A Novel NMDA Receptor Modulator, NYX-783, Shows Therapeutic Potential as a Treatment for PTSD and TBI

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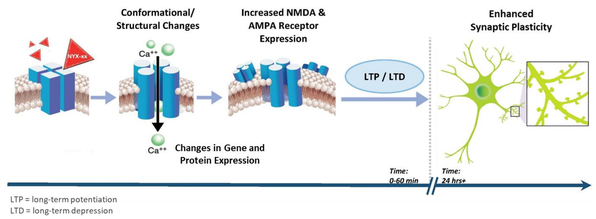
INTRODUCTION

N-Methyl-D-Aspartate receptors (NMDARs) are a family of ligand-gated ionotropic glutamate receptors that are found predominantly in the central nervous system (CNS) and play a pivotal role in mediating normal neuronal functions. NMDAR dysfunction has been implicated in a variety of CNS disorders, including post-traumatic stress disorder (PTSD), traumatic brain injury (TBI), cognitive impairment, mood disorders, and neuropathic pain. Aptinyx has developed a family of novel, small molecule, orally bioavailable synthetic NMDAR modulators. Mechanistically, these molecules bind directly to NMDARs, modulating (rather than inhibiting or over-activating) them and triggering a neurobiological cascade leading to enhancement of synaptic plasticity. Here, NYX-783 was evaluated for its ability to enhance learning and memory, as well as to ameliorate affective and cognitive deficits in preclinical models of PTSD and TBI.



1. NYX-783 improves novel object recognition

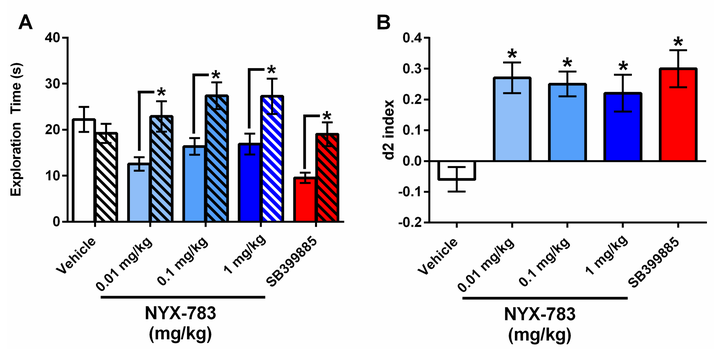


Figure 1. Novel Object Recognition Task. Rats were habituated to empty test arenas, then allowed to explore 2 identical objects for 3 min (sample) trial. Twenty-four hours later, during the test trial, rats were returned to the test arenas and allowed to explore a familiar and a novel object. SB399885 (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 the normalized difference (d2) score. *versus* vehicle: * $p < 0.05$. Data source: *Transpharmation Ltd.*

2. NYX-783 improves performance in a medial prefrontal cortex-dependent learning task

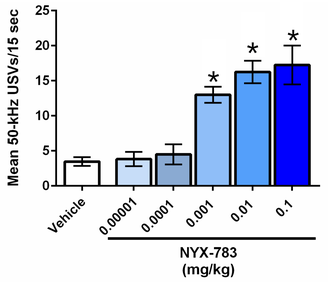


Figure 2. Positive Emotional Learning (PEL). Rats underwent a single 3-min trial that consisted of 6 15-sec periods of tickling interleaved with 6 15-sec periods during which the rat was left undisturbed. The number of frequency-modulated 50-kHz ultrasonic vocalizations emitted during the fifth and sixth 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 ultrasonic vocalizations (USVs) emitted in response to a conditioned stimulus associated with heterospecific rough and tumble play 1 h post-dose. *$p < 0.05$ versus vehicle.

