NYX-2925, a novel NMDA receptor modulator, improves chronic pain and its affective state in rats with paclitaxel-induced neuropathy

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476.15 / G4

Introduction

N-methyl-D-aspartate receptors (NMDARs) are ligand-gated ionotropic glutamate receptors that are predominately expressed in the central nervous system. NMDARs play a major role in the processes associated with both pain and emotion in the brain. NYX-2925 is a novel, orally bioavailable, small molecule NMDA receptor modulator currently in clinical development for the treatment of chronic pain, including painful diabetic peripheral neuropathy (DPN) and fibromyalgia. Chemotherapy induced peripheral neuropathy (CIPN) is a chronic neuropathic pain condition that has been attributed to previous use of chemotherapeutic agents, such as paclitaxel. Administration of paclitaxel (4 x 2 mg/kg, IP) to rats impacts both sensory and affective state in the rodent, similar to that seen in humans. Paclitaxel-injected rats show tactile and thermal allodynia and hyperalgesia in addition to increased negative affect. In the studies presented here, analgesic effects of NYX-2925 were evaluated in a rat model of CIPN using measures of mechanical and thermal allodynia as well as affective aspects of pain, as measured by aversion- and hedonia-associated ultrasonic vocalizations (USVs).

Conclusions

1. NYX-2925 administration results in significant and long-lasting mechanical analgesia in paclitaxel-induced CIPN, with an optimal dose range of 10-30 mg/kg and a duration of effect of at least 24h after a single dose.
2. The analgesic effect of NYX-2925 persists after repeat dosing for at least 3 administrations.
3. NYX-2925 also reverses thermal allodynia induced by paclitaxel treatment.
4. CIPN results in higher rates of aversion-associated 20-kHz USVs and lower rates of hedonia-associated 50-kHz USVs
5. Administration of NYX-2925 normalizes rates of both 20-kHz and 50-kHz USVs in CIPN rats
6. NYX-2925 decreases the latency to self-administer heterospecific play in rats with paclitaxel-induced CIPN.
7. NYX-2925 has high oral bioavailability and brain penetration and its pharmacokinetics are not affected by paclitaxel administration.
8. NYX-2925 administration does not result in any adverse events or overt drug-drug interactions when given alone or in combination with paclitaxel, at doses up to 10 x higher than those effective for pain relief.

Acknowledgements

This research was supported by NIH/NCI: 6R43 CA-199928 (PI: Burgdorf, JS)

Financial Disclosures

NGH, JSB, JMP, JDA, AML, MSB, CNC, & JRM received financial compensation and stock from Aptinyx, Inc. NASDAQ : APTX

Other Aptinyx Posters

118.15 / B21 (Sunday afternoon)- NYX-783, a novel NMDAR modulator, rescues the detrimental effects of encephalitis-causing anti-NMDAR antibodies on GluN2B-NMDAR expression in vitro
286.04 / C14 (Monday morning)- NYX-458, a novel NMDA receptor modulator, improves age-related, hippocampal-dependent learning impairment and reverses changes in plasticity, spine morphology, and protein expression in rat hippocampus
570.13 / H5 (Tuesday afternoon) - NMDA receptor modulation with NYX-458 rescues cognitive impairment and peripheral growth hormone levels in a clinically relevant rat model of repeat concussion
748.17 / G2 (Wednesday afternoon) - The novel NMDA receptor modulator, NYX-2925, enhances NMDAR-mediated current and LTP, induces changes in cell intrinsic properties, and alters firing properties in layer 5 pyramidal neurons of rat mPFC

Acute and Repeat NYX-2925 Administration Reverses Paclitaxel-Induced Mechanical Allodynia

A. Treatment Timeline

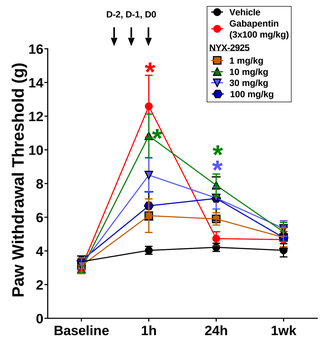
Acute Dosing

		D-2	D-1	D0	D1	D2	D3	D4	D5	D6	D7
20-25 Days post Paclitaxel 1st Injection	Treatment	G	G	G							
	Treatment			V							
	Treatment			NYX							
	Von Frey Test			X (1h)	X (24h)						X (1wk)

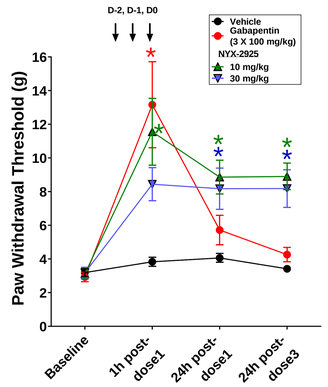
Repeat Dosing

		D-2	D-1	D0	D1	D2	D3
20-25 Days post Paclitaxel 1st Injection	Treatment	G	G	G	V	V	
	Treatment			V	V	V	
	Treatment			NYX	NYX	NYX	
	Von Frey Test			X (1h)	X (24h)		X (24h)

