Phenotypic evaluation of SOD1-G93A transgenic mice as a model of amyotrophic lateral sclerosis and the potential of CMAP (compound muscle action potential) as an early biomarker

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BACKGROUND & PURPOSE

SOD1-G93A transgenic mice, expressing human SOD1 with the G93A mutation under the control of the cistronic human SOD1 promoter, have been widely utilized as a valuable preclinical model to investigate neuromuscular disorders, specifically familial amyotrophic lateral sclerosis (ALS). ALS, also known as Lou Gehrig's disease, is a devastating neurodegenerative condition primarily associated with mutations in the SOD1 gene.

In this study, we characterized the phenotypic similarities between SOD1-G93A mice and human ALS, while exploring the potential therapeutic effects of two compounds (Riluzole and donepezil).

METHODS

Treatment groups

- Male wildtype (WT) and transgenic SOD1-G93A (TG) mice at 10 weeks of age were used for this study.
- TG mice were treated with vehicle (G2), 8 mg/kg of riluzole (G3), or 1 mg/kg of donepezil (G4) by oral gavage (PO), once a day (QD). WT mice (G1) were treated with vehicle.

Animal observation

- Body weight and disease score was measured 3 times a week up to 16 weeks of age, and then once a day.
- Motor function was measured using the rotarod test measured at 10 (baseline; before treatment), 11, 14, 17 and 20 weeks of age. After a training session, mice were tested 3 times with the speed changing from 0 to 40 RPM, and the latency to fall from the rod was measured.

Compound muscle action potential (CMAP)

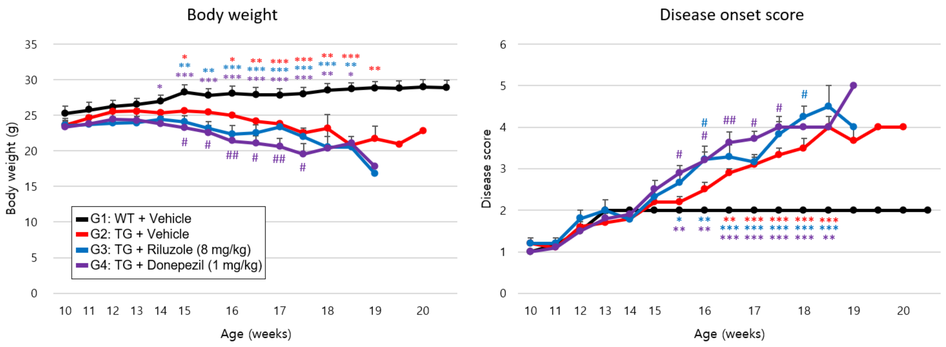
- The compound motor action potential (CMAP) measurement is a fast and sensitive method to evaluate nerve conduction in mice.
- The CMAP measurements were made for the sciatic nerve to assess nerve functionality. The CMAP was recorded with 27G needle electrodes in the fore- and hindlimb using the Ultra S Pro100 (Natus).

Immunohistochemistry

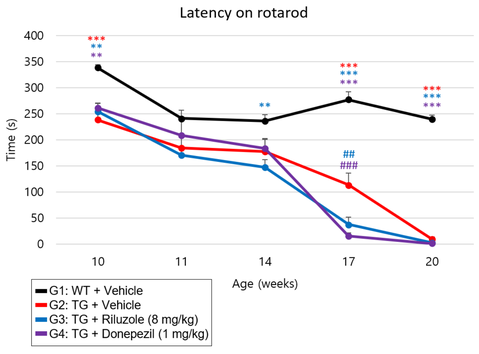
- A separate cohort of animals were sacrificed to analyze the effect of treatment on neuromuscular junctions (NMJ) of the gastrocnemius muscle at 17 weeks of age.

