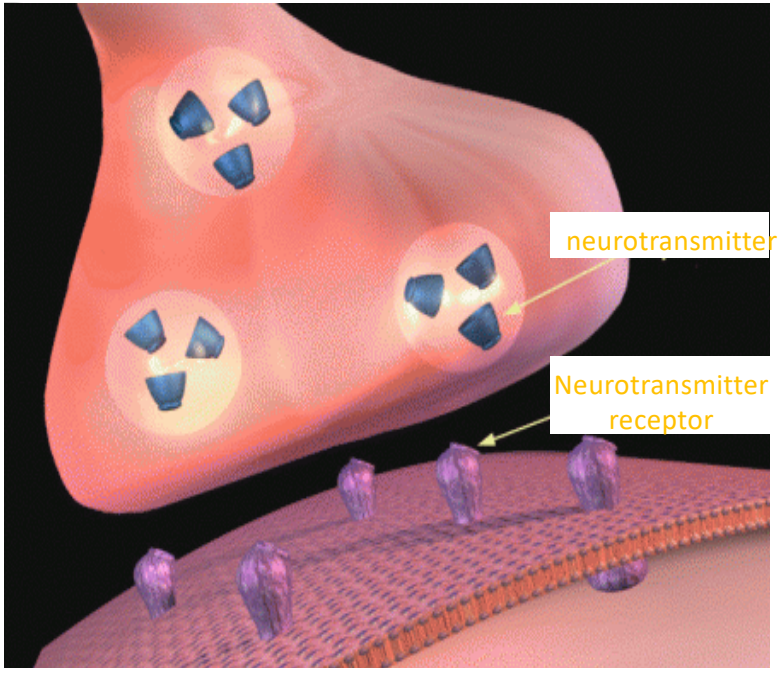
Neuromodulators Can Enhance Synaptic Transmission

- Neurons communicate by releasing chemical neurotransmitters that bind to specific receptors on the adjacent neuron.
- Glutamate is the major excitatory neurotransmitter and GABA is the major inhibitory neurotransmitter.
- Neuromodulators do not act directly at the neurotransmitter binding site and have no intrinsic activity of their own, but instead act at accessory sites that enhance or reduce the actions of neurotransmitters.
- Neuromodulators offer the possibility of developing “kinder and gentler” neuropharmacological drugs with greater pharmacological specificity and reduced side effects



Project Endeavor – Ampakines

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1. Identify Target

AMPAKINES – A NOVEL CLASS OF DRUGS

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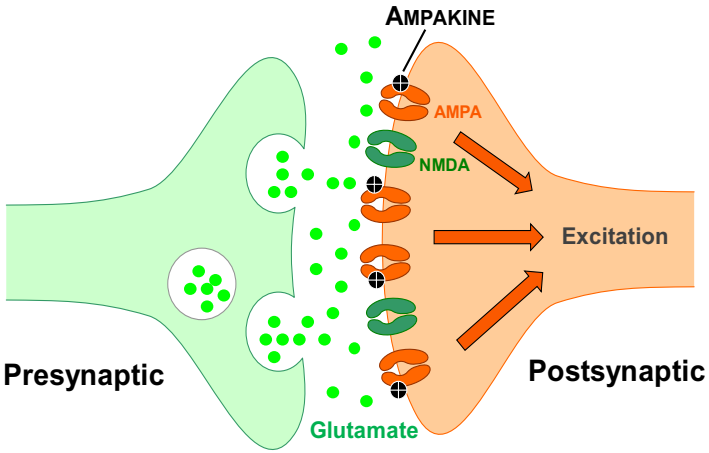
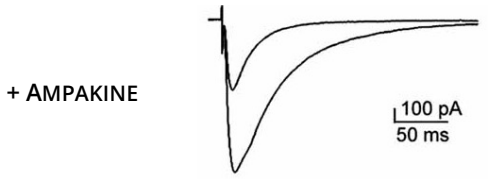
- Glutamate is the major excitatory neurotransmitter in the CNS
- Fast excitatory transmission is mediated by AMPA-type glutamate receptors
- Ampakines are positive, allosteric modulators of the AMPA-type glutamate receptor
- Prolong and strengthen synaptic transmission





AMPA Glutamate Receptor Structure

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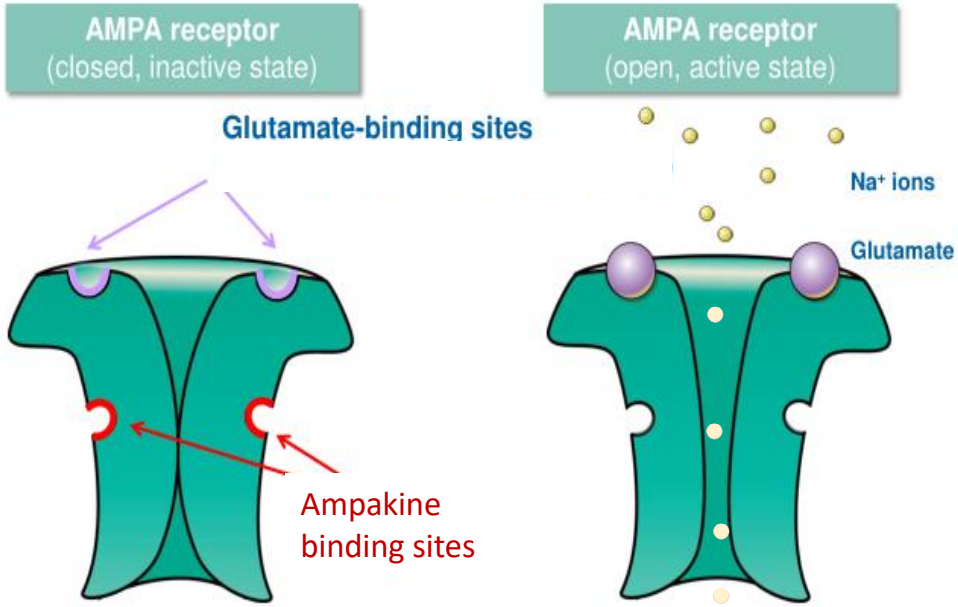
- The AMPA receptor is composed of four transmembrane proteins that form a pore, which when activated by glutamate opens and allows positive ions to enter the cell.
- Ampakine binding sites are located adjacent to the glutamate binding sites and increase the normal excitatory response to glutamate.
- As opposed to direct acting agonists that constantly bombard the glutamate binding site in a non-physiological manner, ampakines act by enhancing the natural actions of glutamate.
- *The AMPA receptor proteins are heterogeneous and form various combinations allowing for subtype specificity and neuroanatomical and pharmacological selectivity.*



The receptors ion channel allows influx of Na^+ and Ca^{2+} ions into the neuron

[1]Wilcox KS *et al. In: Epilepsy: a comprehensive textbook.* 20
[2]Clements JD *et al. J Neurosci* 1998;18:119–121.

AMPA Receptor - Physiology

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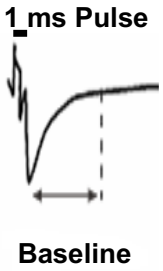
Deactivation



Desensitization

Effects of CX614 and CTZ were examined in patches excised from hippocampal CA1 pyramidal neurons.

Project Endeavor – Ampakines

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1. Identify Target
2. Design Drugs

The Lego School of Drug Design

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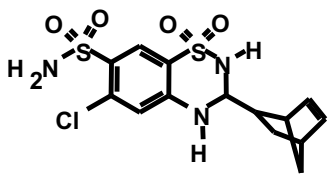
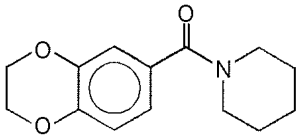
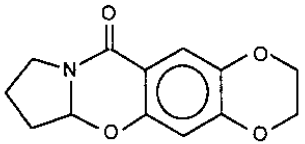
cyclothiazide



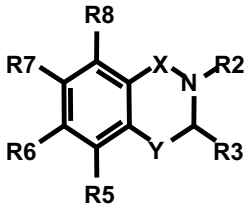
CX546



CX614



Neurosearch



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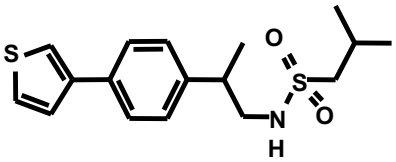
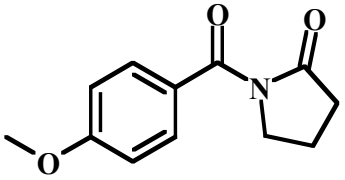
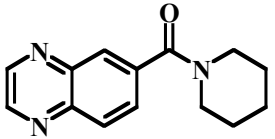