B. Acute Dosing

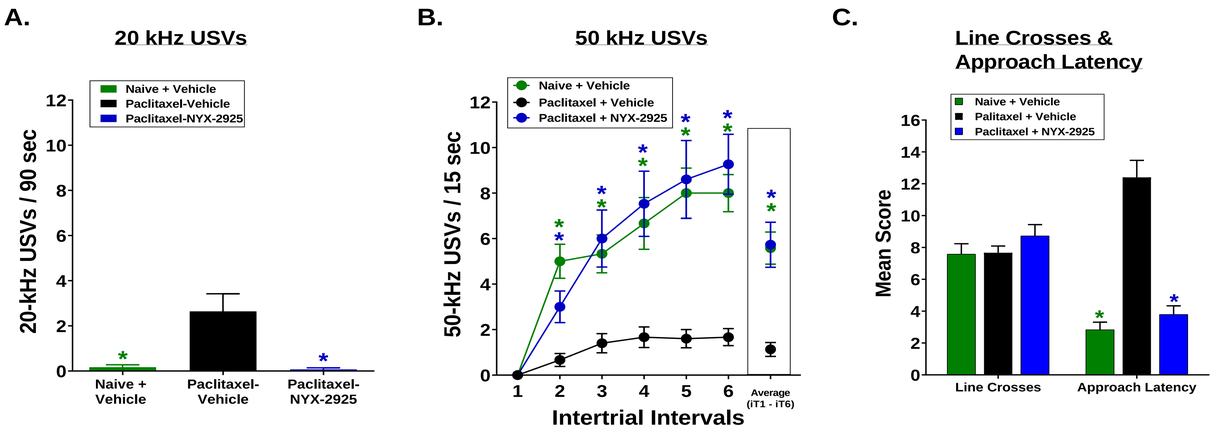


C. Repeated Dosing



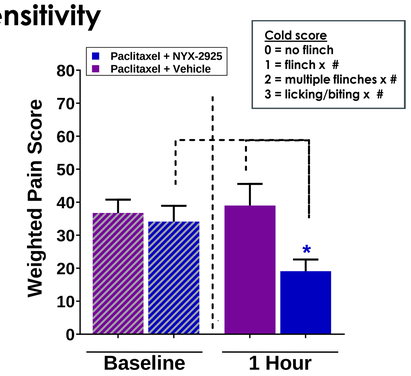
Both acute and repeated NYX-2925 administrations alleviated mechanical hypersensitivity. A. Treatment timeline. Acute dosing: Two different cohorts of rats with paclitaxel-induced neuropathy (baseline 20 - 25 days post-paclitaxel) were administered NYX-2925 (1-100 mg/kg, PO), vehicle (0.5% CMC, PO), or gabapentin (3 x 100 mg/kg over 3 days, PO); all at a volume of 2 mL/kg. Mechanical hypersensitivity was measured via von Frey filaments at 1h, 24h, and 1wk after dosing with test compound by an experimenter blind to treatment. Repeated dosing: NYX-2925 (10 or 30 mg/kg, PO) or vehicle (0.5 % CMC, PO) was dosed daily for 3 days starting 25 days post-initial paclitaxel injection. Gabapentin was dosed at 100 mg/kg (PO) once/day on D-2, D-1, and D0 (1h prior to testing). Testing occurred at 1h, 24h post NYX-29225 dose 1 and again at 24h post dose 3. **B. (Acute Dosing)** NYX-2925 (10 mg/kg, PO) reduced mechanical hypersensitivity compared to vehicle control when tested at 1h. The analgesic effect of NYX-2925 (10 mg/kg) lasted for 24h post administration. NYX-2925 at 30 mg/kg also increased 50% PWT at 1h and 24h, but only significantly at 24h when compared to vehicle treatment. Arrows represent gabapentin treatment days. *N* = 6 -17 rats/group. *$P < 0.05$, 1-way ANOVA followed by a Bonferroni post hoc. Data shown as mean ± SEM. **C. (Repeated Dosing)** NYX-2925 analgesic effect was apparent for up to 24h following 3 daily administrations. Gabapentin (3 x 100 mg/kg, PO) resulted in analgesia at 1h (post-dose 3) on D0. However, gabapentin-mediated analgesia was transient and not seen at the 24h post-last dose time point. Arrows represent gabapentin treatment days. *N* = 10 rats/group. *$P < 0.05$, 1-way ANOVA followed by a Bonferroni post hoc. Data shown as mean ± SEM.