3. NYX-783 reduces immobility in the forced swim task

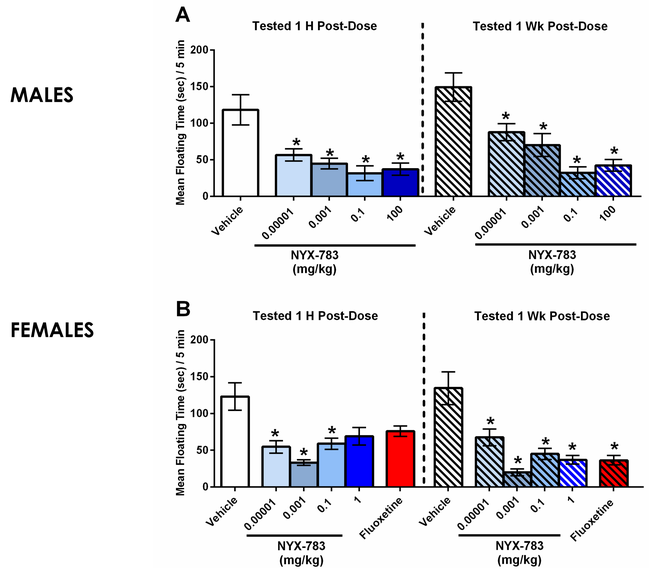


Figure 3. Forced Swim Task. Rats were trained during a 15-min swimming session. Twenty-four hours later, rats were orally dosed with NYX-783 or vehicle. Fluoxetine (20 mg/kg/dose, SC) was dosed 23.5, 5, and 1 h before the first test. Rats were returned to the swim cylinders for a video-recorded 5-min test 1 h and 1 wk post-dose. Floating was manually scored. NYX-783 (PO) decreased floating time *versus* vehicle 1 h and 1 wk in both male (Panel A) and female (Panel B) rats. * $p < 0.05$ *versus* vehicle.

4. NYX-783 facilitates contextual fear extinction and reduces spontaneous recovery of fear

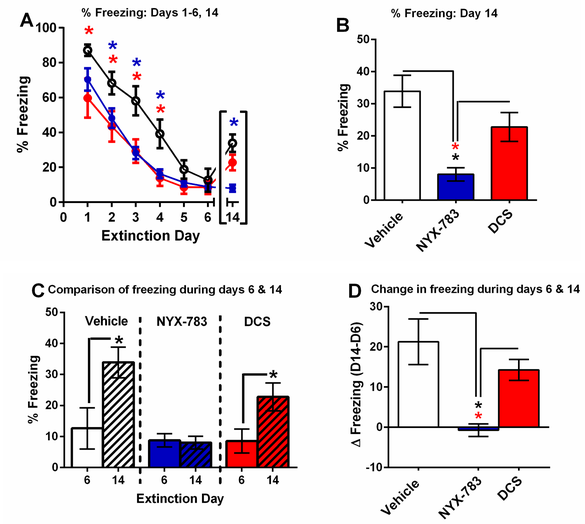


Figure 4. Contextual Fear Extinction. On the training day, rats were placed in a novel chamber for 7.5 min. Shocks (0.5 mA) were delivered for 1 sec at 90, 210, and 330 sec after the rat was placed into the chamber. For extinction trials, rats were placed in the chamber for 5 min. Trial 1 began 1 h post-dosing 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; day 14 occurred 14 days post-training. Between days 6 and 14, rats were returned to their home cages 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**). * $p < 0.05$ *versus* vehicle or DCS.

5. Learning deficits are rescued by NYX-783 following blast-induced injury

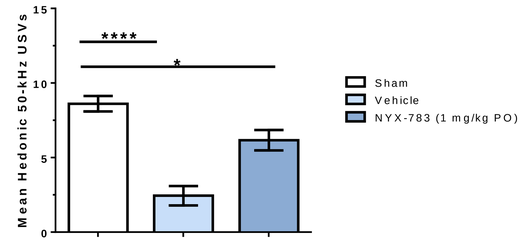


Figure 5. NYX-783 rescues blast-induced deficits in positive emotional learning. Rats were dosed with either vehicle (1 ml/kg) or NYX-783 1 h after receiving a blast injury. 48 h later, rats were engaged in heterospecific rough-and-tumble play, and hedonic ultrasonic vocalizations were recorded between play bouts as a measure of positive emotional learning. NYX-783 rescued the blast-induced impairment to levels at or above those observed in sham (non-injured) rats. * $p < 0.05$; **** $p < 0.001$ *versus* vehicle.

	% F	Brain C_{MAX} (ng/ml)	Plasma C_{MAX} (ng/ml)	Protein Binding (% Bound)
NYX-783 (10 mg/kg)	94	262.7	4746.28	7.8

Table 1. Pharmacokinetics. In rat PK studies, NYX-783 (10 mg/kg, PO) shows high oral bioavailability and brain penetration. Protein binding in rat plasma is low.

CONCLUSIONS

- NYX-783 shows robust, long-lasting effects in behavioral models relevant to psychiatric disorders, including PTSD.
- NYX-783 rescues a learning impairment observed in a blast-induced rodent model of TBI.
- Together, these data form a rational foundation to undertake further clinical studies to assess NYX-783 in both PTSD, for which it has been granted Fast Track designation by the FDA, and TBI.
- NYX-783 has been evaluated in a Phase I clinical study and has demonstrated a favorable safety and tolerability profile in healthy volunteers.

FINANCIAL DISCLOSURES

EC, LPC, KL, JSB, ALG, MS, RAK, MAK, CNC, TMM and JRM are employees of Aptinyx, Inc.