JY-515,317 (NYX-2925), a NMDA receptor modulator with glycine site partial agonist-like properties, has neuroprotective effects in a rat model of blast-induced traumatic brain injury

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INTRODUCTION

Modulating N-methyl D-aspartate receptor (NMDAR)–mediated synaptic activity is a growing focus for the development of pharmaceuticals that have wide applicability across CNS disorders. The NMDAR plays a critical role in learning and memory. Decline in NMDAR function is observed in humans and other mammals and is directly correlated with impaired performance in learning-dependent tasks.

Aptinyx Inc. has developed a platform of NMDAR modulators that are orally bioavailable and work via a novel mechanism: functional glycine-site partial agonist modulation of the NMDAR. Unlike NMDAR antagonists, the Aptinyx compounds appear to be both highly tolerable and efficacious in both psychiatric and neurologic disease models. The goal of the present study was to specifically characterize neuroprotective effects of one of these compounds, JY-515,317, in a rat model of blast-induced traumatic brain injury.

TRAUMATIC BRAIN INJURY

- The Department of Defense reported 352,619 cases of traumatic brain injury between 2000 and 2016, 82.3% of which were classified as mild (Defense Medical Surveillance System, Theater Medical Data Store provided by the Armed Forces Health Surveillance Center).
- 10-20% of returning Iraq and Afghanistan veterans have suffered a traumatic brain injury.
- Around 40% of TBIs reported by returning service members may be attributable to blast exposure (Elder et al., 2010, *Psychiatr Clin North Am*).

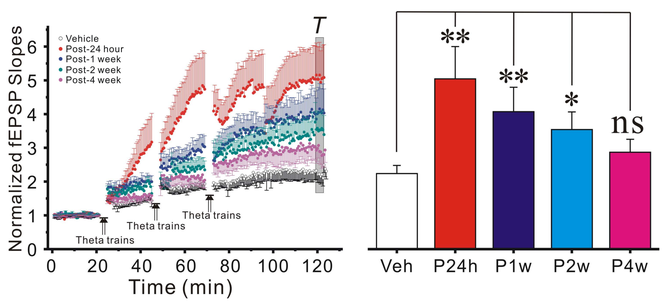
ADDITIONAL POSTERS

- JY-515,317, which preferentially binds to NMDAR2B and facilitates LTP, is orally bioavailable and enhances learning and memory without sedative or ataxic effects (**see poster #609.08 / CC4**).
- JY-515,317 has also shown rapid-acting and long-lasting therapeutic potential for the treatment of neuropathic pain (**see poster #609.03 / BB17**).

FINANCIAL DISCLOSURES

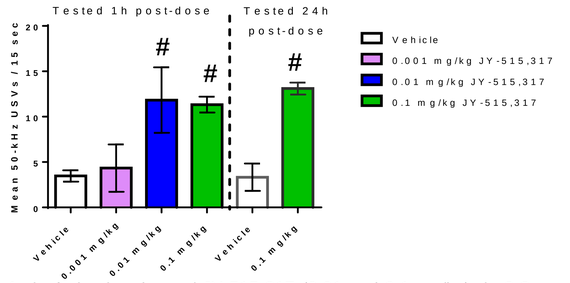
PKS is a paid consultant for Aptinyx Inc.
EMC, JSB, ALG, RAK, MAK, CC, TM, and JRM are all employees of Aptinyx Inc.

JY-515,317 facilitates ex-vivo LTP in hippocampus



Orally-dosed JY-515,317 (10 mg/kg; ex-vivo recordings 24 h – 4 weeks post-dosing) in adult male Sprague Dawley (SD) rats enhanced the magnitude of long-term potentiation of synaptic transmission at Schaffer collateral-CA1 synapses compared to control. LTP was induced by theta burst stimulation (arrows) at 32^{0}C. Data are mean ± SEM. *p< 0.05, **p<0.01 compared to untreated control slices.

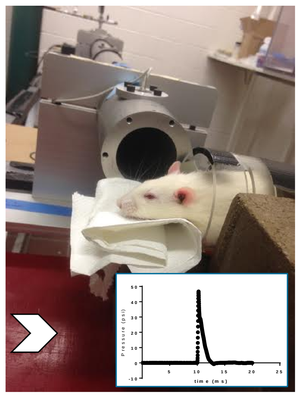
JY-515,317 enhances positive emotional learning in healthy animals



A single in vivo dose of JY 515-317 (0.01 and 0.1 mg/kg) in 2-3 month old male SD rats increases the number of hedonic ultrasonic vocalizations (USVs) emitted in response to a conditioned stimulus associated with heterospecific rough and tumble play. The effect was seen at both 1 hr (left) and 24 hr (right) post-dose. #, significantly greater than vehicle-treated rats, $p < 0.05$.