High Impact

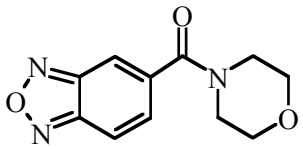
Aniracetam - Roche



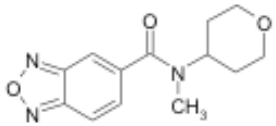
CX516 - Ampalex™



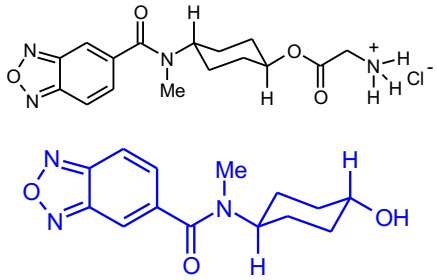
CX717



CX1739



CX1942/CX1763



Low Impact

AMPAKINES – High Impact

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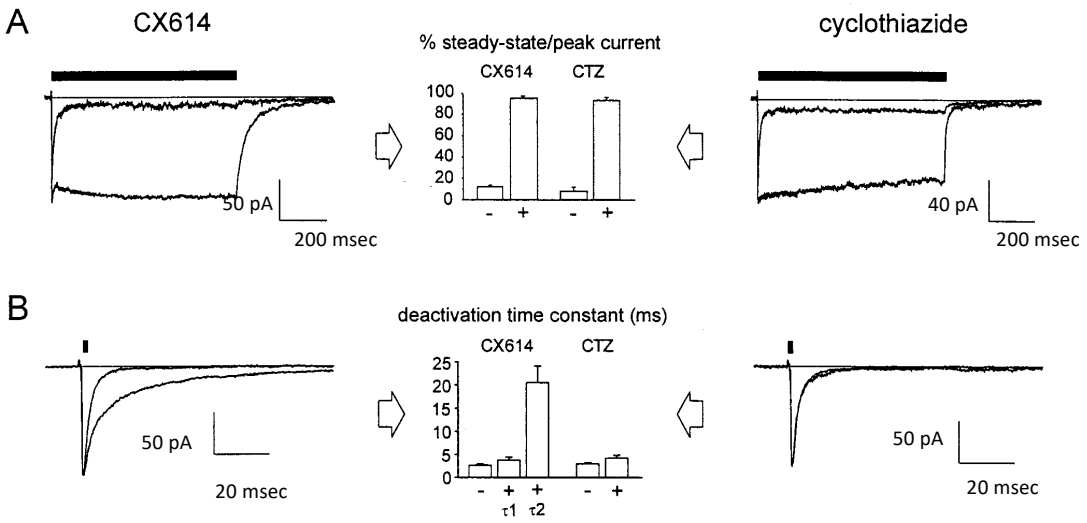

Effects of CX614 and CTZ were examined in patches excised from hippocampal CA1 pyramidal neurons. Patches were equilibrated with the drug before glutamate was applied. A. Effects of CX614 and CTZ on inward currents induced by 100msec application of 10 mM glutamate. Traces were taken from a representative experiment in which both drugs were applied at 100 M to the same patch. The bar graph at the center summarizes the effect of the drugs on the steady-state current as a percentage of the peak current and shows the corresponding control values without drug. Data (mean and S.E.M.) are from 10 (CX614) and 8 patches (CTZ). B. Effects on responses induced by 1-ms application of 10 mM glutamate. The decay phase was fitted with a single-exponential (control and CTZ) or a two-exponential function (CX614). Summarized data are shown at the center. The deactivation time constant in the absence of drug was 2.6 0.3 ms (*n* 8). For CX614, both the fast (1) and the slow (2) component are shown. The effects of the drugs were compared within the same patches (6 pairs).

AMPAKINES – Low Impact

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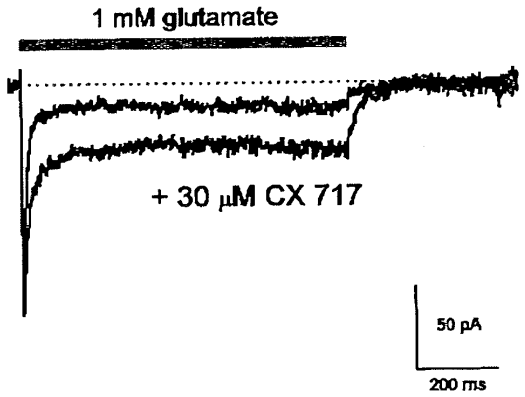
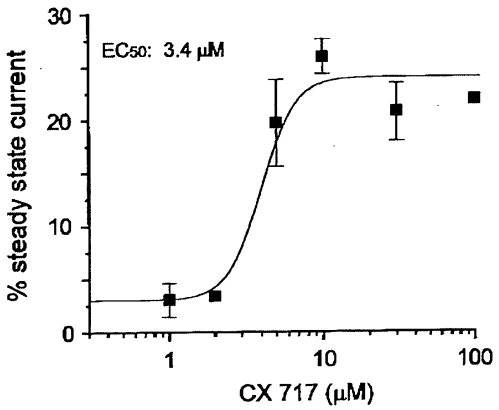
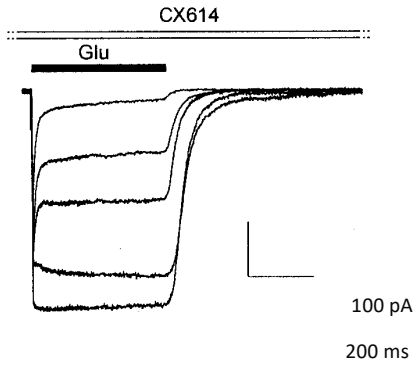
A



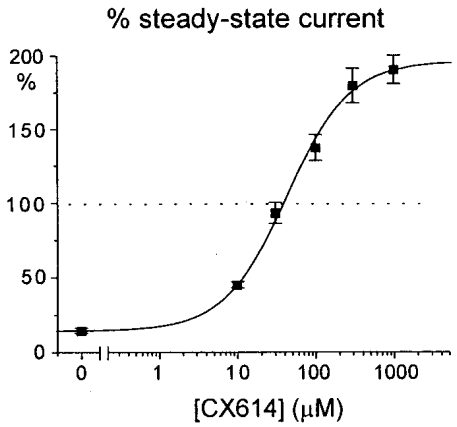
B



C



D



AMPAKINES – Low Impact

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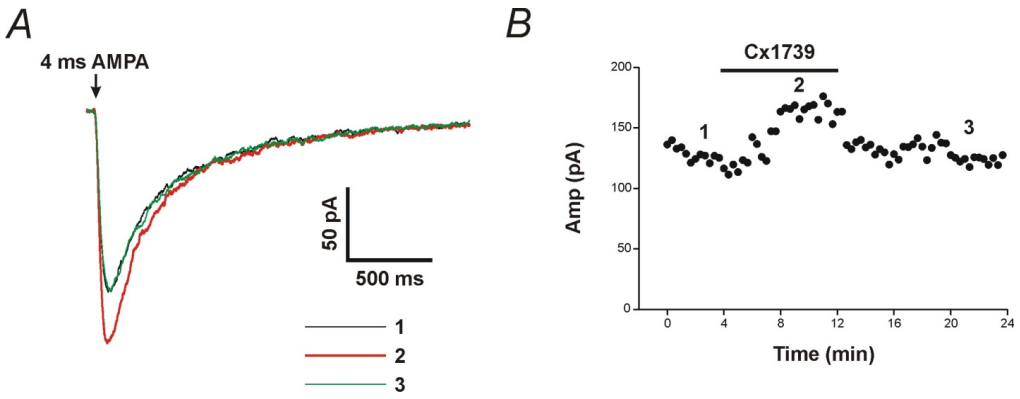

Effects of Cx1739 on AMPAR-mediated currents in CA1 pyramidal neurons. *A*, In the presence of TTX (1 µM), puffing AMPA (0.5 mM, 4 ms pulse, 0.1-0.2 psi) induced a fast current (Black trace and 1) that could be blocked by NBQX (20 µM, results not shown). Application of Cx1739 (200 µM) enhanced the amplitude of AMPAR-currents (Red trace and 2), and could be washed out (Green trace and 3). ***B***, The time course of Cx1739 effects.

High Impact Ampakines – Tissue Model of Convulsions

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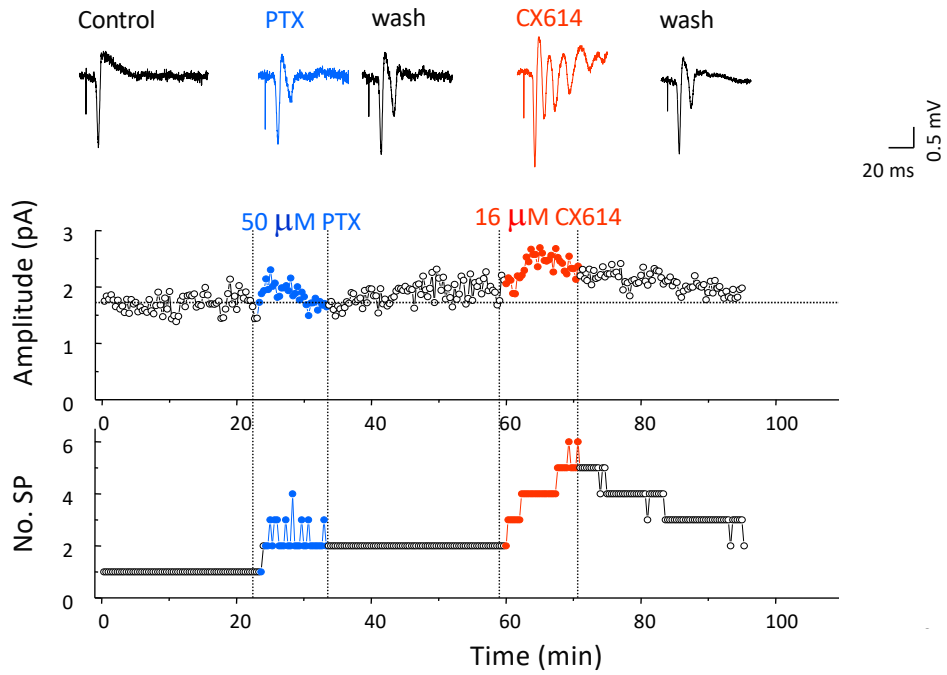

Extracellular field potentials (Population Spikes) from CA1 pyramidal cells were recorded with glass micropipettes after single pulse electrical stimulation of the Schaffer-commissural fiber afferents. The maximal amplitude of PS was determined by increase stimulating intensity until a second spike appeared. Then the intensity was decreased to induce a 50% to 60% of maximal response. The amplitude of PS was measured for each response and plotted against time.

