NYX-783 is a Novel NMDA Receptor Modulator with Therapeutic Potential for the Treatment of Post-Traumatic Stress Disorder (PTSD)

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BACKGROUND

Aptinyx has developed a novel class of small molecule NMDA receptor (NMDAR) modulators with broad applicability across neurologic and psychiatric diseases including post-traumatic stress disorder (PTSD).

- NYX-783 is a spiro-β-lactam NMDAR modulator and is distinct from known NMDAR agonists or antagonists
- In recombinant human NMDAR2A-2D-expressing HEK cells, partial agonist activity of NYX-783 was demonstrated at all four receptor subtypes.
- NYX-783 exhibits high oral bioavailability (94%F), high brain penetration (0.11 CSF / plasma ratio), and has shown efficacy after oral administration in several animal models of psychiatric disease without demonstrating side effects.

Here, the *in vitro* and *in vivo* pharmacological properties of NYX-783 are further characterized.

NYX-783 has a Dose-Dependent Effect on NMDAR Current in Rat Hippocampal Pyramidal Neurons

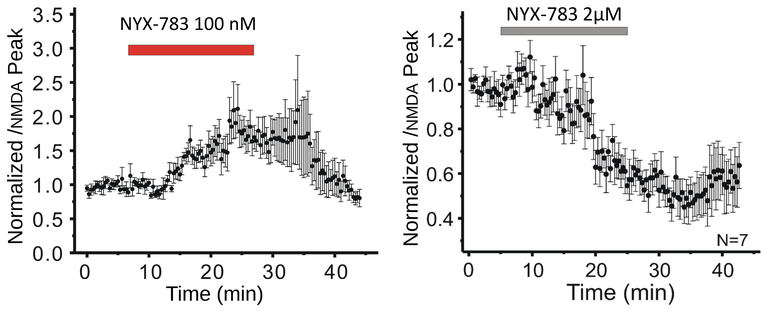

Figure 1. NMDA Receptor Subtype Activation. As measured in a [3H]MK-801 potentiation assay with recombinant human NMDARs expressed in HEK cells, NYX-783 facilitated channel opening at all 4 receptor subtypes.

The Effect of Orally-Delivered NYX-783 on Hippocampal LTP is Long-lasting and Concentration Dependent

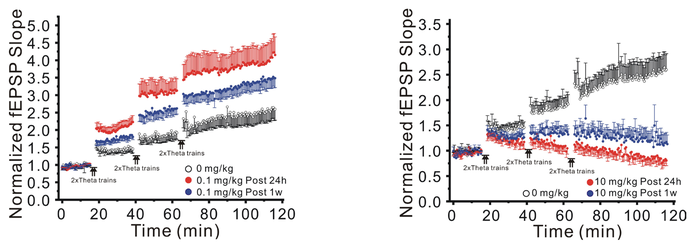

Figure 3. Ex Vivo LTP. One day (red) or 1 wk (blue) after oral dosing with 0.1 (left) or 10 (right) mg/kg NYX-783, LTP was induced by theta burst stimulation (arrows). 0.1 mg/kg NYX-783 enhanced LTP at Schaffer collateral-CA1 synapses; 10 mg/kg NYX-783 inhibited LTP induction.

NYX-783 Increases Hedonic Vocalizations in the Positive Emotional Learning Assay

Figure 7. Positive Emotional Learning (PEL). Rats underwent a single 3-min trial (1 h post-dose) that consisted of 6 15-sec periods of tickling interleaved with 6 15-sec periods during which the rat was left undisturbed. The number of 50-kHz ultrasonic vocalizations (USVs) emitted during the 5th and 6th undisturbed periods was used as an index of PEL. A single in vivo dose of NYX-783 (0.001-0.1 mg/kg, PO) in 2-3 month old male rats increased the number of hedonic USVs emitted in response to a conditioned stimulus associated with heterospecific rough and tumble play 1 h post-dose (left); with a trend toward an effect at 24 h post-dose (right). *, $p < 0.05$.

