Mood Stabilizers Protect Against a Huntington's Disease Animal Model: A Multi-Modal MR Study at 11.7 T

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Abstract: Repeated systemic administration of the succinate dehydrogenase inhibitor 3-nitroproprionic acid (3NP) induces striatal neurodegenerative lesions similar to those found in Huntington's Disease (HD). In recent years the neuroprotective abilities of the mood stabilizers, lithium and valproate, have been explored. In this study, we hypothesized that chronic lithium or valproate administration would decrease the striatal damage induced by 3NP. Utilizing multiple MR modalities we demonstrated a decrease in 3NP lesion extent and severity as a result of chronic (4 week) lithium and valproate pre-administration.

Introduction: In order to examine the neuroprotective capabilities of lithium and valproate, we utilized high-resolution magic angle spinning proton magnetic resonance spectroscopy (HR-MAS ^{1}H MRS) and quantitative MRI (T2 and ADC) at 11.7 Tesla.

Methods: *Animals:* Male Lewis rats were treated with 3NP (35-mg/kg i.p. bid for 5 days). Mood stabilizers were delivered in custom formulated rat chow for four weeks prior to 3NP injections. Chow was developed to produce plasma levels similar to those attained in humans during the treatment of bipolar disorder (lithium: 0.5–1.0 mEq/l; VPA: 56.8 ± 39.2 µg/ml). *MRI:* Multi-slice multi-spin-echo imaging was preformed with: TR: 2029 ms, 10 consecutive TEs ranging from 11.8 ms to 118 ms, 16 contiguous slices, acquisition time: 17 minutes. Spin-echo diffusion weighted imaging was used for ADC mapping with: TR = 1500 msec, TE = 23.3 msec. Images were acquired at the following B values: 53.35, 195.1, 472, 876.7 and 1409 s/mm^2. *HR-MAS ^{1}HMRS:* Animals were sacrificed, brains rapidly removed, and 2mm coronal slices obtained. Punches (2.1 mm) representing the anterior dorsal lateral striatum were obtained, and frozen on solid CO_2. For analysis, tissue (~5 mg) was placed in Bruker zirconium rotor and inserted into the 11.7T (Bruker Avance 500) MR spectrometer. Sample temperature was maintained at 4˚C and the rotor spun at a MAS rate of 4200 Hz using a rotor synchronized CPMG pulse sequence with the following parameters: TR=3500 msec, spectral width 8 kHz,16k complex points and 256 averages for a total acquisition time of 15m38s. Analysis and quantification of the HR-MAS ^{1}H-MRS data was performed with LCModel (1).

Results: As seen in Figure 1A-B, 3NP induced a prominent hyper-intensity in the striatum compared to controls. The hyper-intensity corresponded with significant T2 and ADC changes (Fig 1C)(ADC data not shown). In mood stabilizer pretreated animals T2 and ADC changes were minimized. Volumetric analysis showed that lesion extent was also significantly decreased with pretreatment (Fig 1D). HR-MAS ^{1}H MRS analysis of 3NP treated animals showed that 3NP alone significantly ($p \leq 0.01$) elevated striatal succinate (+150-200%) (Figure 1E). The succinate increase was consistent with 3NP-induced inhibition of succinate dehydrogenase. Lithium and valproate pre-administration decreased succinate 25-50% ($p<0.01$) in cortical and striatal tissues in both control and 3NP treated animals. Other MRS findings (not shown) include increased endogenous antioxidants (GSH, Taurine) in the striatum of pretreated animals. [Due to abstract space constraints additional MRS findings will be presented on the poster.]