Low Impact Ampakines – Tissue Model of Convulsions

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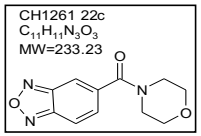
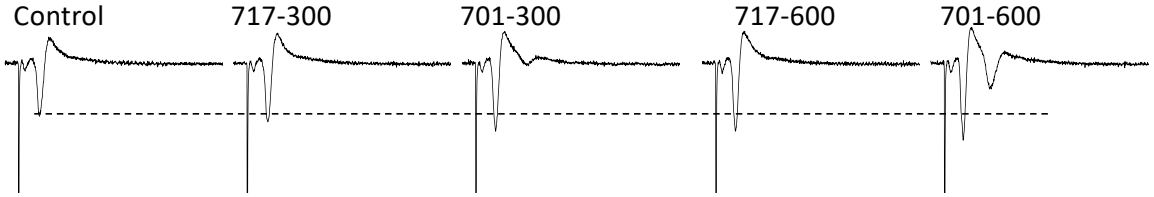
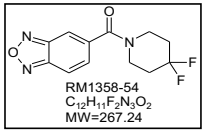
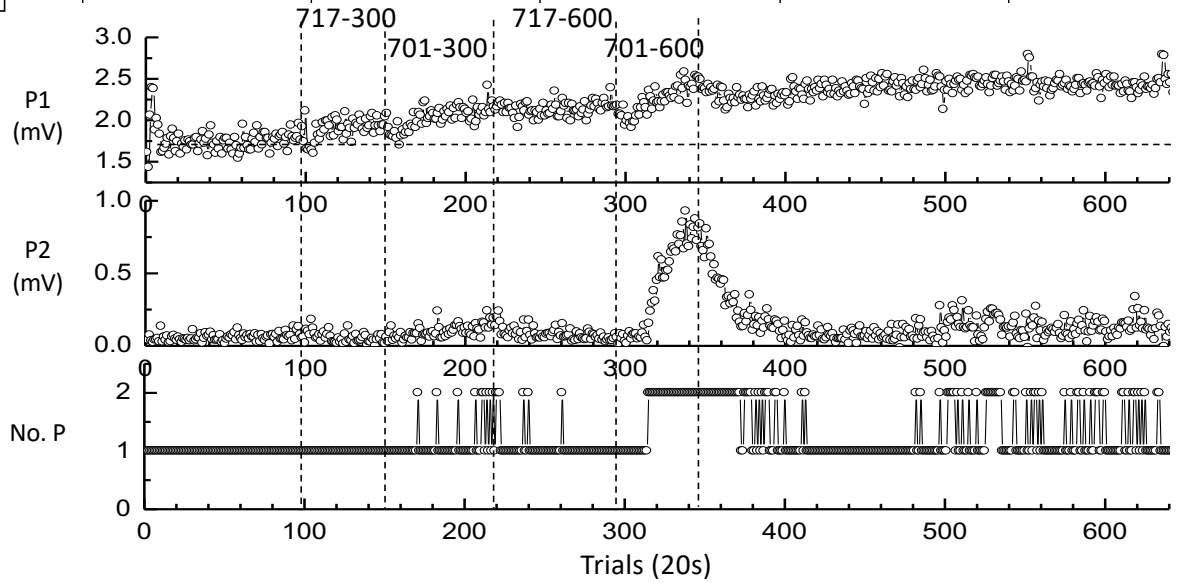
Seizure Potential of CX717-701 (SSPA)









Low Impact Ampakines – Tissue Model of Convulsions

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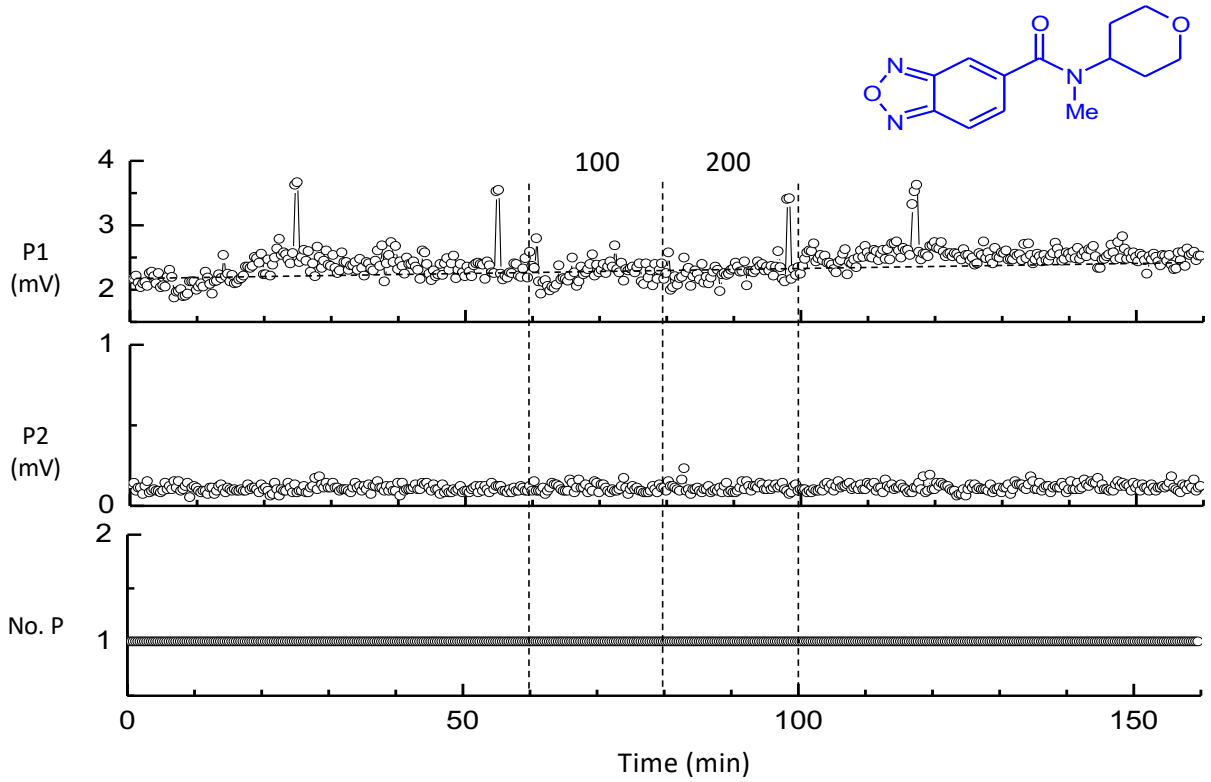
Seizure Potential of CX1739