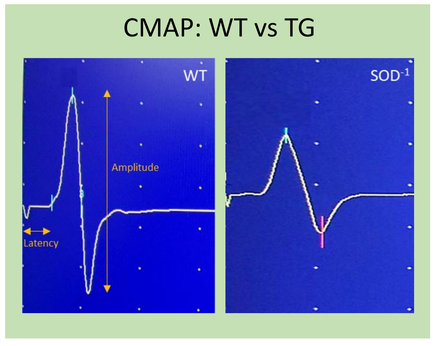
RESULTS

1. Body weight and disease scores

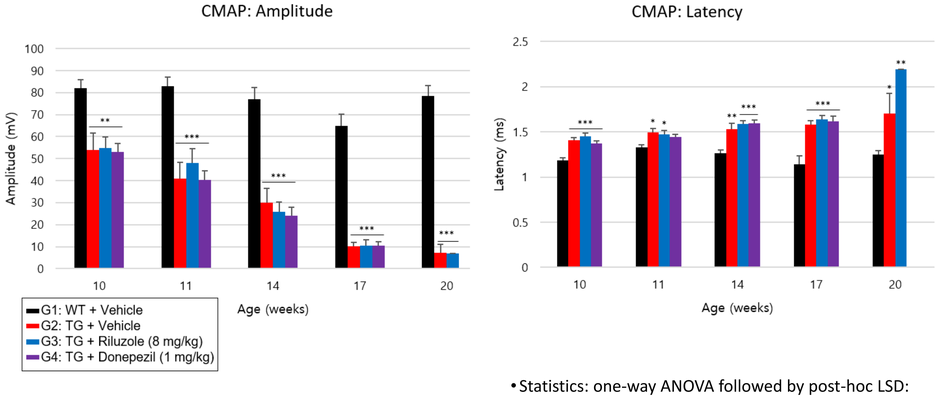


2. Motor function (rotarod test)



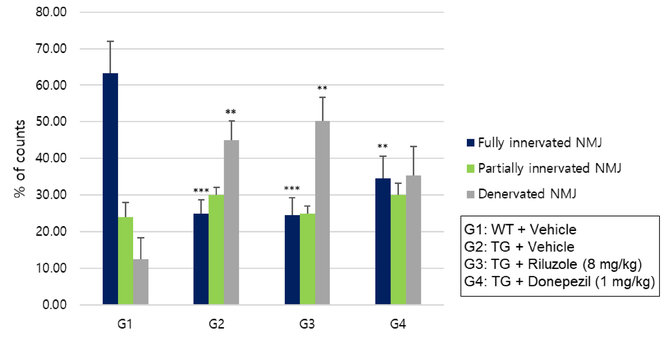


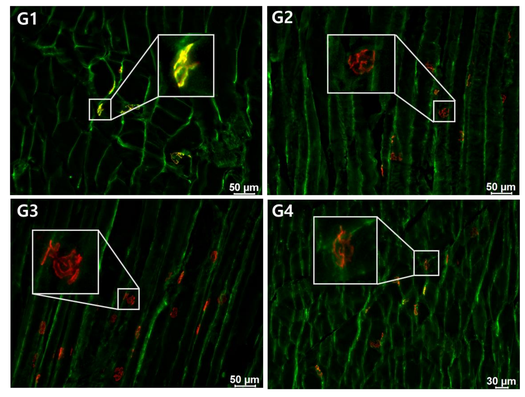
3. Compound muscle action potential (CMAP)



• Statistics: one-way ANOVA followed by post-hoc LSD:
*p<0.05, ** p<0.01, *** p<0.001 compared to G1;
# p<0.05, ## p<0.01, ### p<0.001 compared to G2

4. NMJ innervation in the gastrocnemius muscle





CONCLUSIONS

1. TG mice exhibited age-dependent body weight loss, and disease scores (DS) increased significantly after 15 weeks of age. Alterations in rotarod performance (RR) were evident from 14 weeks of age .
2. CMAP analysis revealed a significant difference between WT and TG mice as early as 10 weeks of age, suggesting CMAP's potential as an early-stage biomarker for ALS.
3. The relative amount of fully innervated NMJs in the gastrocnemius muscle was significantly reduced in the TG mice compared with WT mice.
4. Neither riluzole or donepezil exhibited a curative effect on the tested symptoms of ALS in our experimental model.
5. Collectively, our findings highlight CMAP as a potential early-stage biomarker for ALS, surpassing other functional assessments. These observations underscore the necessity for alternative therapeutic strategies in the treatment of ALS.