

- There is an unmet **need** for effective therapeutic strategies in **Huntington's disease (HD)** and **drug abuse**.
- **GluN3A** is a **novel target** that regulates synapse plasticity and neuronal connectivity.
 - Its expression is reactivated in CNS pathologies including HD, cocaine and alcohol abuse.
 - Proof of Concept: Knock-Out mice in HD and shRNA in drug abuse.
 - Safety: lacking in healthy adult brain.

Scope of the problem

- HD is a rare disease: its average frequency ranges from estimated 4 to 10 individuals per 100,000 people, with symptoms usually occurring by late 40s. There is, at present, no cure and only one FDA-approved symptomatic treatment.
- Cocaine abuse is widespread and is becoming a major public health issue. The prevalence of cocaine use in the world is approximately 13 million people or 0.23% of the global population.

New target

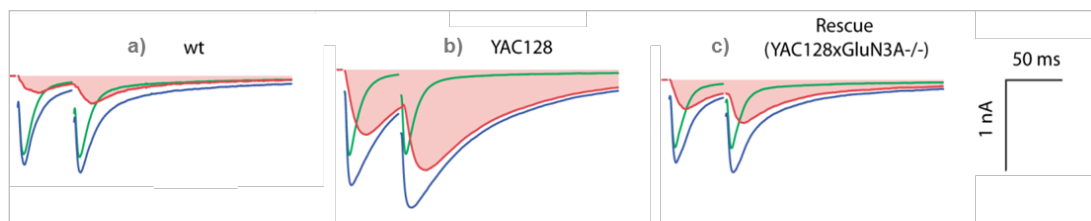
- **GluN3A** subunits form part of NMDA receptors during early postnatal and juvenile stages, but are mostly absent in adult brain (human data).
- Adult reactivation of GluN3A is pathological: inhibits synaptic plasticity and triggers synapse loss (*Neuron*, 2009).

Clinical Impact

- Adult reactivation of **GluN3A** protein expression has been described:
 - in striatum of Huntington's disease individuals (*Nat Med*, 2013)
 - after cocaine administration (*J Neuroscience*, 2013; *Neuron*, 2013)
 - after prenatal alcohol exposure (*J Neuroscience*, 2013).

Proof of Concept

Suppressing aberrant reactivation blocks impaired plasticity (using shRNA in cocaine addiction), synapse loss and neurodegeneration (using GluN3A-KO mice in HD).



Excitatory Postsynaptic Currents (EPSCs) after intense afferent stimulation
 Genetic deletion of GluN3A expression blocks the enhancement in extrasynaptic NMDA receptor currents observed in YAC128 mice (b vs c)
 Extrasynaptic NMDA receptor currents (shaded) were evoked by high-intensity intrastratial stimulation.

Safety

Lacking in adult brain: lesser side-effects than previously failed approaches to target brain NMDA receptors.

Reference

- Marco S et al. Suppressing aberrant GluN3A expression rescues synaptic and behavioral impairments in Huntington's disease models. *Nature Medicine*. 2013 Aug;19(8):1030-8.
- Yuan T et al. Expression of cocaine-evoked synaptic plasticity by GluN3A-containing NMDA receptors. *Neuron*. 2013 Nov 20;80(4):1025-38.
- Wesseling and Pérez-Otaño. Modulation of GluN3A expression in Huntington disease: a new n-methyl-D-aspartate receptor-based therapeutic approach?. *JAMA Neurology*. 2015 Apr 72:468-473.