NYX-458, a novel small molecule NMDA receptor modulator, enhances novel object recognition in rats

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Objective: Aptinyx has developed a novel class of small molecule N-methyl-D-aspartic acid receptor (NMDAR) modulators with broad applicability across neurologic and psychiatric disorders. One of these, NYX-458, was evaluated for efficacy in the novel object recognition (NOR) task, an animal model of recognition memory.

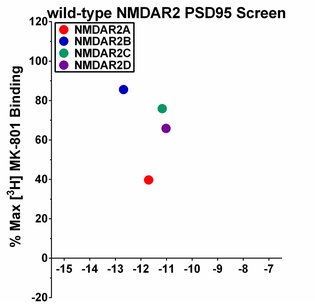

Figure 1. NYX-458 preferentially binds GluN2B-containing NMDARs. As measured in a [^{3}H]MK-801 potentiation assay with PSD95/NR1:NR2 expressed in HEK cells, NYX-458 facilitated channel opening of all four subtypes (NDMDAR2A, 2B, 2C, and 2D).

	% F	Brain C_{MAX} (ng/ml)	Plasma C_{MAX} (ng/ml)	Plasma Protein Binding (% Bound)
NYX-458 (10 mg/kg)	100	1107.2	4746.28	46

Table 1. NYX-458 demonstrates favorable pharmacokinetics. In rats, NYX-458 (10 mg/kg, PO) shows high oral bioavailability and brain penetration. Plasma protein binding is low.

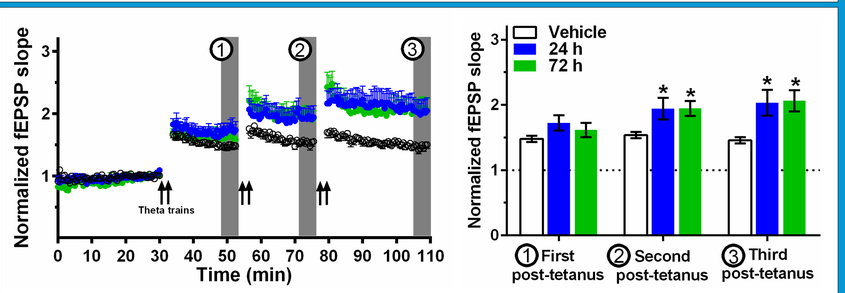

Figure 2. NYX-458 enhanced LTP at Schaffer collateral-CA1 synapses 1 and 3 days post- oral dose. One (blue) or three (green) days after oral dosing with 1 mg/kg NYX-458, LTP was induced by theta burst stimulation (arrows; two trains, 3 min apart of 10 x 100 Hz/ 5 pulse bursts, 200 ms interburst interval). **Left**: Timecourse of the response; **Right**: Group means. *, $p < 0.05$ *vs.*vehicle.

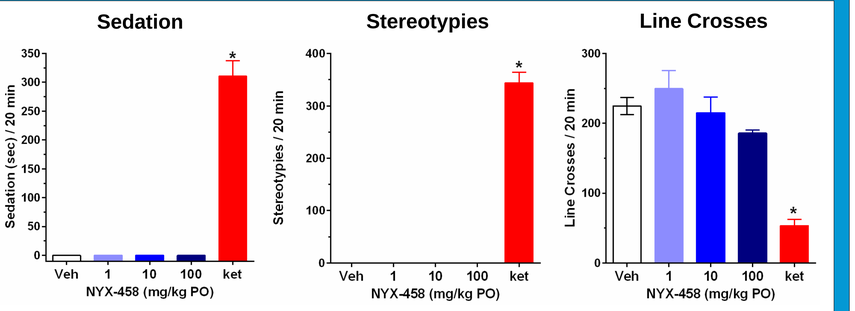

Figure 3. NYX-458 does not produce sedation or stereotypies, or impair locomotion. Rats were placed into an open field for 20 min either 1 h post-dose with vehicle (0.5% CMC in water, PO) or NYX-458 (1-100 mg/kg, PO), or immediately post-dose with ketamine (10 mg/kg, IV). Sedation, stereotypies, and decreased locomotion were observed for ketamine, but not NYX-458 or vehicle. *, $p < 0.05$ *vs.* vehicle-dosed rats.