Low Impact Ampakines – Tissue Model of Convulsions

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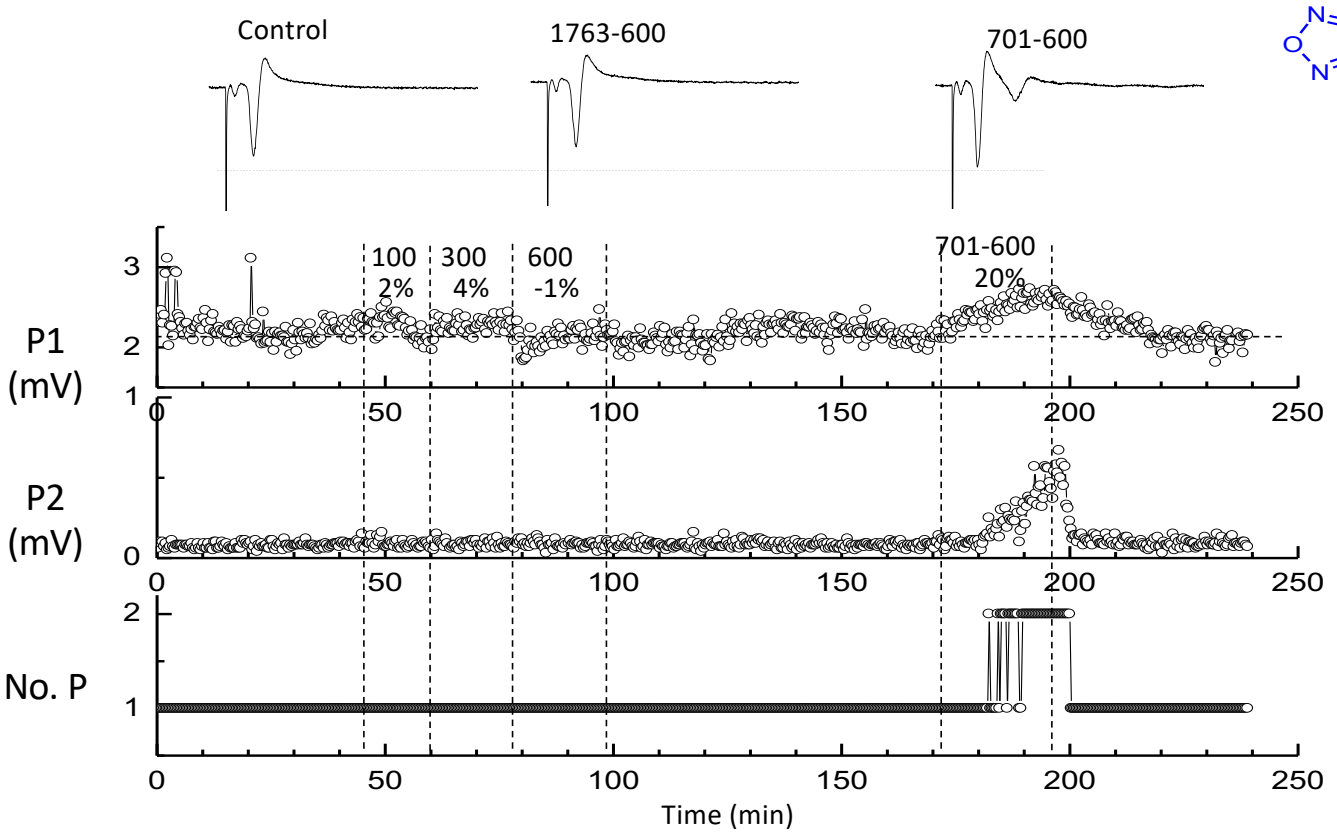
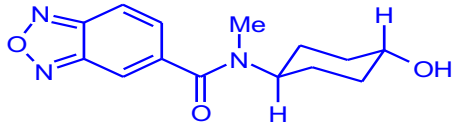
Seizure Potential of CX1763 (SSPA)





AMPAKINE Properties

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Characteristics of Low Impact and High Impact AMPAKINE® Molecules

Properties	Low Impact	High Impact
Mechanism of action	Increases probability of channel opening	Inhibits desensitization
Bind to cyclothiazide site	No	Yes
Increase EPSP *in vivo*	Yes	Yes
Increase long term potentiation	Yes	Yes
Effective in cognition tests	Rat/primate	Rat/primate
Increase BDNF	Yes	Yes
Antagonize respiratory depression	Animals/humans	Rats
Rat post-stoke recovery	No	Yes
Huntington's disease model	No	Yes

Project Endeavor – Ampakines

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1. Identify Target
2. Design Drugs
3. Verify Target Site Engagement

- In Vitro Cellular Models
- In Vivo Animal Models
- Clinical Studies

IDENTIFICATION OF KEY RHYTHMOGENIC NEURONS*

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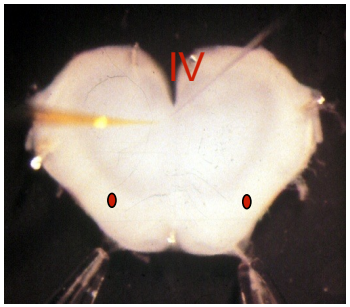

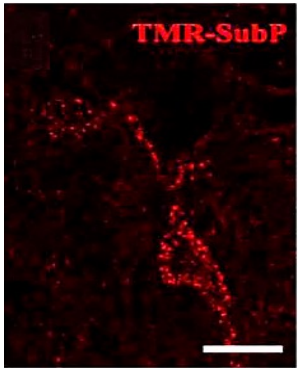

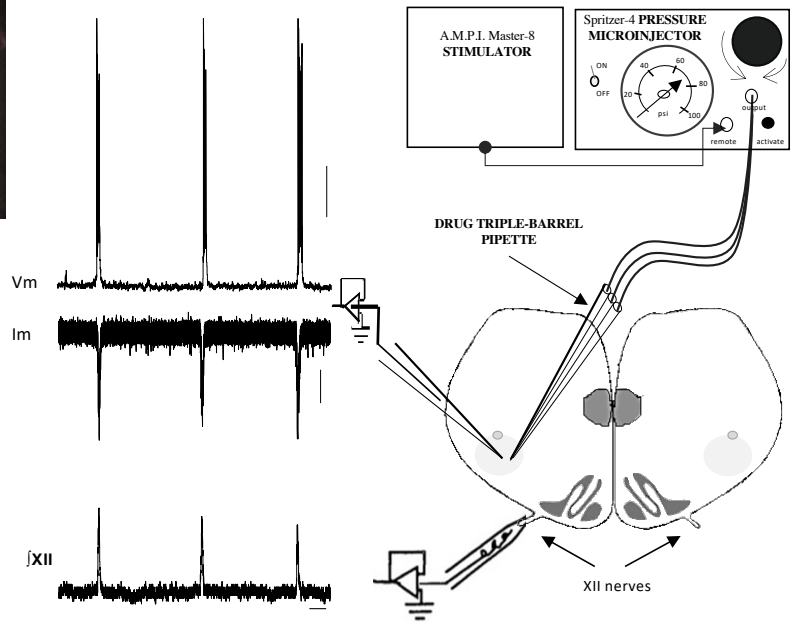

Schematic diagram of a rhythmically-active medullary slice (700 µm) preparation used for recordings of preBötC neurons and XII nerves activity. PreBötC (light grey circles) inspiratory neuron display spontaneous inspiratory depolarizing discharges in current-clamp recording (upper trace; scale bar 10 mV) and input currents in voltage-clamp recording (lower trace, scale bars 100pA and 2sec). Hypoglossal nerve activity is recording at the same time as a reference for inspiratory motor outputs. Drugs can be added to the bath or locally pressure injected via a triple-barrel drug pipette that can each contain up to three different drugs. The pressure injector is controlled by a stimulator. All parameters for the microinjections (duration, intervals, etc.) can be monitored by the stimulator.

* From Laboratory of Dr. John Greer

AMPA Receptors Modulate Respiratory Neurons

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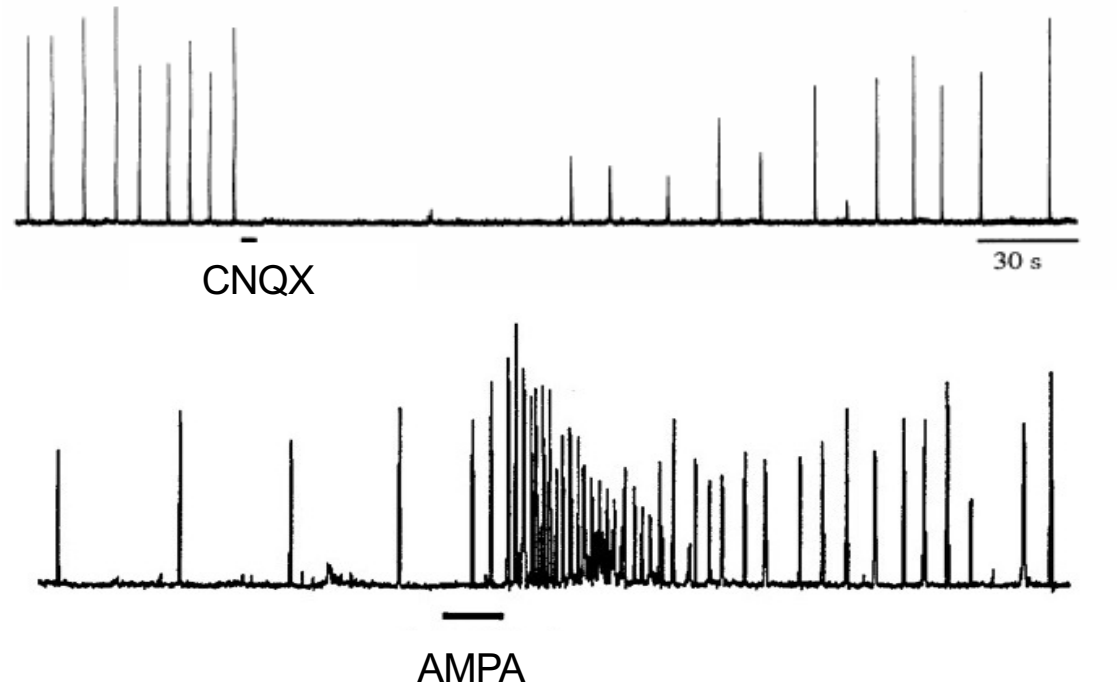
RESPIRATORY FREQUENCY IS MODULATED VIA AMPA RECEPTORS



