JY-515,317 (NYX-2925), an NMDA receptor modulator with glycine site partial agonist-like properties, shows therapeutic potential for the treatment of neuropathic pain

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INTRODUCTION

N-methyl-D-aspartate receptor (NMDARs) dependent synaptic plasticity processes play an important role in central sensitization and maintenance of chronic pain. Literature suggests NR2B-subunit containing NMDARs, in particular, are potential targets for therapeutic intervention due to their location in pain-relevant brain and spinal cord structures and due to the NR2B upregulation seen with pain.

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 multiple animal models of psychiatric and neurologic disease. JY-515,317 (NYX-2925) is a NR2B-preferring NMDAR modulator discovered and developed by Aptinyx. The goal of the present study was to specifically characterize the efficacy of JY-515,317 in various pain models.

CONCLUSIONS

- JY-515,317 (1-30 mg/kg) produced rapid-acting (1h post-dosing) and long-lasting (24h and 1wk post-dosing) mechanical (CCI model) and thermal (SNI model) analgesia
- JY-515,317 (1-10 mg/kg) showed rapid acting and long-lasting efficacy in alleviating mechanical hypersensitivity in the STZ-induced diabetic neuropathy model and the chemo-induced (Taxol®) neuropathy model.
- JY-515,317 (1-10 mg/kg) also reduced flinching in the late phase of the formalin test 1h post dosing.
- JY-515,317 (1-10 mg/kg) was ineffective in the tail flick model of acute pain.
- Lastly, JY-515,317 (1-100 mg/kg PO) did not induce a sedative / ataxic effect in the Rota-rod test when measured up to 2h post-dosing, whereas a therapeutic dose of gabapentin (150 mg/kg PO) did produce sedative / ataxic effects at 1h and 2h post-dosing.

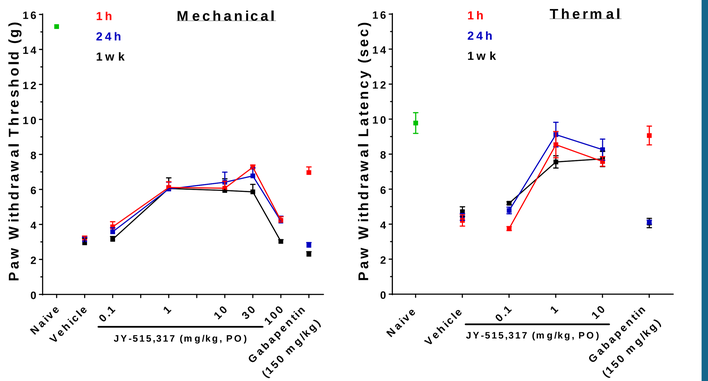
ADDITIONAL POSTERS

- JY-515,317 is a NMDA receptor modulator with glycine site partial agonist-like properties: *in vitro* and *in vivo* pharmacology (**see poster #609.08 / CC4**).
- JY-515,317 has shown neuroprotective effects in a rat model of blast-induced brain injury (**see poster #609.12 / CC8**).

FINANCIAL DISCLOSURES

All authors are employees of and are financially compensated by Aptinyx Inc.

JY-515,317 Produces Long-lasting Mechanical Analgesia in the Bennett / CCI model and Thermal Analgesia in the SNI Model of Neuropathic Pain



Mechanical Hypersensitivity:
%Analgesia = [(log (x) -y) / (log (15) - y) * 100
Where: x = paw withdrawal threshold (g)
y = the average of the log (x) values for the vehicle treated group

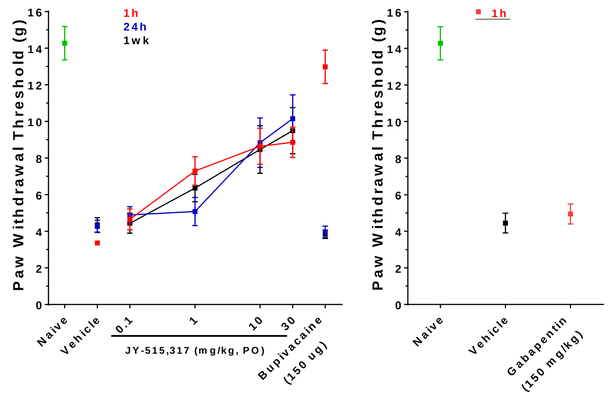
% Analgesia	1 h	24 h	1wk
JY-515,317 0.1 mg/kg	10.2 ± 4.5	9.0 ± 3.7	6.2 ± 3.8
JY-515,317 1 mg/kg	40.0 ± 3.2	39.3 ± 4	41.1 ± 6.6
JY-515,317 10 mg/kg	38.5 ± 4.1	41.34 ± 5.5	41.2 ± 7.1
JY-515,317 30 mg/kg	53.1 ± 1.1	49.4 ± 4.2	43.5 ± 4.3
JY-515,317100 mg/kg	15.1 ± 1.8	18.9 ± 3.7	4.7 ± 1.2
Gabapentin 150 mg/kg	48.7 ± 3.0	-6.5 ± 3.9	-12.0 ± 3.9
Vehicle	0 ± 2.0	0 ± 3.1	0 ± 5.1