NYX-783 Reduces Floating Time in the Porsolt Assay for at Least 1 week in Both Males and Females Over a Wide Dose Range

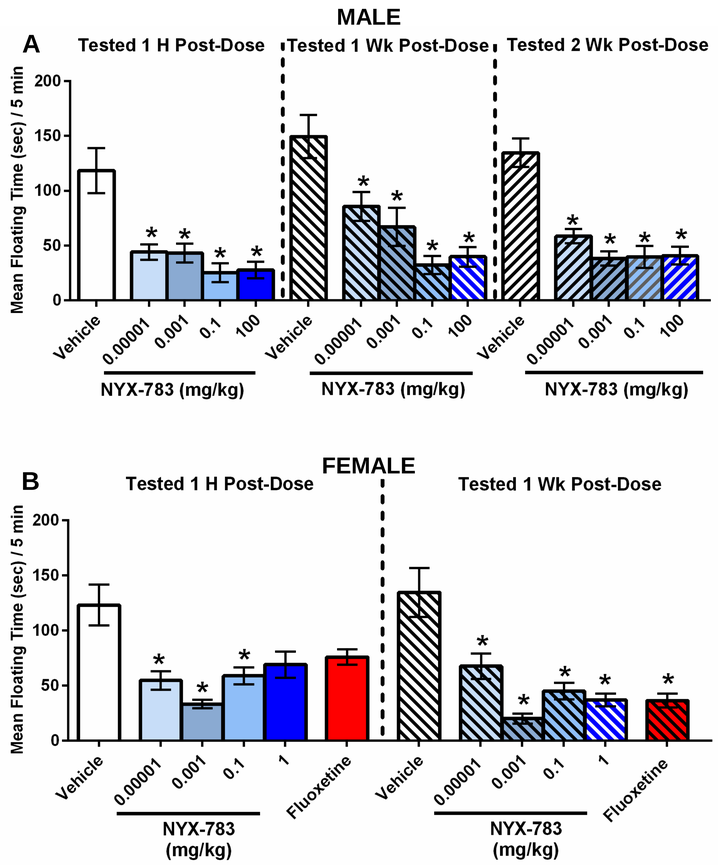

Figure 5. Forced Swim (Porsolt) Test. Rats were trained during a 15-min swimming session. Twenty-four hours later, rats were orally dosed with NYX-783 or vehicle. Fluoxetine (20 mg/kg/dose, SC) was dosed 23.5, 5, and 1 h before the first test. Rats were returned to the swim cylinders for a video-recorded 5-min test 1 h, 1 wk, and 2 wk (**Panel A** only) post-dose. Floating was manually scored. NYX-783 (PO) decreased floating time *vs.* vehicle 1 h , 1 wk, and 2 wk in male rats (**Panel A**), and at 1 h and 1 wk in female rats (**Panel B**). *, $p < 0.05$.

NYX-783 Enhances Memory when Delivered Prior to T1 in the Novel Object Recognition Assay

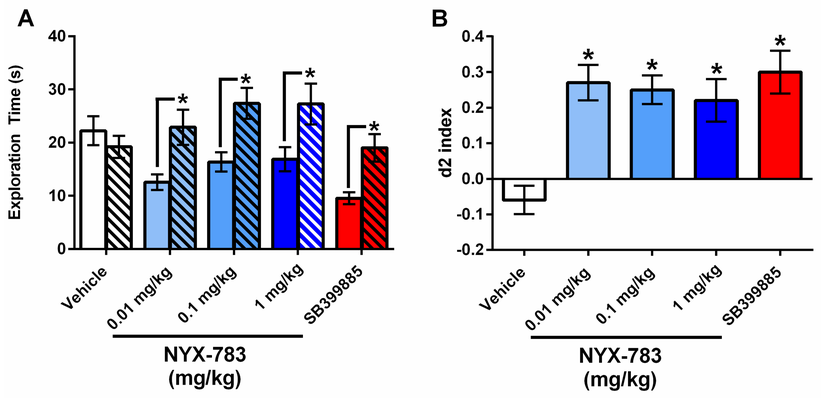

Figure 6. Novel Object Recognition Task. Rats were habituated to empty test arenas, then allowed to explore 2 identical objects for 3 min (sample) trial. Twenty-four hours later, during the test trial, rats were returned to the test arenas and allowed to explore 1 familiar and 1 novel object. SB399885 (10 mg/kg, PO) was administered 4 h before both the sample and the test trials; NYX-783 (0.01 – 1 mg/kg, PO) was administered 1 h before the sample trial. **A:** Rats dosed with SB399885 or NYX-783 explored the novel (hatched columns) more than the familiar (solid columns) object during the test trial. **B**: Treatment with SB399885 or NYX-783 increased rats' normalized difference (d2) score *vs.* vehicle. *, $p < 0.05$. **Study completed by Transpharmation Ltd**.