Funk et al. J. Neurophysiology 1997, 78:1414-20

AMPAKINES Antagonize Opioid Induced Respiratory Depression

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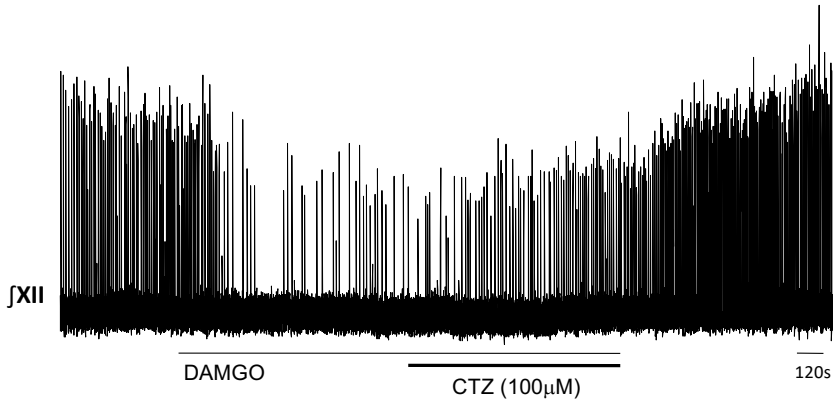

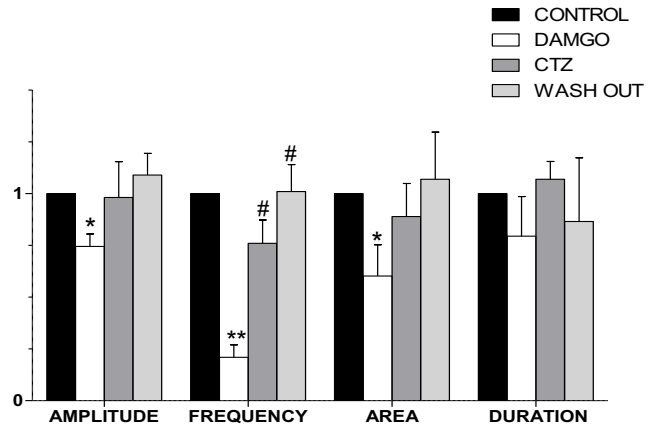

Cyclothiazide reverses DAMGO-induced respiratory drive depression in *in vitro* medullary slice of neonatal rat

AMPAKINES Antagonize Opioid Induced Respiratory Depression

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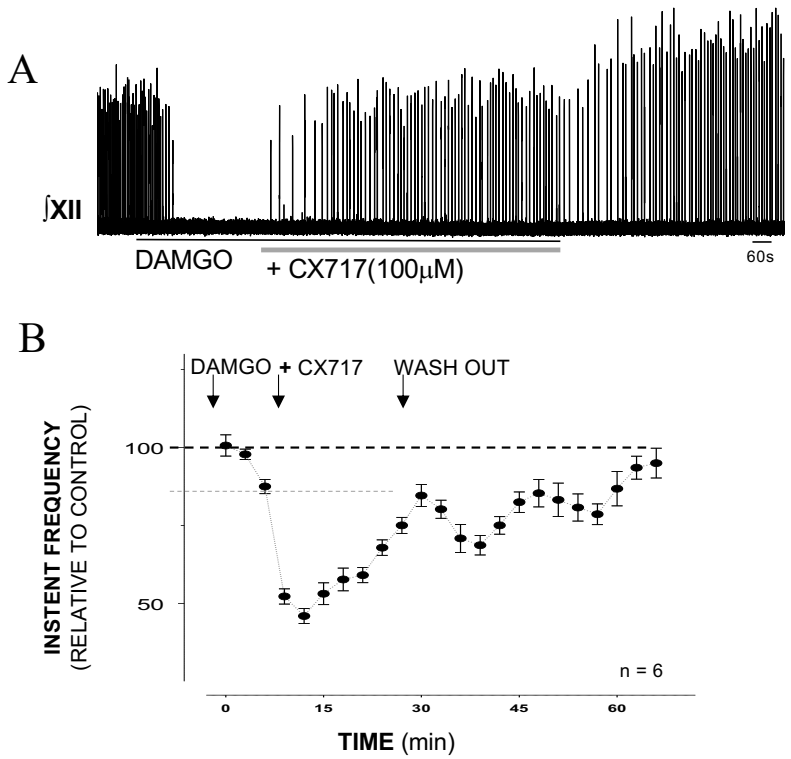

Ampakines Reverse Opioid-Induced Suppression of Respiratory Frequency in a medullary slice preparation. Integrated recordings of XII nerve bursts during bath application of CX717 following 400nM DAMGO bath application.

AMPAKINES Antagonize Opioid Induced Respiratory Depression

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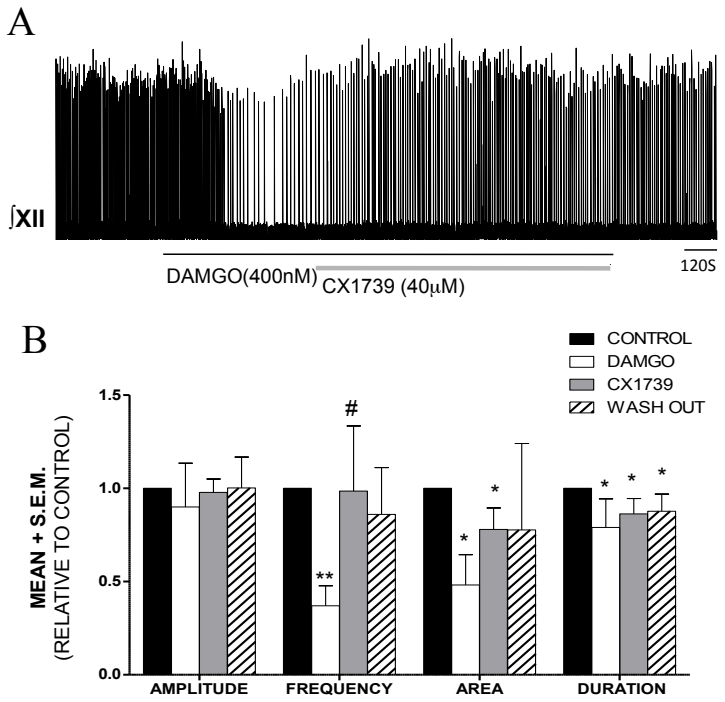

Ampakines Reverse Opioid-Induced Suppression of Respiratory Frequency in a medullary slice preparation. Integrated recordings of XII nerve bursts during bath application of (A) CX1739 following 400nM DAMGO bath application.

AMPAKINES Antagonize Opioid Induced Respiratory Depression

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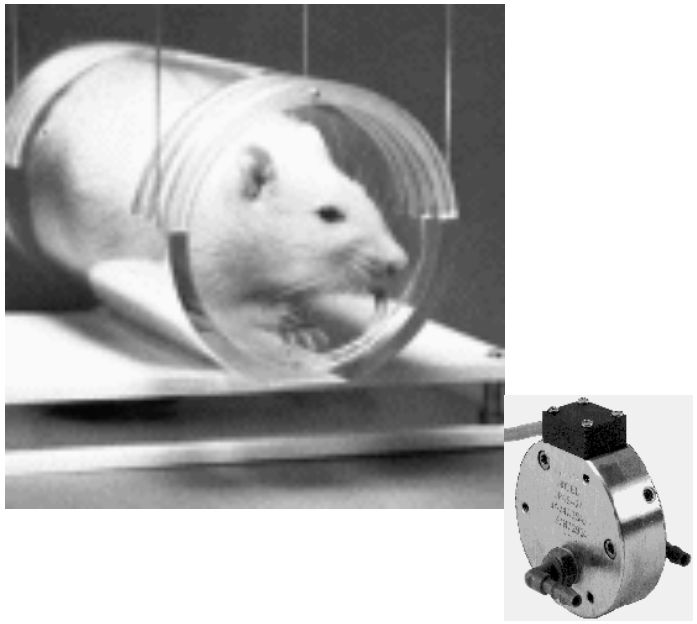
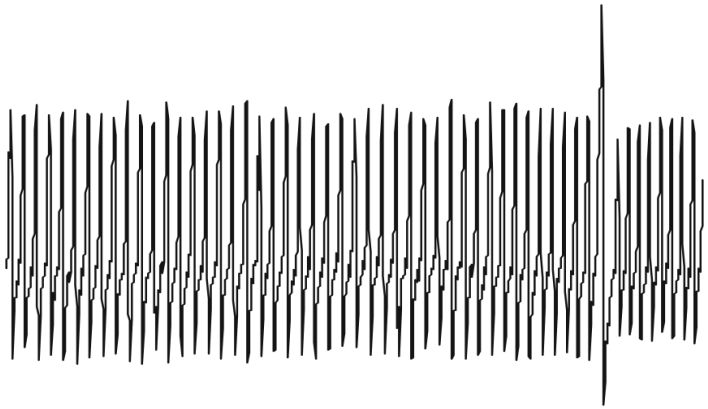
WHOLE-BODY PLETHYSMOGRAPHIC RECORDINGS
TAIL INFUSION OF OPIATES AND AMPAKINES





Ren et al. (2006). American Journal of Respiratory and Critical Care Medicine. 174:1384-1391
Ren et al. (2009) Anesthesiology. 110(6):1364-70

