THE NMDA RECEPTOR MODULATOR NYX-2925 SHOWS THERAPEUTIC POTENTIAL IN PRECLINICAL MODELS FOR THE TREATMENT OF NEUROPATHIC PAIN

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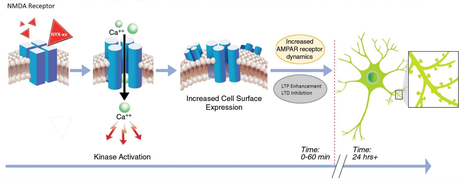
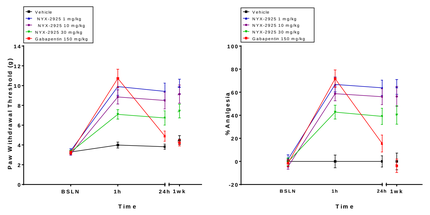
NYX-2925 Mechanism of Action



INTRODUCTION

Neuropathic pain (NP) is a highly prevalent condition caused by a primary lesion or dysfunction of the nervous system. Current treatments for neuropathic pain are only modestly effective and in only a minority of patients. There is a high unmet medical need for more effective therapeutics for neuropathic pain conditions.
Glutamate *N-methyl-D-aspartate* receptor (NMDAR) dependent synaptic plasticity processes may play a role in the establishment of neuropathic pain and as such, the NMDAR is a potential therapeutic target.
NYX-2925 is an orally bioavailable, small molecule NMDAR modulator that has recently completed Phase 1 clinical trials. NYX2925 has rapid-acting and long lasting efficacy in animal models of neuropathic pain. The present studies examine the effect of NYX-2925 in rat models of neuropathic pain when administered over a wide dose range as a single dose or two weeks of daily dosing.

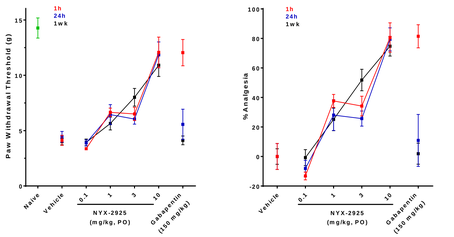
NYX-2925 Produces Long-lasting Analgesia in the CCI Neuropathic Pain Model



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

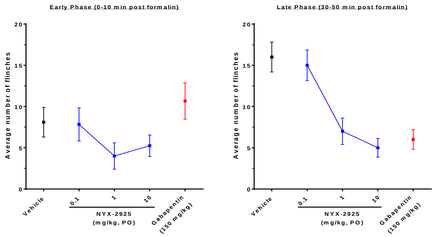
CCI surgery was performed as previously described (*Bennett* and *Xie*, 1988). Testing occurred once animals reached a stable baseline (~2 weeks post-surgery). On each test day, NYX-2925 (0.1-100 mg/kg PO), gabapentin (150 mg/kg PO), or vehicle (0.5% Na-CMC in 0.9% sterile saline) was administered to the rats and mechanical hypersensitivity at 1h, 24h, and 1wk post dosing was measured using von Frey filaments and Dixon's up-down method (*Chaplan et al., 1994*).

NYX-2925 Produces Long-Lasting Analgesia in the STZ Model of Diabetic Peripheral Neuropathy



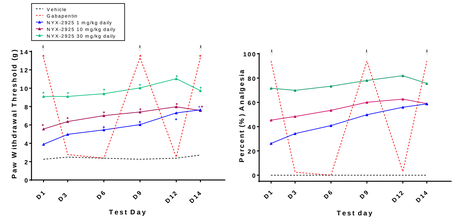
Rats were injected with streptozotocin (STZ; Sigma S0130) at 20 mg/kg IP, daily for 5 consecutive days after which they were given drinking water supplemented with sucrose (15 g/L) for 48 h to limit early mortality. Blood glucose levels were assessed weekly to evaluate hyperglycemia and the rats with fasting blood glucose of over 15 mmol/L (280 mg/dL) with the paw withdrawal threshold of ≤5 g were placed in the study. Testing occurred approximately 2 weeks post STZ. On test day, NYX-2925 (0.1-10 mg/kg PO), gabapentin (150 mg/kg PO), or vehicle (0.5% Na-CMC in 0.9% sterile saline) was administered to the rats and mechanical hypersensitivity at 1h, 24h, and 1wk post dosing was measured using von Frey filaments and Dixon's up-down method (*Chaplan et al., 1994* and *Calcutt et al., 1996*).

NYX-2925 Reduces Spontaneous Paw Flinching Behavior in the Formalin-induced Persistent Pain Model



The formalin test of neuropathic pain was conducted as previously described (*Wood et al., 2008*). Rats were dosed with vehicle (0.5% CMC), NYX-2925 (0.1, 1, or 10 mg/kg), or the positive control gabapentin (150 mg/kg) PO 30 min prior to the formalin injections. Rats were acclimated on the formalin rack for 15 min prior to the formalin injections. At T=0, each rat was restrained and 50 µl of 5% formalin (in injectable saline) was injected into the dorsal center of the right paw using a 0.5 ml insulin syringe. For the pain scores number of flinches and licking/biting were counted by a researcher blind to treatment condition. NYX-2925 showed similar analgesic effects for the late phase licking/biting as that of the flinches.

Chronic Daily Dosing of NYX-2925 Maintains Analgesia in the CCI Neuropathic Pain Model



Gabapentin dosed
NYX-2925 dosed daily: D1-D13
D14 measurement at 24h post D13 dose

CCI surgery was performed as previously described (*Bennett and Xie, 1988*). Testing occurred once animals reached a stable baseline (~2 weeks post-surgery). NYX-2925 (1-30 mg/kg PO) or vehicle (0.5% Na-CMC in 0.9% sterile) was orally administered daily to the rats for 13 consecutive days. For the gabapentin group, Gabapentin (100 mg/kg PO) was dosed on D1, D9, and D14, with water dosed on other treatment days. Paw withdrawal threshold was measured 24h post vehicle or compound and 1h post gabapentin by using von Frey filaments and Dixon's up-down method (*Chaplan et al., 1994*).

Data source: PsychoGenics Inc.

NYX-2925 Has High Oral Bioavailability and Is a 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**

- NYX-2925 is rapidly absorbed after PO administration and has a bioavailability of 50% in rat and 100% in dog.
- NYX-2925 is detected at significant concentrations in the brain, as measured in CSF

RESULTS

A single oral dose of NYX-2925 produced a rapid-acting (1h post-dosing) and long-lasting (24h and 1 week post-dosing) analgesia in the CCI and STZ models with statistically significant efficacy over vehicle seen between 1-30 mg/kg in the CCI model and 1-10 mg/kg in the STZ model. In contrast, the gabapentin (150 mg/kg PO) only produced analgesic effect 1h post-dosing in the both models. A single oral dose of 1-10 mg/kg NYX-2925 also reduced flinching in the late phase of the formalin test 1h post dosing to a similar degree as gabapentin (150 mg/kg PO). Daily oral administrations of NYX-2925 over 14 days results in significant efficacy over vehicle that was sustained throughout the dosing period.

CONCLUSIONS

- NYX-2925 shows an analgesic effect after a single dose in multiple models of neuropathic pain that is both rapid (occurring within 1 h of administration) and long lasting (at least 1 week after a single administration).
- Daily dosing results in significant and sustained efficacy.
- There are no signs of adverse effects with daily chronic dosing of NYX-2925.
- NYX-2925 is rapidly absorbed after PO administration, has a bioavailability between 50-100% and is detected at significant concentrations in the brain

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AFFILIATION and FINANCIAL DISCLOSURES

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