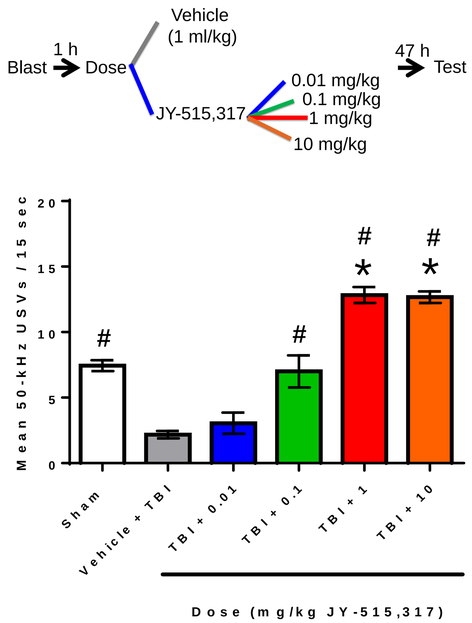
JY-515,317 rescues blast-induced deficits in positive emotional learning

Apparatus



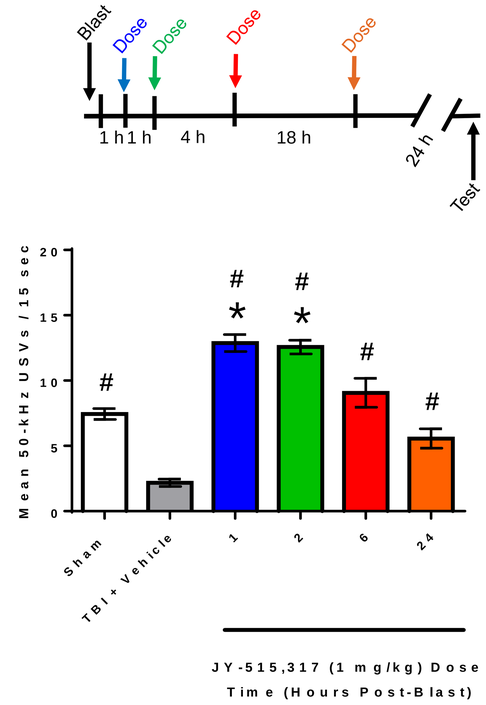
Adult (2-3 months old) male SD rats were anesthetized with isoflurane and positioned 10 cm from the end of an aluminum shock tube. Each rat received a single blast of helium (≈42-48 psi or 290-330 kPa; inset) generated by puncturing 0.012-0.014" mylar film. Note that all of the rat's body except for the head is placed out of the direct blast radius and is also shielded by a modified restraint, thus preventing systemic effects of the blast (i.e. all effects are local/cerebral). Sham controls were anesthetized with isoflurane and placed outside the blast radius (arrowhead).

Dose-Response



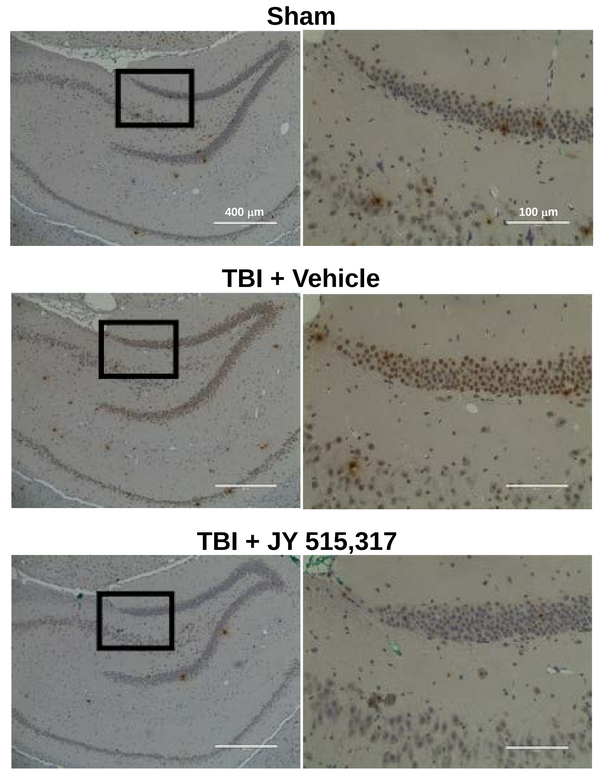
Animals were treated with vehicle or JY-515,317 (0.01, 0.1, 1, or 10 mg/kg, PO) 1 hour post-blast. All rats underwent the positive emotional learning task 48 hours post-blast. *, significantly greater than sham controls, $p < 0.05$; #, significantly greater than vehicle-treated rats, $p < 0.05$.

Time Course



Animals were treated with vehicle or JY-515,317 (1 mg/kg, PO) 1, 2. 6, or 24 hours post-blast. All rats underwent the positive emotional learning task 48 hours post-blast. *, significantly greater than sham controls, $p < 0.05$; #, significantly greater than vehicle-treated rats, $p < 0.05$.

JY-515,317 decreases phospho-tau (pSer202+Thr205) protein levels in the hippocampus post-blast



Animals were sham-blasted, or treated with vehicle or JY-515,317 (1 mg/kg, PO) 1 hour post-blast. Animals were deeply anesthetized and transcardially perfused 24 hours post-blast. Sections from the hippocampus were processed to reveal the level of phospho-tau.

CONCLUSIONS

- In healthy rats, JY-515,317 enhances hippocampal LTP recorded ex vivo up to 2 weeks post-dose. In addition, JY-515,317 enhances positive emotional learning in healthy rats both 1 hour and 24 hours post-dose.
- In rats subjected to blast-induced traumatic brain injury, treatment with JY-515,317 (1 mg/kg) up to 24 hours post-blast produces a neuroprotective effect.
- In rats dosed 1 hr post-blast, treatment with 0.1 mg/kg JY-515,317 improved rats' performance on the positive emotional learning task to the level of untreated, unblasted controls (shams). TBI'ed rats treated with 1 and 10 mg/kg JY-515,317 perform better than untreated (i.e. undosed) sham controls.
- Preliminary evidence suggests that, in rats dosed 1 hr post-blast, JY-515,317 decreased the level of phospho-tau in the hippocampus (assessed 24 hr post-blast).