The mitochondrial targeted peptidomimetic SBT-272 protects corticospinal motor neurons with mutant TDP43 pathology

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Background

Mitochondrial defects are considered to be one of the major contributors to neurodegeneration. Structural and functional alterations in mitochondria, suggest improving mitochondrial health as a rational target for drug design. SBT-272, an investigational drug in phase I clinical trials, is a peptidomimetic which has been derived from the mitochondrial targeting peptide elamipretide, a compound currently in late-stage clinical development. While both compounds target the mitochondrial phospholipid cardiolipin, reduce the production of mitochondrial reactive oxygen species and improve mitochondrial bioenergetics, SBT-272 displays significantly higher CNS exposure.

We have recently demonstrated that SBT-272 is protective in the SOD1 G93A mouse model (1). As prior studies revealed mitochondrial dysfunction as one of the major causes of upper motor neuron (UMN) degeneration with TDP-43 pathology in both CSMN of mice and Betz cells of ALS patients (2), we now investigate whether SBT-272 improves UMN health when TDP43 pathology is present.

Hypothesis

Improving mitochondrial function of diseased motor neurons will have therapeutic value in ALS.

Methods

Drug levels in Sprague Dawley rat perfused brain homogenate were determined by LC-MS/MS. Cerebral ischemia in rats was induced by middle cerebral artery occlusion, and mitochondrial respiration was assessed in brain homogenates by high resolution respirometry. Mixed cortical cultures were prepared from prp-TDP-43^{A315T}-UeGFP mice, in which UMNs are labeled by eGFP. Cultures were treated with serum free medium in the presence or absence of SBT-272. Improved UMN health was investigated by at least 3 independent experiments.

Results

Brain Cmax following systemic drug administration was significantly higher for SBT-272 than elamipretide [Figure 1]. When given prior to onset of ischemic stroke in rats, SBT-272 preserved mitochondrial respiration in brain homogenates [Figure 2]. Application of SBT-272 significantly improved the structural integrity, axon outgrowth and arborization of UMNs that become diseased due to mutant TDP43 in ALS [figure 3-5]. Characterizations of mitochondrial structure and function in the presence of drug are on-going.

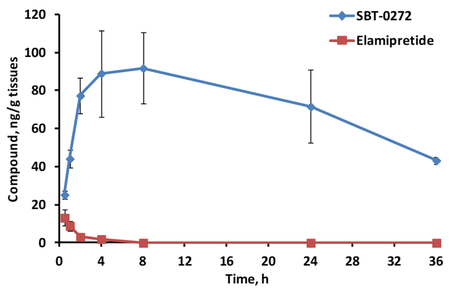

Figure 1: Brain accumulation of SBT-272 following subcutaneous administration in rats

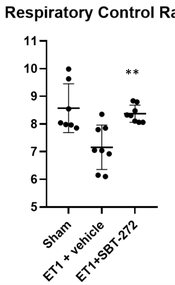

Figure 2: SBT-272 prevents loss of mitochondrial respiratory control in brain following cerebral ischemia-reperfusion injury. Depicted are individual Oxygraph O2K results per individual animal. ET1 = Endothelin -1 vasoconstrictive peptide.
** p < 0.01