NYX-783 Facilitates Extinction and Inhibits Spontaneous Recovery of the Fear Response in the Contextual Fear Extinction Assay

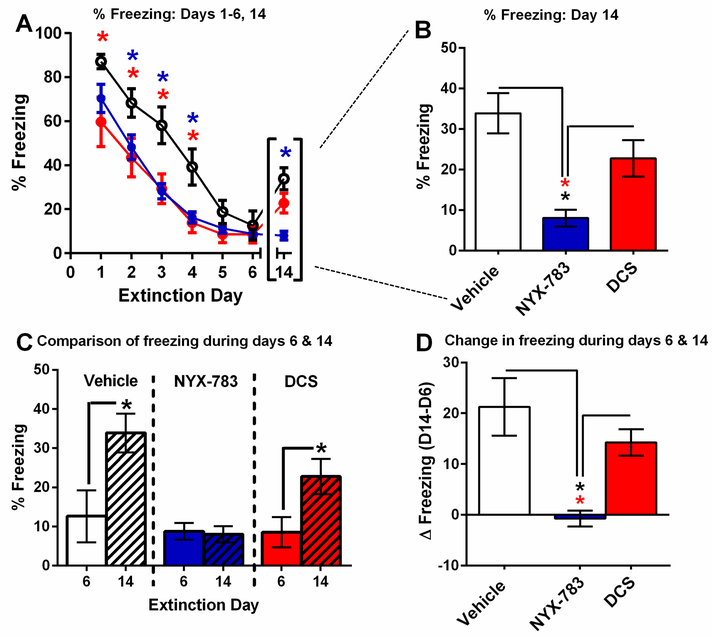

Figure 8. Contextual Fear Extinction. On the training day, rats were placed in a shock chamber for 7.5 min. Shocks (0.5 mA) were delivered for 1 sec at 90, 210, and 330 sec after the animal was placed into the chamber. For extinction trials, rats were placed in the chamber for 5 min. Trial 1 began 1 h post-dosing with vehicle (1 mg/kg, PO or SC), d-cycloserine (DCS; 15 mg/kg, SC), or NYX-783 (1 mg/kg, PO). Extinction days 1-6 occurred on 6 consecutive days; and again 14 days post-training. Between days 6 and 14, rats were returned to their homecages and left undisturbed. DCS significantly facilitated fear extinction on days 1-4; NYX-783 significantly facilitated fear extinction on days 2-4 (**Panel A**). Unlike DCS, NYX-783 prevented spontaneous recovery of conditioned fear on day 14 (**Panels B-D**). *, $p < 0.05$.

Unlike Ketamine, NYX-783 has no Sedative or Ataxic Effects

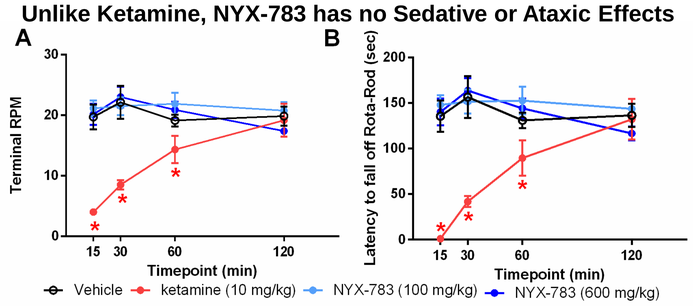

Figure 4. Rota-Rod. On the training day, rats were placed onto the Rota-Rod for 2 min, starting at a constant speed of 4 rpm with acceleration up to 12 rpm. During the testing phase, rats were placed onto the Rota-Rod, which started at 4 rpm and accelerated to a maximum speed of 40 rpm, for up to 5 min. Testing was initiated 15 min post-dose with vehicle (PO), ketamine (10 mg/kg, IV), or NYX-783 (100 or 600 mg/kg, PO). NYX-783 did not cause motor impairment (sedation or ataxia) as assessed in the accelerating Rota-Rod task. *, $p < 0.05$ *vs.* vehicle-treated rats.

CONCLUSIONS

- **NYX-783 is an orally available NMDAR modulator enhances NMDA current and facilitates long-term potentiation for at least 1 week post-administration**
- **NYX-783 shows robust, long-lasting efficacy in several behavioral models relevant to PTSD including models of depression, learning and fear extinction, with no adverse effects in the accelerating Rota-Rod task.**
- **NYX-783 represents a novel and differentiated therapeutic option for the treatment of PTSD.**

AFFILIATIONS AND DISCLOSURES

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