AMPAKINES Antagonize Opioid Induced Respiratory Depression

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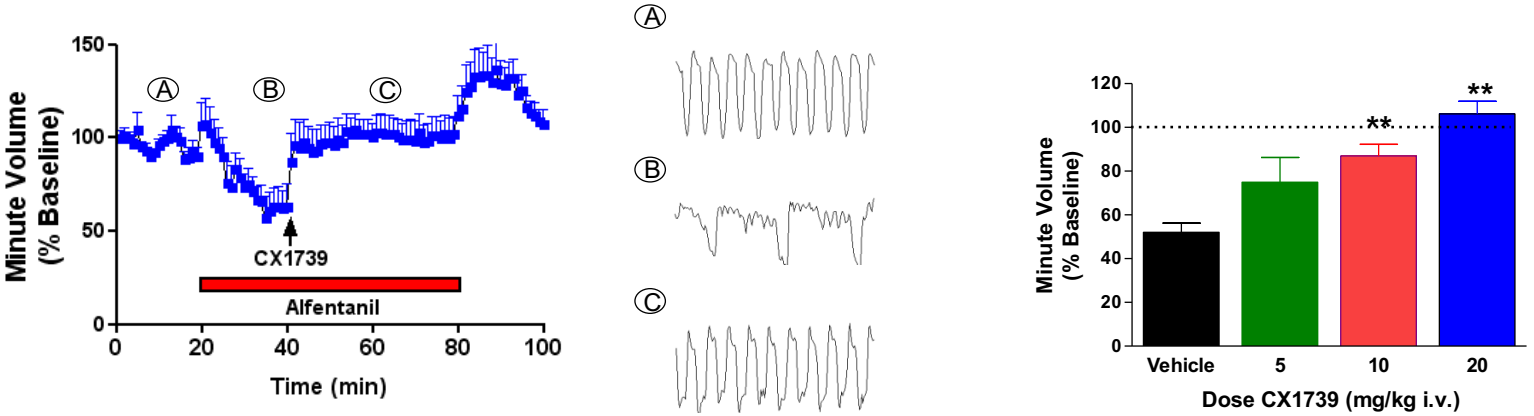

Effect on Alfentanil-induced Respiratory Depression in Rats

Infusion of alfentanil (250 µg/kg/20 min) produces respiratory depression in rats. CX1739 administered intravenously at 20 mg/kg rapidly attenuates respiratory depression induced by alfentanil. Data points represent the mean normalized minute volume and standard error of 8 animals. The 5-second traces on the right are taken from time points at baseline (**A**), during alfentanil infusion (**B**), and following administration of 20 mg/kg CX1739 (**C**).

AMPAKINES Antagonize Opioid Induced Respiratory Depression

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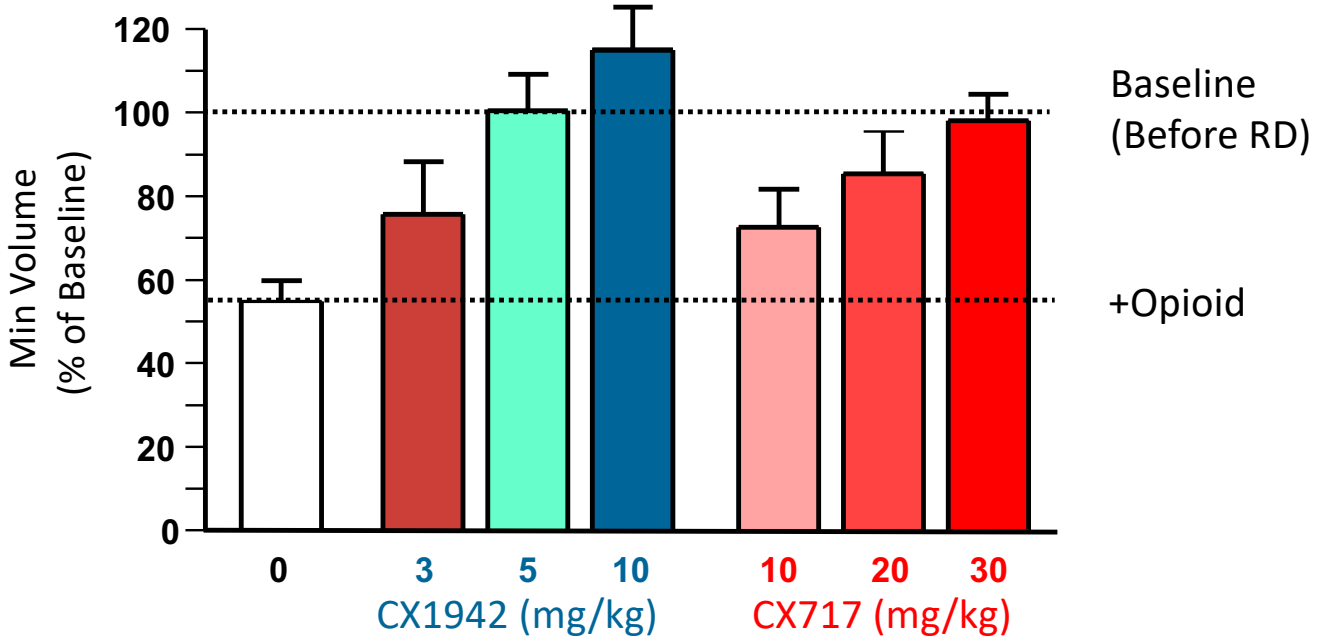

CX1942 and CX717 reverse opioid-induced RD in rats

Alfentanil Induced Respiratory Depression in Humans

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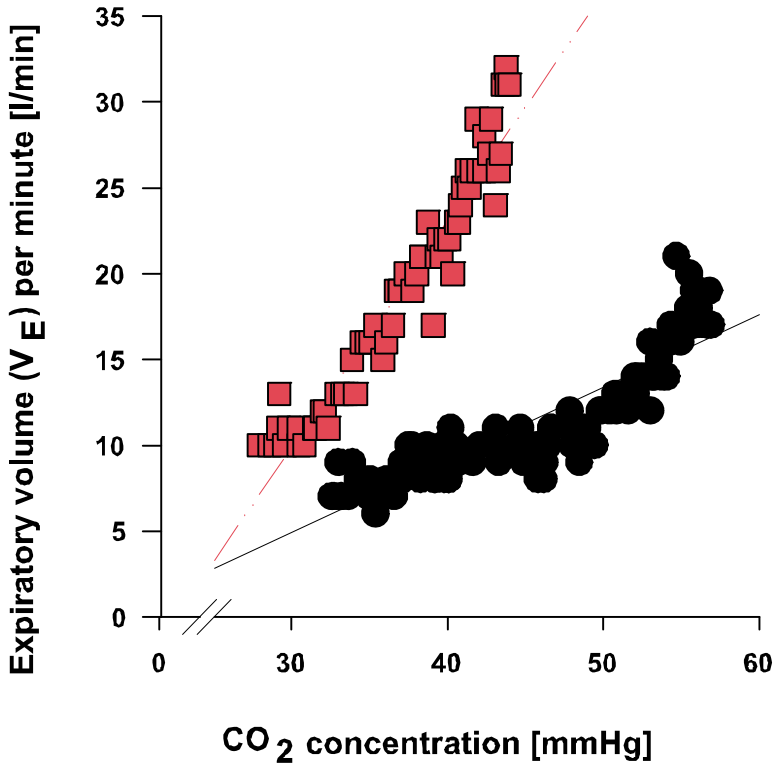
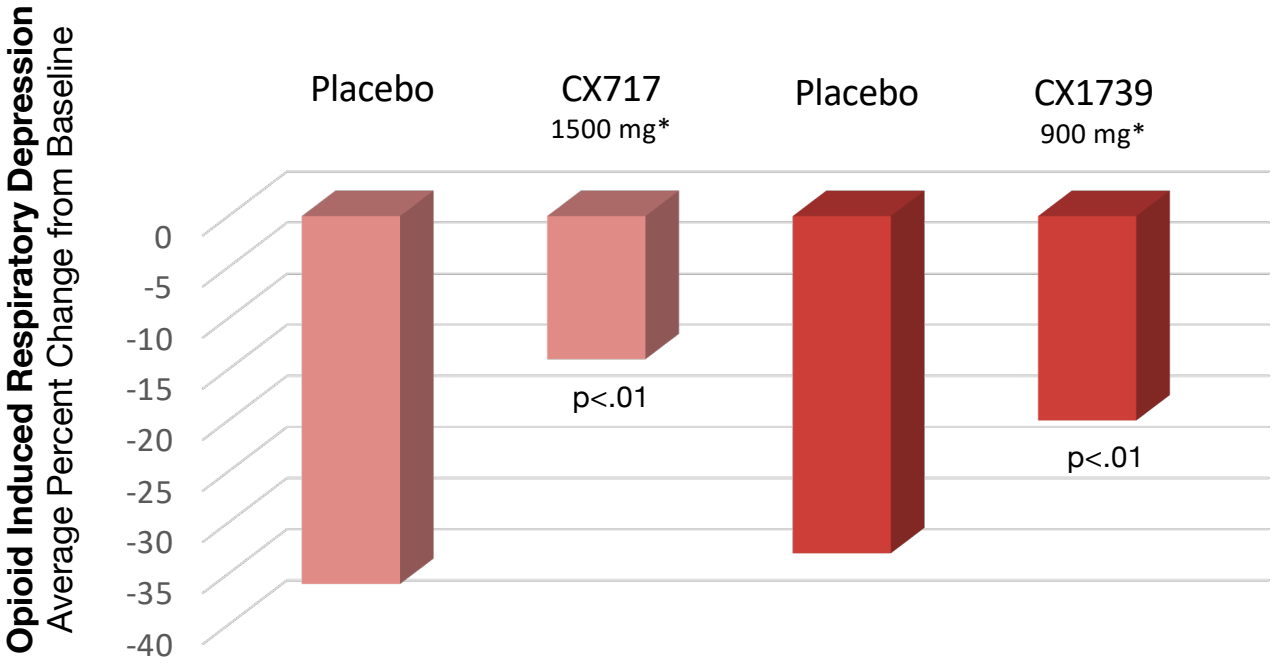