AFFILIATIONS AND DISCLOSURES

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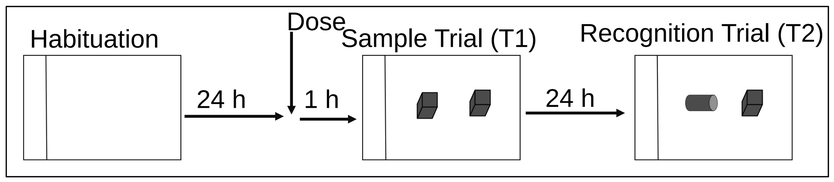


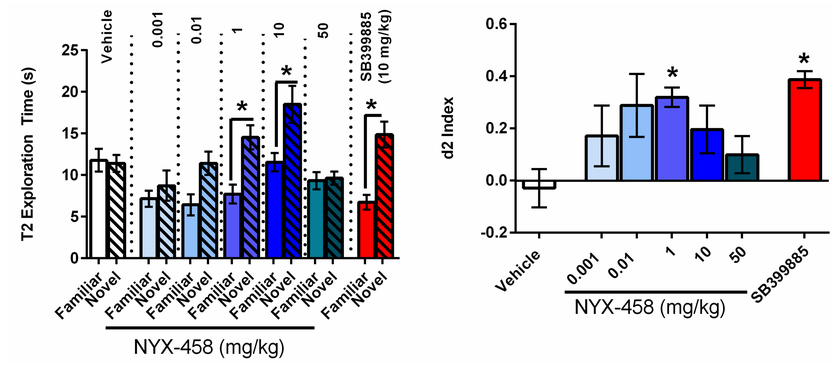
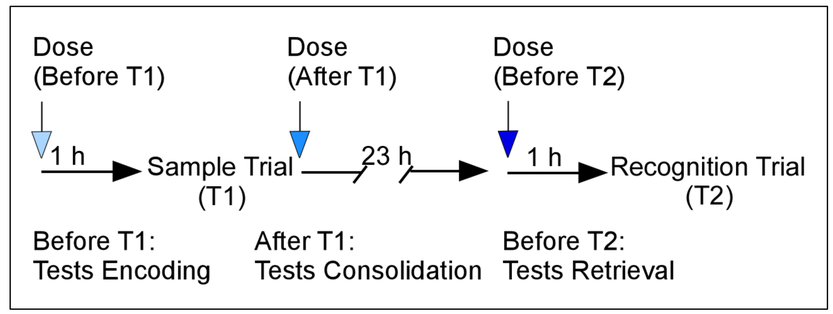


Figure 4. Dose-response of NYX-458 in the Novel Object Recognition (NOR) task. Rats were habituated to empty test arenas and then allowed to explore 2 identical objects for 3 min (T1, sample trial). Twenty-four hours later, during the test trial, rats were returned to the test arenas and allowed to explore 1 familiar and 1 novel object (T2, test trial). The positive control SB399885 (10 mg/kg, PO) was administered 4 h before both the sample and the test trials; NYX-458 (0.001 – 50 mg/kg, PO) was administered 1 h before the sample trial. **Left:** Rats dosed with SB399885 or NYX-458 (1 and 10 mg/kg) explored the novel (hatched columns) more than the familiar (solid columns) object during T2. **Right**: Dosing with SB399885 or NYX-458 (1 mg/kg) increased the normalized difference (d2) score *vs.* vehicle. *, $p < 0.05$.



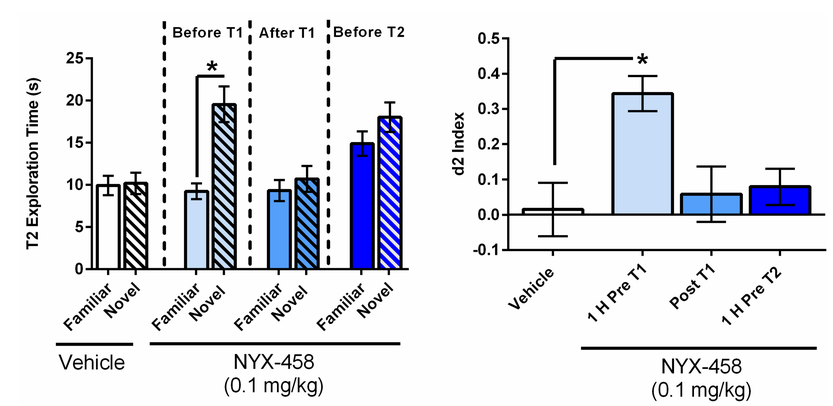
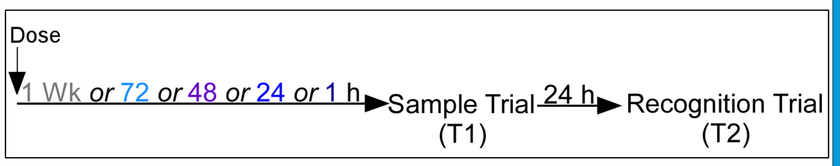


Figure 5. NYX-458 selectively enhances encoding in the NOR task. Rats were habituated to empty test arenas and then allowed to explore 2 identical objects for 3 min (T1, sample trial). Twenty-four hours later, during the test trial, rats were returned to the test arenas and allowed to explore 1 familiar and 1 novel object (T2, test trial). Vehicle was dosed 1 h before T1; NYX-458 (0.1 mg/kg) was dosed either 1 h before, immediately after T1, or 1 h before T2. **Left:** Rats dosed with NYX-458 1 h before T1 explored the novel (hatched columns) more than the familiar (solid columns) object during T2. **Right**: Dosing with NYX-458 1 h before T1 increased the normalized difference (d2) score *vs.* vehicle. *, $p < 0.05$.