Thermal Hyperalgesia:
%Analgesia = [(treated PWLi – av vehicle PWLi) / (av vehicle PWLc – av vehicle PWLi)] * 100.
Where: i = ipsilateral paw withdrawal latency (sec)
c = contralateral paw withdrawal latency (sec)

% Analgesia	1h	24h	1wk
JY-515,317 0.1 mg/kg	-9.3 ± 1.9	7.5 ± 3.2	9.6 ± 1.3
JY-515,317 1 mg/kg	86.3 ± 12.9	113.6 ± 18.9	59.9 ± 5.9
JY-515,317 10 mg/kg	67.2 ± 4.6	78 ± 10.6	59.3 ± 7.5
Gabapentin 150 mg/kg	96.8 ± 9.1	-6 ± 2	-12.7 ± 4.5
Vehicle	0 ± 5.5	0 ± 3.4	0 ± 4.7

For the mechanical analgesia studies, chronic constriction injury surgery was performed as previously described (Bennett and Xie, 1988). For the thermal analgesia studies, a spared nerve injury surgery was performed as described by Decosterd and Woolf, 2000. Testing for both tests occurred 1-2 weeks post-surgery. Testing occurred 1h, 2 h and 1wk post-dosing with JY-515,317 (0.1-100 mg/kg PO), gabapentin (150 mg/kg PO), or vehicle (0.5% Na-CMC in 0.9% sterile saline). Mechanical analgesia was measured using Von Frey filaments and Dixon's up-down method (Chaplan et al., 1994). Thermal analgesia was measured using the Plantar Test (Hargreaves Apparatus; Ugo Basile, Italy).

JY-515,317 Produces a Long Lasting Mechanical Analgesic Effect in the Taxol® Model of Neuropathic Pain



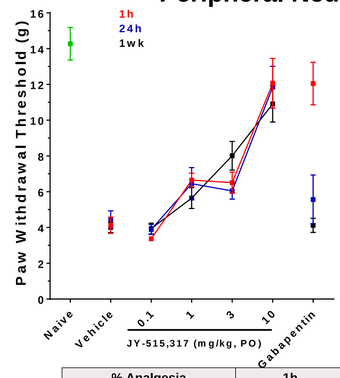
% Analgesia	1h	24h	1wk
JY-515,317 0.1 mg/kg	19.3 ± 8.4	11.27 ± 7	2.2 ± 9.4
JY-515,317 1 mg/kg	47.9 ± 7.7	8.6 ± 10.8	28.0 ± 9.1
JY-515,317 10 mg/kg	56.7 ± 9.6	46.0 ± 14.0	44.4 ±12.8
JY-515,317 30 mg/kg	61.8 ± 6.2	6.13 ±11.3	58.4 ± 12.5
Bupivacaine 150 µg/µL	89.5 ± 5.8	-5.5 ± 5.3	-7.6 ± 4.6
Vehicle	0 ± 1.8	0 ± 5.4	0 ± 7.0

Mechanical Hypersesitivity:
%Analgesia = [(log (x) -y) / (log (15) - y) * 100
Where: x = paw withdrawal threshold (g)
y = the average of the log (x) values for the vehicle treated group

% Analgesia	1h
Gabapentin 150 mg/kg	8.7
Vehicle	0

To induce neuropathy, rats were dosed with Taxol® (2 mg/kg, IP) or vehicle (0.5% Na-CMC in 0.9% sterile saline, 1 ml/kg) on D1, D3, D5, and D7 (Polomano et al. 2001). Testing was conducted 1 month after the start of Taxol® dosing. Testing occurred 1 h, 24 h and 1 wk post-dosing with JY-515,317 (0.1-30 mg/kg PO), gabapentin (150 mg/kg PO), or 0.5% Na-CMC in 0.9% sterile saline. Bupivacaine (150 µg in 50 µl SC into the footpad) was administered 30 min before testing. Mechanical analgesia was measured using Von Frey filaments and Dixon's up-down method (Chaplan et al., 1994).

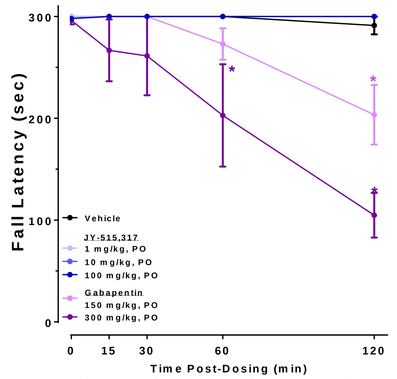
JY-515,317 Produces Long-Lasting Mechanical Analgesia in the STZ Model of Diabetic Peripheral Neuropathy



Rats were injected with streptozotocin (STZ; Sigma S0130) at 20 mg/kg, IP, daily for 5 consecutive days after which they were given drinking water supplemented with sucrose (15 g/L) for 48 h to limit early mortality. Blood glucose levels were assessed weekly to evaluate hyperglycemia and the rats with fasting blood glucose of over 15 mmol/L (280 mg/dL) were placed in the study.