Results

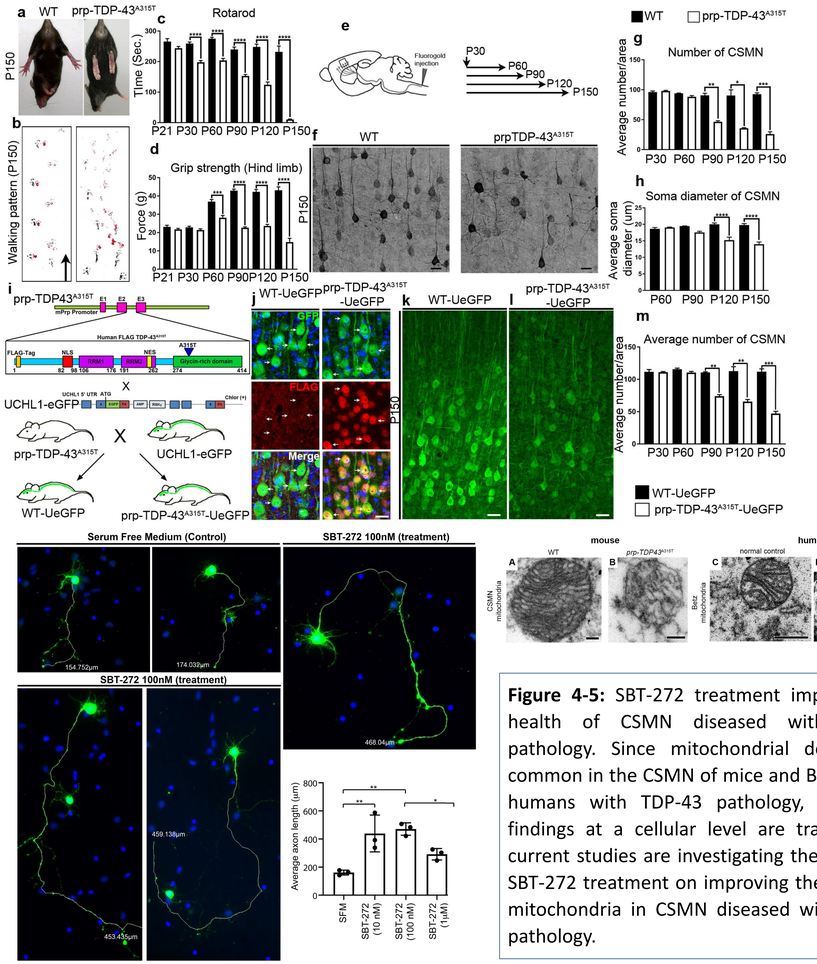

Figure 4-5: SBT-272 treatment improves the health of CSMN diseased with TDP-43 pathology. Since mitochondrial defects are common in the CSMN of mice and Betz cells of humans with TDP-43 pathology, and since findings at a cellular level are translational, current studies are investigating the impact of SBT-272 treatment on improving the health of mitochondria in CSMN diseased with TDP-43 pathology.

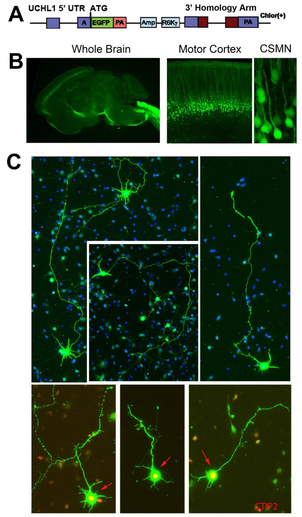

Figure 3-4: The CSMN reporter line with TDP-43 pathology is generated. The timing and the extent of CSMN degeneration are revealed. These mice recapitulate disease pathology observed in humans. eGFP expression is restricted to CSMN in the motor cortex and eGFP expression is retained *in vitro*, enabling identification of CSMN among other cells in culture.

Conclusions

TDP43 pathology has emerged as the single most prominent histological finding among both sALS and ALS/FTLD patients. It has been shown to directly contribute to upper and lower motor neuron death through impact on mitochondrial structure and function (2-4). Here, by using a novel reporter line for UMNs diseased with TDP-43 pathology, we demonstrate that SBT-272, which is known to prevent the generation of mitochondrial reactive oxygen species (ROS) and to improve mitochondrial respiration through increased oxidative phosphorylation under conditions of cellular stress, show protection and improve neuronal health of CSMN diseased due to TDP-43 pathology. These data support further investigation of SBT-272 for the treatment of motor neurons that become diseased due to TDP-43 pathology.

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