~~while recording field excitatory postsynaptic potentials in the CA1 area of hippocampal slices and layer II of primary motor cortex slices. In the presence of FC (200μM), hippocampal synaptic responses were significantly lower in pre-symptomatic mSOD1 mice, when compared with wt mice. In the symptomatic phase, mSOD1 mice exhibited higher post-tetanic potentiation and LTP magnitudes, when compared with wt mice. However, astrocytic inhibition impaired significantly LTP, as well as synaptic responses, in both wt and mSOD1 mice. Regarding the motor cortex, pre-symptomatic mSOD1 mice showed an impairment in LTP magnitude and basal synaptic transmission. Interestingly, presence of FC (100μM) led to an impairment of LTP only in wt mice, to similar levels that of mSOD1 mice, in both stages of disease.~~

~~Altogether, we further explored alterations in synaptic plasticity and transmission, as well as the role of astrocytes, in two affected regions of the mSOD1 mice model. These findings suggest that, in the hippocampus, astrocytes are essential for the maintenance of LTP in healthy and ALS conditions. More importantly, in the motor cortex, mSOD1 mice present early alterations in synaptic function and plasticity, and astrocytes seem to be impaired even before the onset of symptoms.~~

MTU10-16 | Geldanamycin and spironolactone enhance the degradation of C9orf72 ALS/FTD dipeptide repeat proteins

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Intronic GGGGCC (G4C2) hexanucleotide repeat expansion within the human C9orf72 gene represents the most common cause of familial forms of amyotrophic lateral sclerosis (ALS) and fronto-temporal dementia (FTD) (C9ALS/FTD). Repeat-associated non-AUG (RAN) translation of repeat-containing C9orf72 RNA results in the production of neurotoxic dipeptide-repeat (DPR) proteins. DPR proteins misfold and aggregate into cytoplasm or nuclei of motor neuron. Here they can alter the proteotoxic response machinery. The protein quality control (PQC) system maintains protein homeostasis by re-folding (by chaperone) or by degradation (by autophagy or proteasome) of misfolded proteins to counteract proteotoxicity. We developed a high-throughput drug screen for the identification of positive and negative modulators of DPR levels. We identify forskolin, a cAMP-elevating compounds, as positive modulators of DPR protein levels. Interestingly, PKA inhibition (by H89) or knockdown reduced translation efficiency of DPRs, while the PKA inhibitor H89 reduced endogenous DPR protein levels in C9ALS/FTD patient-derived iPSC motor neurons. In motor neuron-like cells (NSC34), we evaluated the role of the selected compound in the regulation of the two main degradative pathways of PQC. Using RT-qPCR, WB and IF analysis, we observed that none of the compounds were able to modulate TFEB, SQSTM1/p62, and LC3 expression and localization. Nevertheless, the reduction of DPR levels observed in cells treated with geldanamycin (an HSP90 inhibitor) and with spironolactone (an aldosterone antagonist) is counteracted by autophagy and proteasome inhibitor suggesting that these compounds promote DPR proteins degradation via the proteasome and autophagy pathways, respectively. Together, our results suggest degradative systems as druggable pathways modulating DPR protein levels in C9ALS/FTD.

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~~MTU10-17 | Intranasal administration of nootropics reverses motor symptoms and loss of midbrain dopamine neurons in PINK1 knockout rats~~

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~~**Background:** Parkinson's disease (PD) is a chronic neurodegenerative disease characterized by the progressive loss of *substantia nigra* (SN) neurons that leads to the onset of motor and non-motor symptoms. Current standard of care consists of replenishing the loss of dopamine through oral administration of Levodopa. However, this treatment is not disease-modifying as PD patients eventually develop resistance to standard-of-care with disease progression. A decrease in protein kinase A (PKA) signaling and a reduction in brain-derived neurotrophic factor (BDNF) contributes to neuropathology in murine models of Parkinson's disease. We have published that intraperitoneal administration of forskolin, a labdane dipertene that enhances cyclic AMP-dependent PKA activity, reverses motor symptoms, increases brain energy production, reverses the loss of hindlimb strength and neurodegeneration of midbrain dopamine neurons PTEN-induced kinase 1 (PINK1) knockout rats, *a bone fide* genetic model of PD. In this study, we developed an intranasal formulation to deliver several nootropic agents including foorskolin with high bioavailability in the brain to activate neuroprotective PKA and neurotrophic signaling pathways.~~

~~**Objective:** We surmised that intranasal administration nootropic agents that can pharmacologically PKA signaling and neurotrophic~~