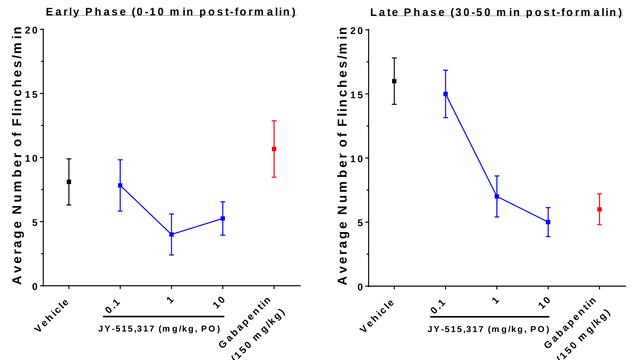
% Analgesia	1h	24h	1wk
JY-515,317 0.1 mg/kg	-13.2 ± 2.6	-8.1 ± 5.6	-0.8 ± 5.4
JY-515,317 1 mg/kg	37.7 ± 4.4	28.0 ± 10.5	25.1 ± 7.7
JY-515,317 3 mg/kg	34.2 ± 6.7	25.5 ± 7.2	51.8 ± 7.3
JY-515,317 10 mg/kg	80.6 ± 10.0	79.4 ± 7.8	74.7 ± 6.7
Gabapentin 150 mg/kg	81.5 ± 7.9	10.9 ± 17.6	1.9 ± 7.1
Vehicle	0 ± 8.9	0 ± 8.8	0 ± 5.3

JY-515,317 Does Not Show Sedative / Ataxic Side Effects in the Rat Rota-Rod Test



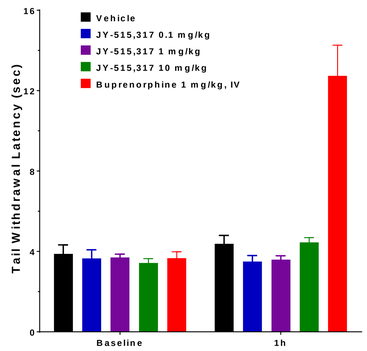
Animals were habituated 3 times before the start of testing with a fourth habituation session occurring right before dosing (0 min timepoint). A fixed speed version (16 rpm) of the Rota-rod test was used. Adult male Sprague Dawley rats were dosed with gabapentin (150,300 mg/kg PO), JY-515,317 (1-100 mg/kg PO) or 0.5% Na-CMC in 0.9% saline vehicle (1 ml/kg PO) 15 min before the first test session. Animals were re-tested 30, 60, 120 min post-dosing. Mean (± SEM) latency to fall of the Rota-Rod was recorded. N = 6-11 per group. * P < .05 Fisher's PLSD post hoc test gabapentin (150 or 300 mg/kg) vs. vehicle for each timepoint.

JY-515,317 Reduces Spontaneous Paw Flinching Behavior in Late Phase of Formalin Model



The formalin test of neuropathic pain was conducted as previously described (Wood et al., 2008). Rats were dosed with vehicle (0.5% CMC), JY-515,317 (0.1, 1, or 10 mg/kg), or the positive control PO 30 min prior to the formalin injections. In order for the rats to acclimate, they were placed individually on the formalin rack 15 min prior to the formalin injections. For better visualization, the rack was equipped with a mirror-attached underneath. At T=0, each rat was restrained and 50 ul of 5% formalin (in injectable saline) was injected into its dorsal center of its right paw using 0.5 ml insulin syringe. Recording was started immediately after injections and continued for 65 min. Scoring of the data was performed in a blinded manner. For the pain scores number of flinches and licking/biting were counted. JY-515,317 showed similar analgesic effects for the late phase licking/biting as that of the flinches.

JY-515,317 Does Not Show an Analgesic Effect in the Rat Tail Flick Model of Acute Pain



Each rat was restrained and placed on the tail flick apparatus (Ugo Basile Tail Flic Cat#: 37360) such that the tip of the tail (at 2-2.5 cm) was placed on top of the mounted window above the IR heat source. IR frequency was set at 50 and the cut off time at 15 sec. The baseline latency (sec) at which the rat removed its tail from the heat source was measured 15 minutes prior to dosing. Rats were then dosed with JY-515,317 (0.1, 1, 10 mg/kg, PO), vehicle (0.5% Na-CMC, PO) or the positive control (buprenorphine 1 mg/kg, IV). Withdrawal latencies were measured at 1 h post dosing.

JY-515,317 Has High Oral Bioavailability and Is CNS Penetrant

	Dog Plasma		Rat Plasma	
Dose (mg/kg)	0.2 (IV)	2 (PO)	1 (PO)	10 (PO)
C_{max} (ng/mL)	311	1960	210	2403
AUC_{0-t} (ng*h/mL)	353	3660	494	5707
T_{max} (h)	0.25	0.5	1.0	0.5
$T_{1/2}$ (h)	1.06	1.26	6.81	4.33

- JY-515,317 is rapidly absorbed after PO administration and has a bioavailability of 50% in rat and 100% in dog.
- JY-515,317 is detected at significant concentrations in the rat brain, as measured in CSF.