Placebo

Alfentanyl infusion – 100ng/ml

Ampakines Reduce Opioid-Induced Respiratory Depression in Phase 2A Clinical Trials



* Approximately 15 and 10 mg/kg on a weight basis, respectively; comparable to animal doses

Validation of Doses for Target Engagement

Project Endeavor – Ampakines

RespireRx Pharmaceuticals Inc

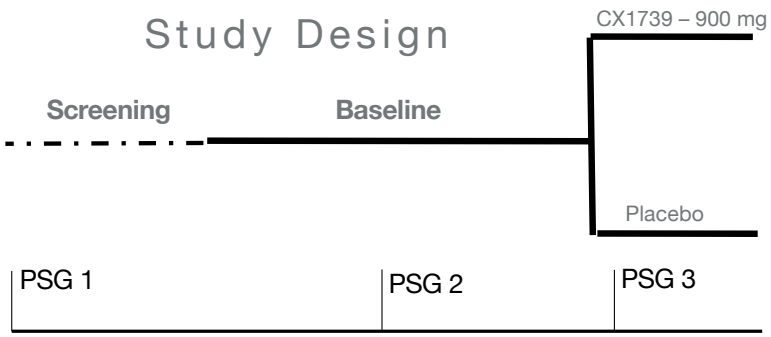
1. Identify Target
2. Design Drugs
3. Verify Target Site Engagement
4. Translational Studies to Demonstrate Efficacy

- Central Sleep Apnea
- ADHD

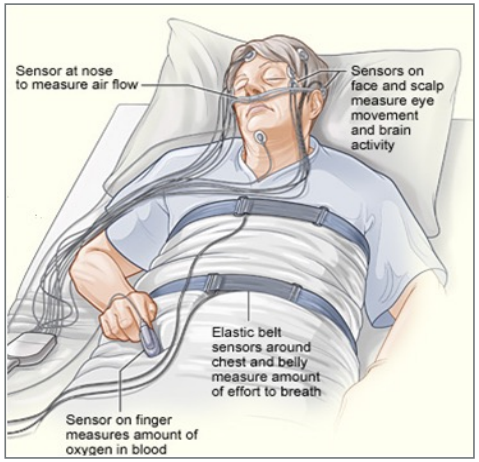
CX1739: Completed Phase 2A in Sleep Apnea – Single Dose

RespireRx Pharmaceuticals Inc

Design	Randomized, double-blind, placebo-controlled study
Population	20 adults with all types of moderate to severe sleep apnea (16 given CX1739; 4 given Placebo)
Dosing	Each subject received either placebo or a single dose of 900mg CX1739 one hour before lights out
Primary Measures	Apnea-Hypopnea measures; Oxygen saturation; Sleep quality, measured by PSG (Apnea: no airflow for >10s; Hypopnea: reduced airflow for >10s)



PSG – Polysomnography, or sleep lab study



Patient Selection: CX1739 Was More Effective in Treating Mixed and Central Sleep Apneas

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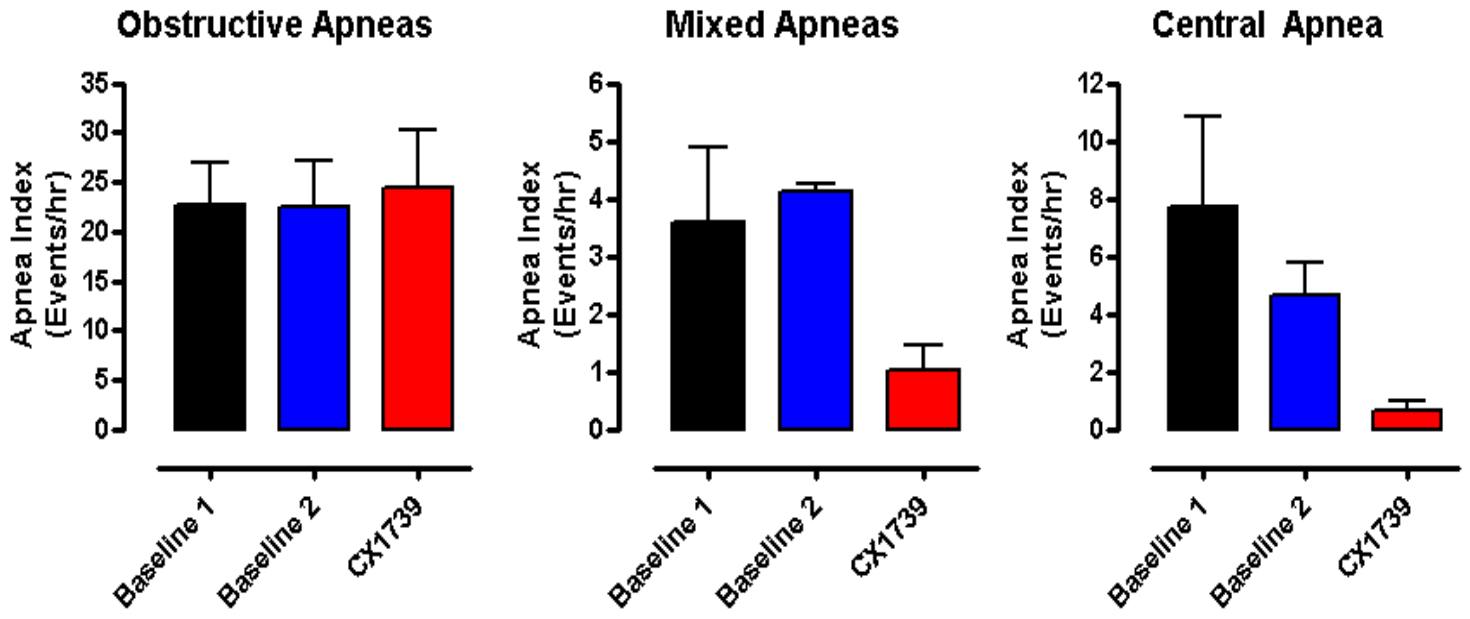

A Phase 2 Trial of CX717 in the Treatment of ADHD

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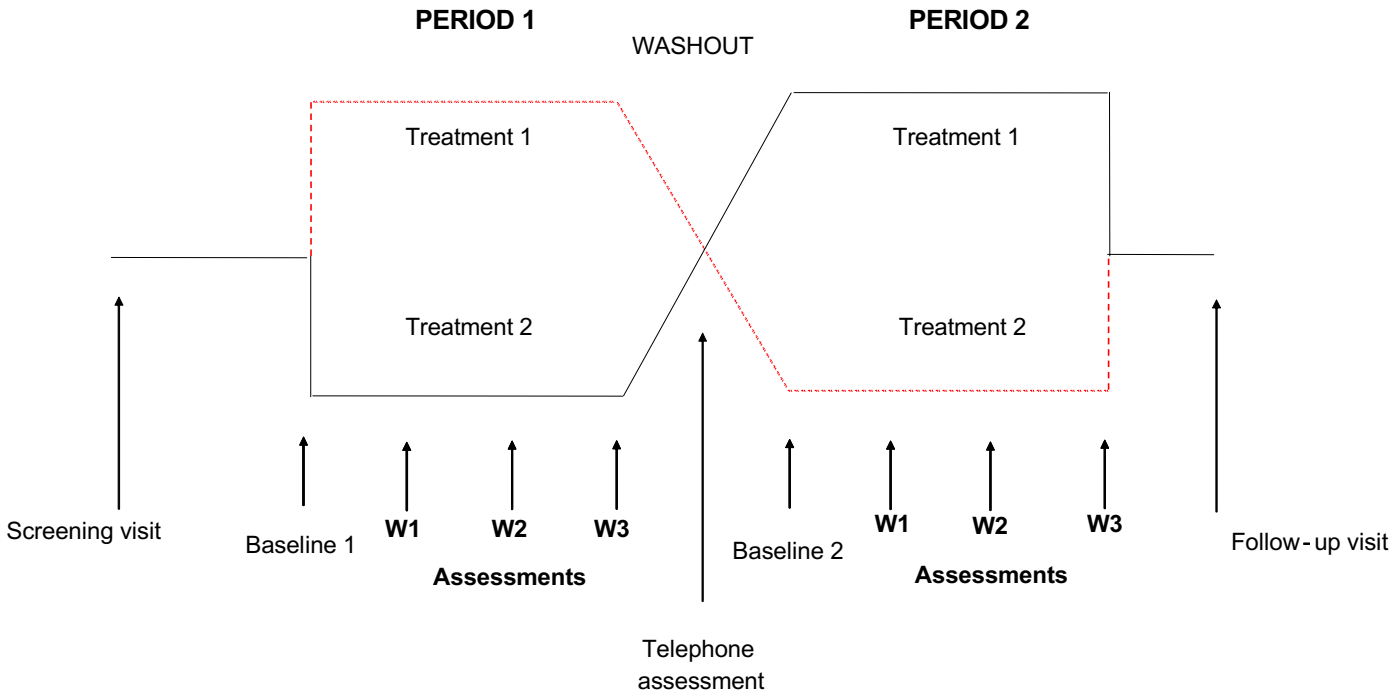
Study Design Schematic



