Assessing the Neuroprotective Effects of Cromolyn Sodium in the SOD1^{G93A} Mouse Model of Amyotrophic Lateral Sclerosis

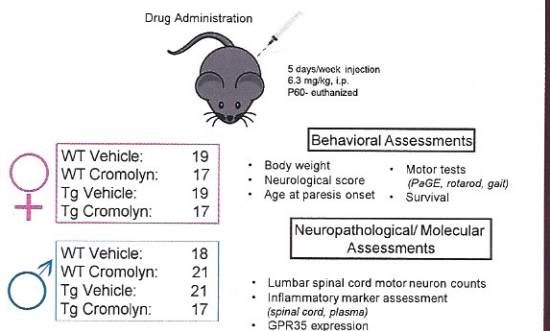
Eric Granucci[1*], Kaly A. Mueller[1*], Ana Griciuc[2*], Hoang Le[2], Amanda M. Dios[1], Alexandra N. Mills[1], David Elmaleh[3], James . Berry[4], Sabrina Paganoni[4], Merit Cudkowicz[4], Rudolph Tanzi[2], **Ghazaleh Sadri-Vakili[1^]**

[1]NeuroEpigenetics Laboratory, MassGeneral Institute for Neurodegenerative Disease (MIND), Massachusetts General Hospital, Boston, MA, USA
[2]MassGeneral Institute for Neurodegenerative disease, Massachusetts General Hospital, Boston, MA, USA
[3]AZTherapies, Boston, MA
[4]Neurological Clinical Research Institute, Massachusetts General Hospital, Boston, MA, USA

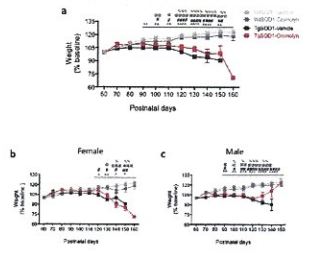
ABSTRACT

Accumulating evidence suggests that neuroinflammatory processes are implicated in the initiation and progression of amyotrophic lateral sclerosis (ALS). Previous reports have demonstrated an increase in microgliosis and astrogliosis in the lumbar spinal cord of SOD1^{G93A} transgenic mice before the onset of symptoms, a neuroinflammatory response which correlated with disease progression. Importantly, early stage homeostatic microglia enhanced motor neuron survival, while pro-inflammatory or ramified microglia were toxic to motor neurons in the SOD1^{G93A} mice. Recent studies from our group have demonstrated that cromolyn sodium, an FDA approved compound, exerts neuroprotective effects in mouse models of Alzheimer's disease by altering microglia activation. Here, we tested the neuroprotective and anti-inflammatory effects of cromolyn sodium in the SOD1^{G93A} mouse model of ALS. Our results indicate that cromolyn sodium treatment significantly delayed the onset of neurological symptoms, and improved deficits in PaGE performance in both male and female mice. Furthermore, there was a significant increase in survival in treated female transgenic mice compared to the vehicle group. There was also a significant increase in motor neuron survival and a decrease in the expression of pro-inflammatory cytokines in the lumbar spinal cord and plasma of cromolyn treated transgenic SOD1^{G93A} mice. Lastly, cromolyn treatment increased GPR35 levels in the lumbar spinal cord of transgenic mice. Together, these findings suggest that cromolyn sodium provides neuroprotection in the SOD1^{G93A} mice and warrants further assessment as a potential therapeutic for ALS.

