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DM1 mice exhibit abnormal transmitter homeostasis and synaptic plasticity in association with RNA mis-splicing in the hippocampus

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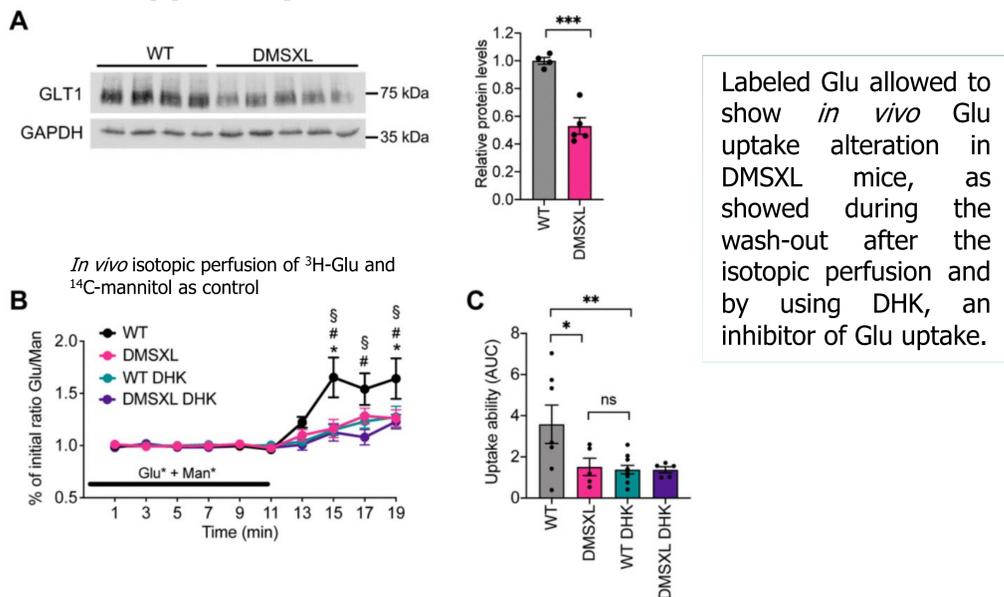
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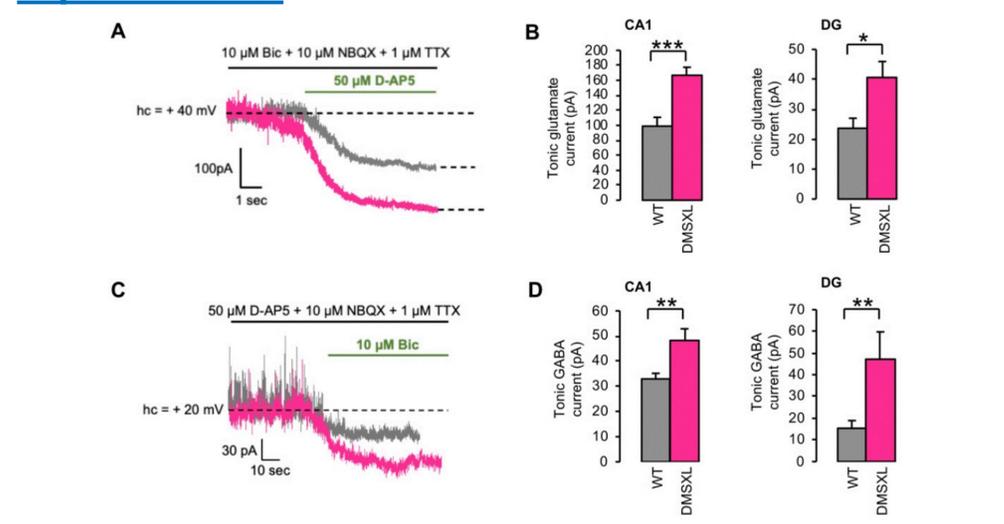
Myotonic dystrophy type 1 (DM1) is a severe neuromuscular disease mediated by a toxic gain of function of mutant RNAs. The neuropsychological manifestations affect multiple domains of cognition and behaviour, but their aetiology remains elusive. Transgenic DMSXL mice carry the human DM1 mutation and show relevant behavioural abnormalities (including altered exploratory behaviour and anhedonia) and express reduced levels of GLT1, a critical regulator of glutamate homeostasis in the brain. However, the impact of glutamate homeostasis dysfunction on neurotransmission in DM1 remains unknown.