NYX-2925 Reverses CIPN-induced Changes in Hedonia-associated Ultrasonic Vocalizations (USVs), Aversion-associated USVs, and Approach Latency in the Rough-and-Tumble Play Assay



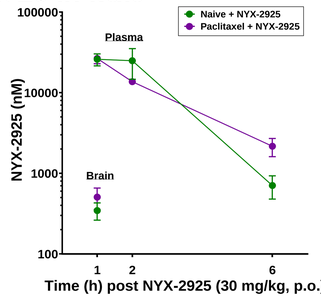
Both hedonia- and aversion-associated ultrasonic vocalizations are differentially modulated by neuropathic pain and NYX-2925, as measured via the heterospecific rough-and-tumble play. A. Rats with neuropathic pain emitted significantly more aversion-associated (20 kHz) vocalizations across non-stimulation periods when compared to paclitaxel-naïve rats. One hour after treatment, a single administration of NYX-2925 (10 mg/kg, PO) to rats with paclitaxel-induced CIPN significantly decreased the number of 20-kHz USVs. **B.** Fewer hedonia-associated (50 kHz) calls were made by rats with paclitaxel-induced CIPN versus paclitaxel-naïve rats. NYX-2925 increased the number of 50 kHz USVs in rats with neuropathic pain when measured 1h post administration. Specifically, a single administration of NYX-2925 1h prior to the first trial, significantly increased 50 kHz USVs between trials 2 through 6, when compared to vehicle-treated control rats with CIPN. Sum of hedonic 50 kHz calls in 90 sec (6 x 15 s) intertrial intervals per group for the data is also shown in B. **C.** Paclitaxel-induced CIPN significantly increased the latency to approach the experimenter's hand to self-administer heterospecific play when compared to the paclitaxel naïve rats. A single administration of NYX-2925 (10 mg/kg, PO) to rats with CIPN significantly decreased this latency when compared to vehicle-administered animals. There were no differences in line crosses between the groups. * $P < 0.05$ compared with the paclitaxel-treated vehicle group when tested 1h after administration of NYX-2925 or vehicle, *n* = 12-15 rats/group. Data represent mean ± SEM.

NYX-2925 Alleviates Paclitaxel-Induced Cold Hypersensitivity



NYX-2925 administration reduced paclitaxel-induced cold hypersensitivity. Rats with paclitaxel-induced CIPN show signs of cold hypersensitivity. The acetone evaporation test was used to measure aversive behavior triggered by evaporative cooling and thus is a measure of cold allodynia. Paclitaxel-induced cold hypersensitivity was measured by topical cold acetone (100 µL) application on the heel of each hindpaw (3 presentations per paw) in an alternating fashion. Acetone was applied, and the number of responses per category within one minute recorded and multiplied by the corresponding four-point weighted score (0 = no response, 1 = flinch, 2 = sequential flinches/shaking, 3 = licking/biting). Pain responses were monitored for 1min after acetone application. The final score was a cumulative measure of 6 scores/rat. Prior to NYX-2925 or vehicle administration, rats were baselined and any rat with baseline cold response score of ≤ 9 was eliminated from the study. NYX-2925 (10 mg/kg, 2 mL/kg, PO) treatment significantly reduced cold hypersensitivity when compared to vehicle (0.5% CMC, 2 mL/kg, PO) treatment when tested at 1h post administration. *$P < 0.05$ compared with the vehicle-treated group, n = 10 rats/group. All data are presented as mean ± SEM.

Paclitaxel Does Not Affect the Plasma or Brain PK of NYX-2925 in Rats



Paclitaxel does not change NYX-2925 pharmacokinetics. A. On D19 post paclitaxel injection, two sets of rats were fasted overnight and then dosed with NYX-2925 (30 mg/kg, 2mL/kg, PO). From one set of rats, plasma was collected at 1h, 2h, 6h, and 24h post-dose. Brain samples were collected from the second set of rats at 1h. Paclitaxel treatment did not alter plasma or brain exposure of NYX-2925, as measured by liquid chromatography tandem mass spectrometry The 24h values were below detection limits for both plasma and brain (data not shown).

NYX-2925 (300 mg/kg, PO) Did Not Show Any Observable Adverse Events

Daily (D0 - D4 post dose) Observable Adverse Effects Evaluation				
	Present / Absent			
	Naïve / Vehicle	Naïve / NYX-2925 (300 mg/kg)	Paclitaxel / Vehicle	Paclitaxel / NYX-2925 (300 mg/kg)
Convulsions	0/4	0/4	0/6	0/6
Vocalizations	0/4	0/4	0/6	0/6
Sensorimotor Reflex	0/4	0/4	0/6	0/6
Respiration	0/4	0/4	0/6	0/6
Grip Strength	0/4	0/4	0/6	0/6
Stereotypy	0/4	0/4	0/6	0/6

Observable adverse effects. On D30, post paclitaxel injection, NYX-2925 (300 mg/kg, p.o.) or vehicle (0.5% CMC, p.o.) was administered orally to the rats with CIPN and the naïve age-matched control. Rats were evaluated daily for 4 consecutive days; clinical observations and toxicology qualitative score (present/absent) were noted. On D4, rats were euthanized, organs were collected, weighed, and evaluated macroscopically and sent for histopathology evaluation. The pathology study was performed by Charles River Laboratories. There were no observable adverse effects seen with the administration of NYX-2925 at 300 mg/kg to the paclitaxel-injected rats.