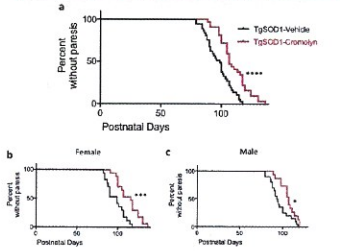
METHODS



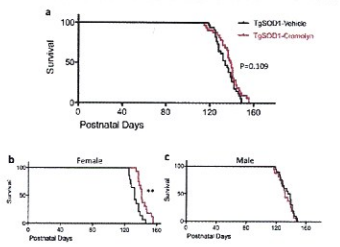
Cromolyn treatment does not affect body weight



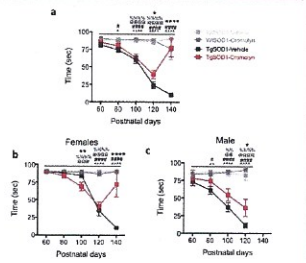
Cromolyn treatment delays paresis onset



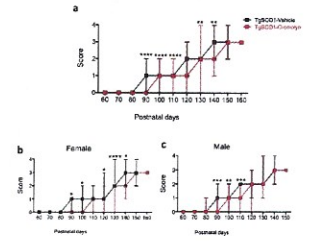
Cromolyn treatment extends survival in female mice



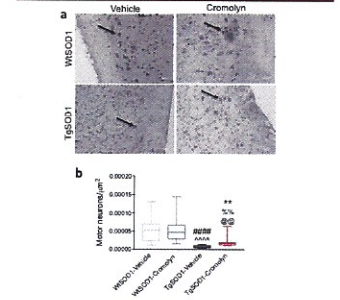
Cromolyn treatment improves performance on PaGE task



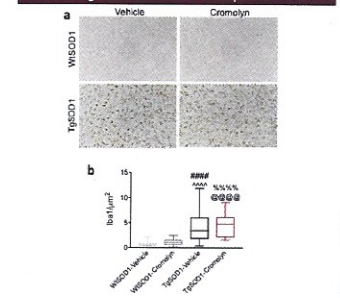
Cromolyn treatment delays disease onset



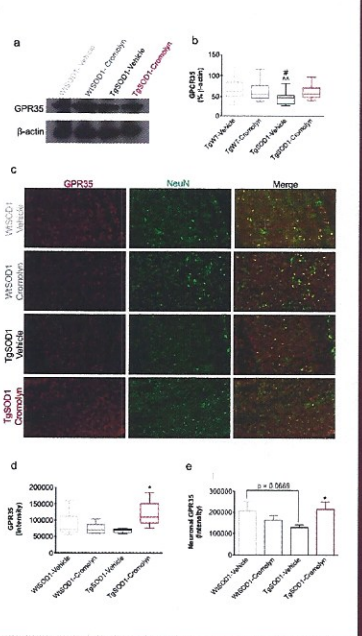
Cromolyn treatment protects lumbar Spinal cord motor neurons



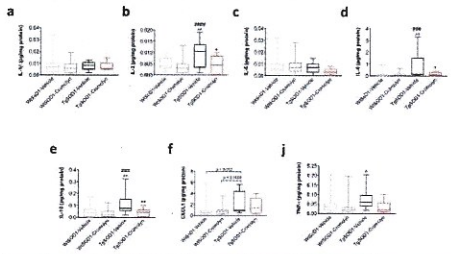
Cromolyn treatment does not alter microglia numbers in spinal cord



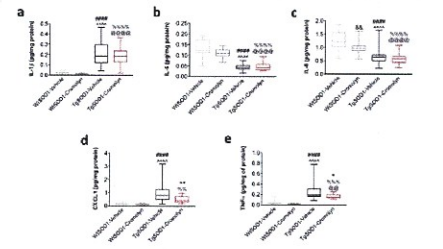
Cromolyn treatment increases GPR35 levels



Cromolyn treatment decreases Inflammatory markers in plasma



Cromolyn treatment decreases Inflammatory markers in spinal cord



SUMMARY

Cromolyn sodium treatment:

- Delays disease onset and progression
- Improves performance on the PaGE task
- Improves survival (female mice only)

- Increases survival of lumbar spinal cord motor neurons
- Reduces pro-inflammatory cytokine/chemokine levels in the spinal cord and plasma
- Increases GPR35 levels in spinal cord

This work was supported by Project ALS