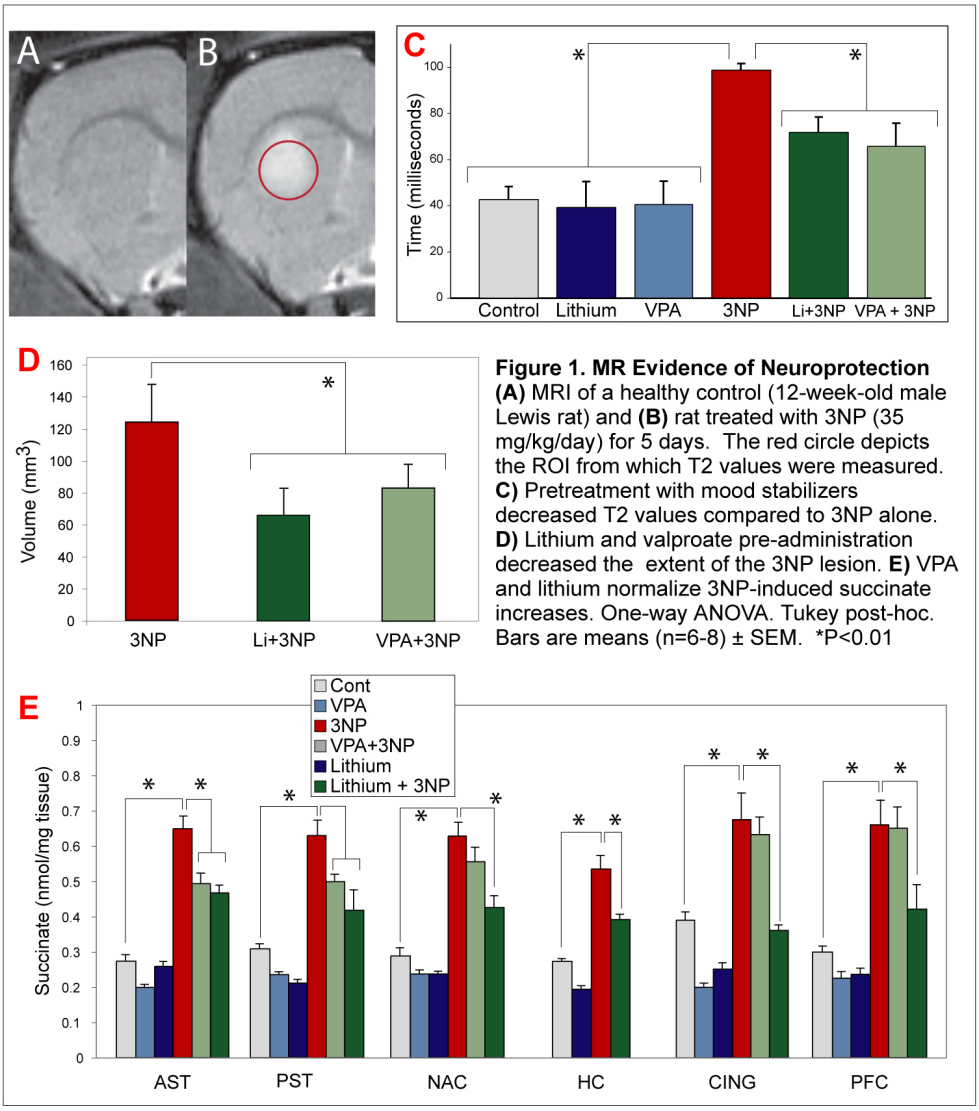

Figure 1. MR Evidence of Neuroprotection **(A)** MRI of a healthy control (12-week-old male Lewis rat) and **(B)** rat treated with 3NP (35 mg/kg/day) for 5 days. The red circle depicts the ROI from which T2 values were measured. **C)** Pretreatment with mood stabilizers decreased T2 values compared to 3NP alone. **D)** Lithium and valproate pre-administration decreased the extent of the 3NP lesion. **E)** VPA and lithium normalize 3NP-induced succinate increases. One-way ANOVA. Tukey post-hoc. Bars are means (n=6-8) ± SEM. *P<0.01

Discussion: It is believed that the mood stabilizer-induced decrease in succinate represents an increase in mitochondrial efficiency that may provide striatal neurons with the moderate level of neuroprotection observed in the T2, ADC and volumetric analyses. Also, the increased antioxidants may offer additional striatal neuroprotection.

References: 1) Provencher SW. Estimation of metabolite concentrations from localized in vivo proton NMR spectra. Magn Reson Med. 1993 Dec;30(6):672-9.