CX717 Shows Significant Improvement in ADHD

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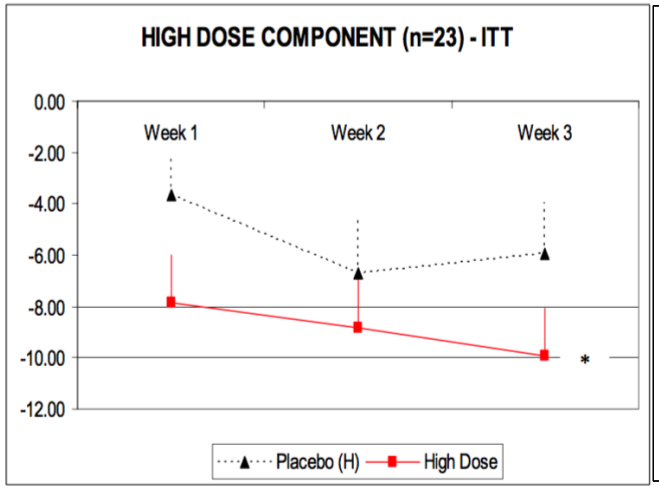
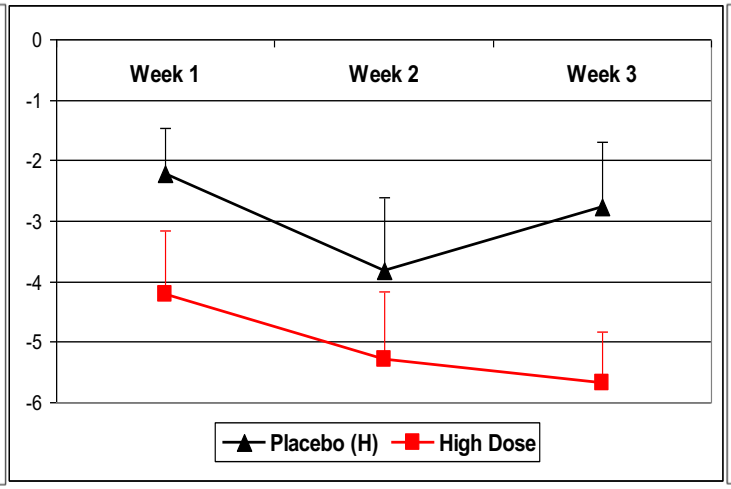
OVERALL ADHR-RS



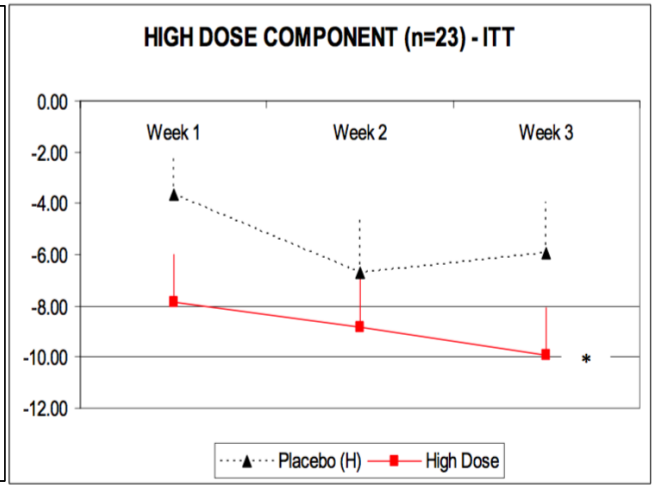
Mean Change from baseline
* Repeated measures analysis , p=0.002

HYPERACTIVITY



Mean Change from baseline
* Repeated measures analysis , p<0.05

INATTENTIVENESS



Mean Change from baseline
* Repeated measures analysis , p<0.04

Phase 2 Study of CX717 in Adult ADHD: Randomized, double-blind, multi-center, 2-period crossover study that compared 2 doses of CX717 (200 or 800 mg BID) with placebo. Statistically significant effects were observed with 800 mg as early as week 1.

CX717 May Be Superior to Strattera ® in the Treatment of ADHD: Comparison of ADHD-RS Scores

RespireRx Pharmaceuticals Inc

Strattera® Phase 3 Pivotal Trials

STUDY 1 (LYAA)

	Placebo (n = 134)	Strattera (n = 133)	Δ	Effect Size
Week 4	-2.4	-4.8	-2.4	0.25
Week 8	-5.6	-9.7	-4.1	0.42
Endpt	-6.0	-9.5	-3.5	0.36

STUDY 2 (LYAO)

	Placebo (n = 124)	Strattera (n = 124)	Δ	Effect Size
Week 4	-2.8	-6.1	-3.3	0.33
Week 8	-6.9	-12.3	-5.4	0.53
Endpt	-6.7	-10.5	-3.6	0.38

Note: SD change for Placebo = 9.3; Strattera = 10.9
taken from endpoint but assumed for all calculations

CX 717 Clinical Trial

	Placebo (n=23)	CX717 (800mg) (n=23)	Δ	Effect Size
Week 1	-3.8	-8.0	4.2	.44
Week 3	-6	-10.0	4.8	.43

* CX717 effective as early as 1 week

* Strattera® takes 4 – 8 weeks to be effective

Michelson D *et al.,* Biol Psychiatry (2003) Strattera Summary Basis of Approval (2001)

Next Step: Phase 2 Clinical Trial
CX1739 +/- AIH in the Treatment of SCI

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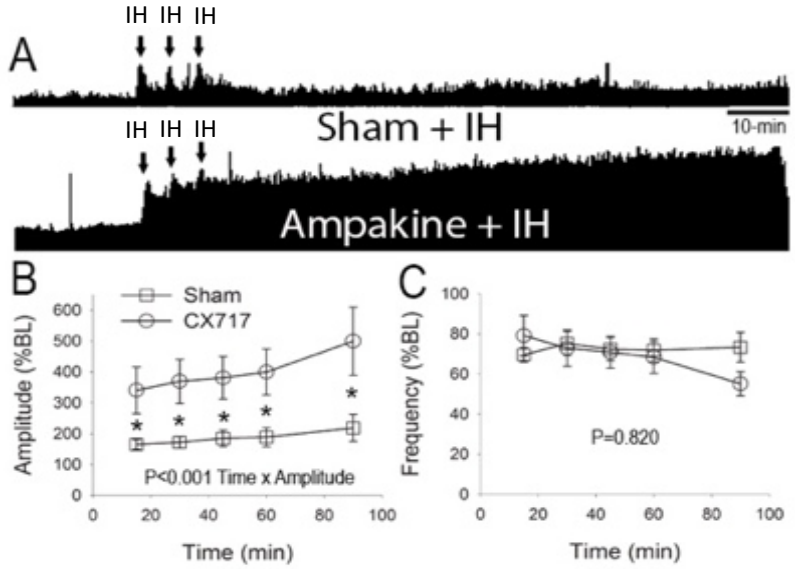
Unilateral hemi-transections at the level of the 2nd cervical vertebra are performed on rats and electrical activity is recorded from phrenic nerves, which innervate the diaphragm and contribute to the regulation of breathing.



8 weeks following surgery, CX717 (15 mg/kg) increases amplitude in electrical recordings taken from rat phrenic nerves

Next Step: Phase 2 Clinical Trial
CX1739 +/- AIH in the Treatment of SCI

RespireRx Pharmaceuticals Inc

Blinded, Placebo-controlled, Escalating-dose Study of CX1739, With and Without Acute Intermittent Hypoxia, in Patients with Incomplete Spinal Cord Injury

Primary Objectives

1. Evaluate the safety of acute CX1739 treatment at escalating doses in patients with SCI
2. Evaluate the safety of multiple daily doses of CX1739 at escalating doses in patients with SCI
3. Evaluate the safety of CX1739 in Combination with Acute Intermittent Hypoxia in Patients with SCI

Secondary Objectives

1. Evaluate the effect of acute CX1739 treatment at escalating doses on motor function and recovery, with and without acute intermittent hypoxia in patients with SCI
2. Evaluate the effect of multiple BID doses of CX1739 treatment on motor function and recovery, with and without acute intermittent hypoxia in patients with SCI

RespireRx Pharmaceuticals Inc

OTC QB: RSPI

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