S01-398: A SUBCOMMISSURAL ORGAN-SPONDIN-DERIVED PEPTIDE (NX210C) PROMOTES GLUTAMATERGIC RECEPTOR-RELATED SYNAPTIC TRANSMISSION AND SIGNALING IN THE MOUSE CNS

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INTRODUCTION

NX210c is a dodecapeptide designed from the subcommissural organ (SCO)-spondin, a glycoprotein intimately involved in central nervous system development. This peptide was demonstrated to promote cognitive recovery in a mice model of Alzheimer's disease. However, knowledge is limited concerning the main mechanisms underlying this effect. The disruption of synaptic function represents a common denominator of many neurodegenerative and psychiatric diseases. Notably, glutamatergic synapses play a primary role in a broad range of cognitive processes. Targeting these synapses may thus be a good way for rebalancing neuronal activity in key networks supporting cognition. Here, we dug deeper into the mechanism of action of NX210c by evaluating its effect on excitatory synaptic function and dysfunction.

METHODS

● **Electrophysiological recordings.** Acute brain slices were obtained from adult mouse and superfused with NX210c (250 µg/mL) to evaluate its effect on (1) NMDAR- and AMPAR-mediated excitatory postsynaptic currents (EPSCs) at hippocampal CA3-CA1 synapses, and on (2) extracellular field excitatory postsynaptic potentials (fEPSPs) at hippocampal and thalamocortical synapses.

● **Phencyclidine (PCP)-induced memory deficits.** From D0 to D11, mice received chronic injections of the NMDA receptor antagonist PCP (SC, 0.2mg/kg, twice daily) to impair synaptic and cognitive functions. Mice were then treated with NX210c (IP, 5mg/kg) as either a single dose at D13 (-24h before T-maze) or D14 (-2h) or repeated doses from D12 to D14 (-48h, -24h, and -2h). At D14, working memory was assessed using the T-Maze. Cerebral cortices were collected to quantify protein levels of GluN2A-NMDAR and phosphorylated CREB (pCREB) by western blotting.

Scan these QR codes for more information about NX210c

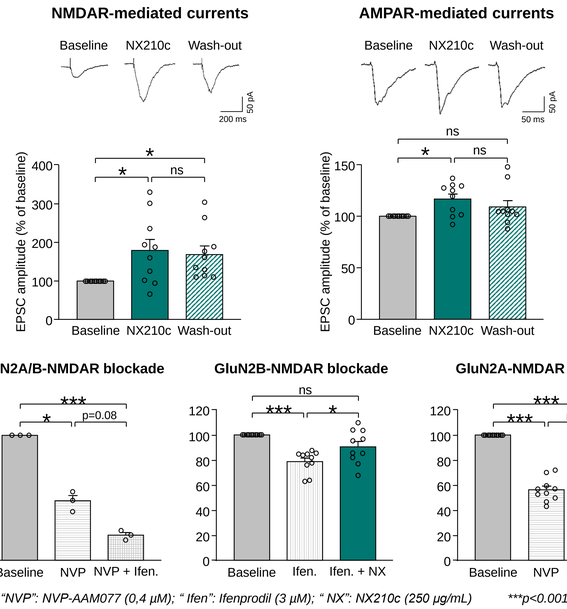
Delétage et al. (2021)

Le Douce et al. (2021)

RESULTS

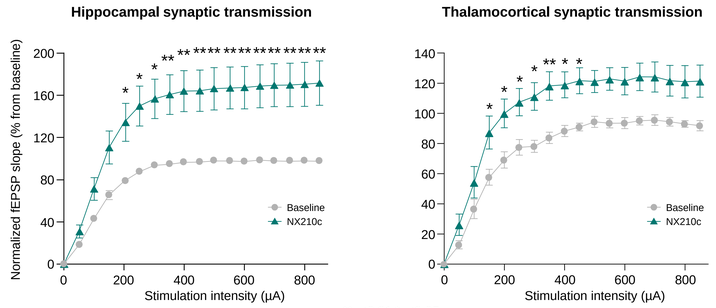
● **NX210c enhances glutamate receptor-mediated currents at CA3-CA1 hippocampal synapses**

NX210c significantly increased the amplitude of both NMDAR-mediated currents (+79,2%, p= 0.0469) and AMPAR-mediated currents (+16.7%, p= 0.0191). Interestingly, the enhancement of NMDAR-mediated currents triggered by NX210c was demonstrated to primarily involve GluN2A-containing NMDAR.



"NVP": NVP-AAM077 (0,4 µM); " Ifen": Ifenprodil (3 µM); " NX": NX210c (250 µg/mL) ***p<0.001,*p<0.05

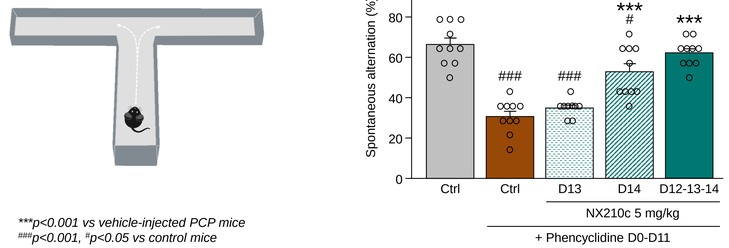
● **NX210c increases both hippocampal and thalamocortical synaptic transmission**



**p<0.01,*p<0.05

● **NX210c restores memory in a mouse model of cortical synaptic dysfunction**

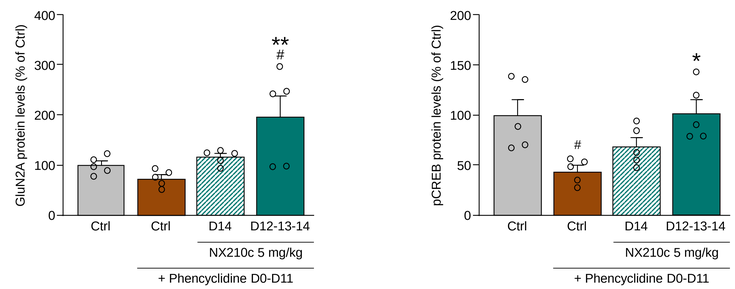
A single acute administration of NX210c in PCP-injected mice restored working memory (-35.7 and -13.5% of T-maze alternations for vehicle- and NX210c-treated PCP mice *vs* control mice). Repeated daily administrations also restored memory (-4.3% of alternations for NX210c-treated PCP mice *vs* control mice).



****p<0.001 vs vehicle-injected PCP mice*
###p<0.001, #p<0.05 vs control mice

● **Cortical pCREB and GluN2A protein levels were raised in mice chronically treated with NX210c**

In addition, repeated daily administrations of the peptide induced a two-fold increase in GluN2A-NMDAR protein levels and reversed PCP-induced decrease in pCREB.



**p<0.05, **p<0.01 vs vehicle-injected PCP mice, #p<0.05 vs control mice*

CONCLUSION

The beneficial effects triggered by NX210c through GluN2A-NMDAR and AMPAR represent an innovative therapeutic opportunity to ameliorate outcomes in patients suffering from central nervous system disorders with crippling synaptic dysfunctions.

Disclosures ►►► SL, MS and JLD are employed by Axoltis, YG is the CEO and a shareholder of Axoltis.