Keywords: GABA; RNA splicing; glutamate uptake; synaptic plasticity; transgenic mouse model

Experiment #1: Glutamate uptake evidenced *in vivo* in the dorsal hippocampus of DMSXL mice

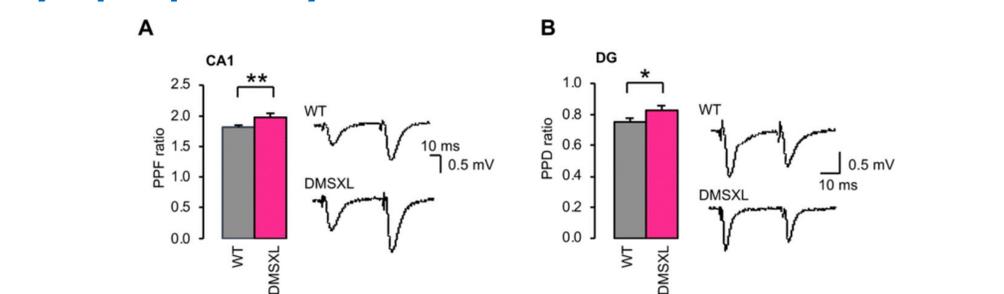


Experiment #3: Tonic currents vs ambient neurotransmitters

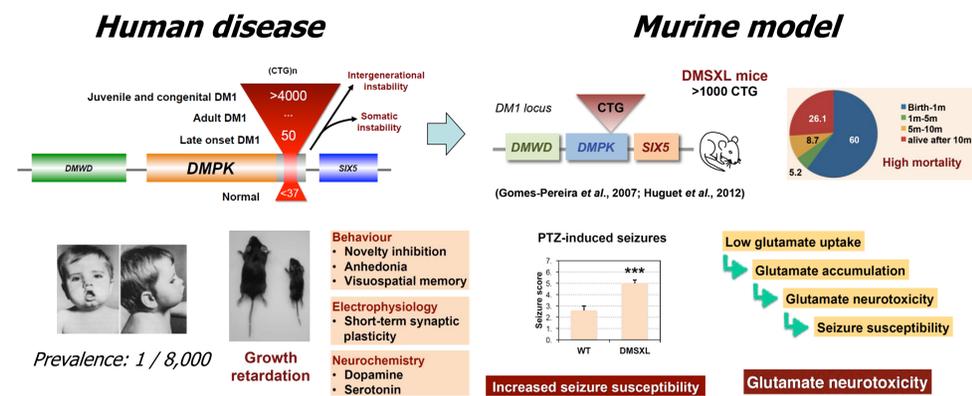


Patch-clamp recordings of CA1 pyramidal neurons and DG granule cells in hippocampal slices from DMSXL mice revealed an increased tonic excitation, likely mediated by higher levels of ambient glutamate at the vicinity of extrasynaptic NMDA receptors. An unexpected elevated extracellular GABA level in DMSXL mice associated with an increase in tonic inhibition and a higher GABA release