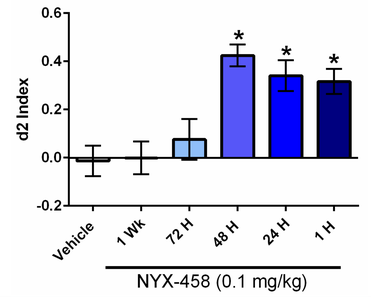


Figure 6. NYX-458 enhances object recognition memory when administered up to 48 h before T1. Rats were habituated to empty test arenas and then allowed to explore 2 identical objects for 3 min (T1, sample trial). Twenty-four hours later, during the test trial, rats were returned to the test arenas and allowed to explore 1 familiar and 1 novel object (T2, test trial). NYX-458 (0.1 mg/kg, PO) was administered 1 wk, 72 h, 48 h, 24 h, or 1 h T1. Dosing with NYX-458 up to 48 h before T1 increased the normalized difference (d2) score *vs.* vehicle. *, $p < 0.05$.

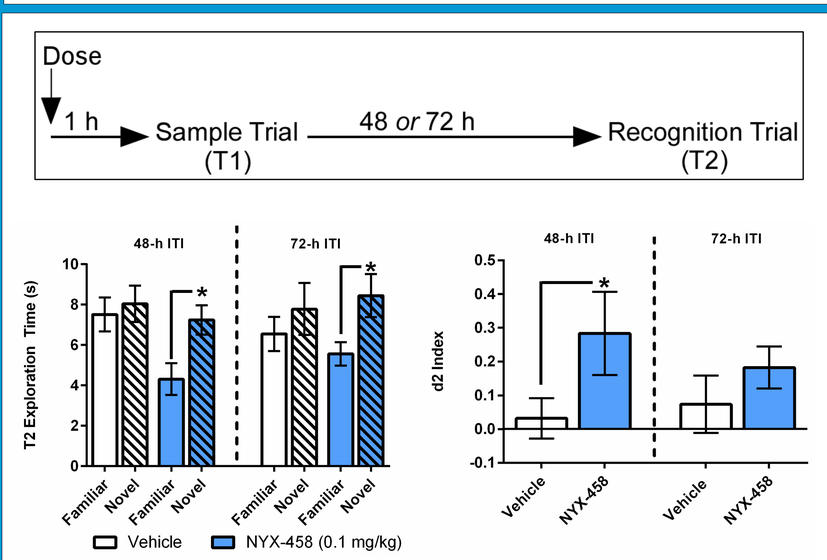


Figure 7. NYX-458 enhances object recognition memory with a 48-h T1-T2 interval when administered 1 h before T1. Rats were habituated to empty test arenas, and then allowed to explore 2 identical objects for 3 min (T1). Either 48 or 72 h later, rats were returned to the test arenas and allowed to explore 1 familiar and 1 novel object (T2). NYX-458 (0.1 mg/kg, PO) was administered 1 h before T1. **Left:** Rats dosed with NYX-458 explored the novel object (hatched columns) more than the familiar object (solid columns) during T2. **Right**: Dosing with NYX-458 increased rats' normalized difference (d2) score *vs.* vehicle when the T1-T2 interval was 48 h, but not 72 h. *, $p < 0.05$.

CONCLUSIONS

- **NYX-458 is a NMDAR modulator with activity at all four NMDAR2 receptor subtypes.**
- **NYX-458 enhances hippocampal LTP 24 or 72 h after oral administration.**
- **NYX-458 exhibits high oral bioavailability and brain penetration with low plasma protein binding, and shows no adverse effects in the open field or Rota-Rod task.**
- **NYX-458 produces long-lasting pro-cognitive effects in the novel object recognition (NOR) assay when given up to 48 h before the encoding phase of the task.**

Summary: NYX-458 is a novel NMDAR modulator that exhibits cognitive enhancement in the NOR assay; this effect is selective for the encoding phase of the task. These data support the ongoing development of NYX-458 for the treatment of cognitive impairment.

RELATED POSTER

NYX-458, a NMDA receptor modulator, when tested in aged F344 rats, facilitates LTP and reverses age-related cognitive deficits as measured by the Morris water maze. Poster **HHH8 (11/7, 10-11 AM)**