Experiment #4: Basal synaptic transmission and short-term synaptic plasticity

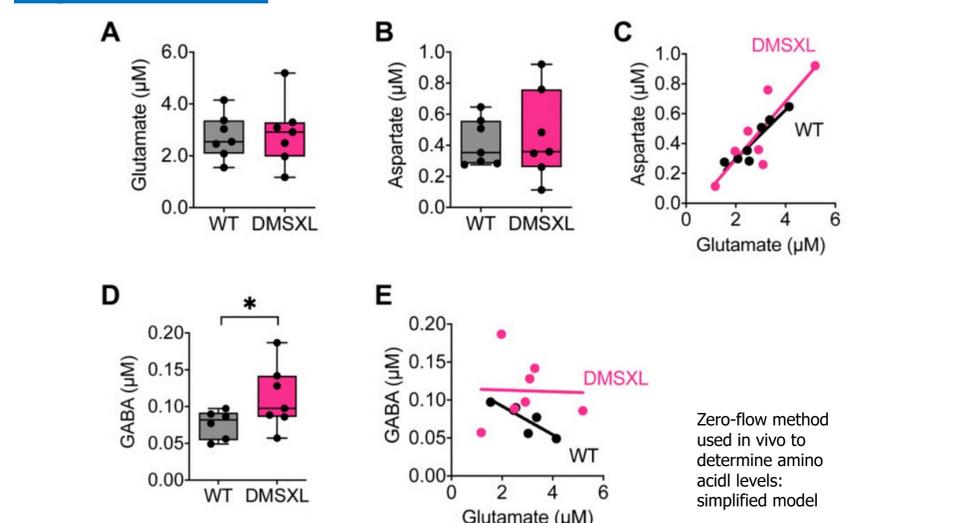


Abnormal short-term plasticity in the DG and CA1 area, suggestive of synaptic dysfunction in DMSXL mice, was evidenced.



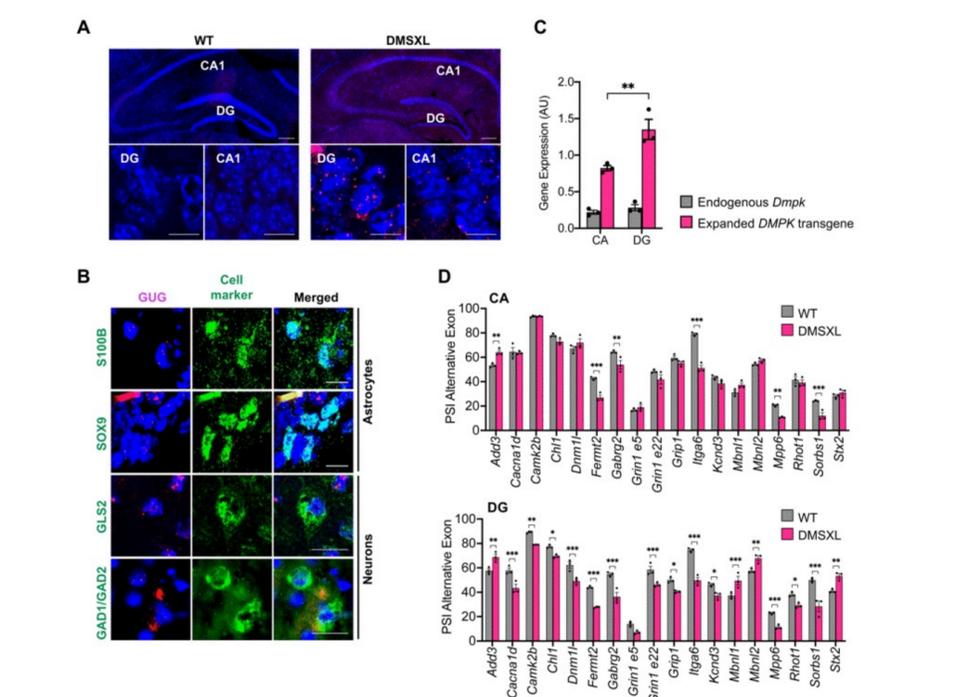
Aim: understand a suspected glutamate miscommunication

Experiment #2: Basal extracellular levels



Extracellular glutamate and aspartate levels sampled in the dorsal hippocampus using zero-flow quantitative microdialysis were unaltered, but we found an unexpected elevated extracellular GABA level in DMSXL mice

Experiment #5: Regional distribution of RNA toxicity and molecular defects in DMSXL mice



Synaptic dysfunction was accompanied by the accumulation of RNA foci that are more abundant and larger in the DG than in CA1 area, and by the mis-splicing of candidate genes with relevant functions in amino acidergic neurotransmission (ion channels, neurotransmitter receptors and synaptic proteins, as well as proteins involved in neuronal vesicle trafficking).

Taken together, molecular and functional changes triggered by the accumulation of toxic RNA may induce synaptic abnormalities in restricted brain areas of the brain, causing neuronal dysfunction.