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Abstract Title

Preclinical Assessment of Borsantrazole in a Drosophila melanogaster Model of Amyotrophic Lateral Sclerosis (ALS)

Authors

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Background

Amyotrophic Lateral Sclerosis (ALS) is an incurable neurodegenerative disease. It involves the progressive loss of upper and lower motor neurons, causing a lack of voluntary muscle control. While the majority of ALS patients are diagnosed later in life, juvenile ALS is a rare type of ALS affecting those under 25. Juvenile ALS can be symptomatic from early childhood. ALS has been linked to mutations in various genes, including SOD1 (superoxide dismutase 1) and TARDBP (TAR DNA-binding protein). Even without a mutation in the TARDBP gene, over 90% of ALS patients experience aggregation and mislocalization of its protein product, TDP43. Increasing evidence has implicated oxidative stress as a mechanism of motor neuron damage and death. Current treatments include riluzole, a glutamate antagonist, and edaravone, a free radical scavenger. While both of these treatments can provide modest benefit in symptom progression and lifespan, effort is needed to improve patient medications. This has led us to the synthesis and assessment of Borsantrazole, a novel boron-based small molecule capable of targeting oxidative stress and hydrogen peroxide in tissues. Borsantrazole has been tested for safety and efficacy in a SOD1 mice model, with promising effects.

Objective

Our goal is to continue the characterization of Borsantrazole's efficacy by testing it in Drosophila models.

This allows us to rapidly screen different variants to determine their individualized response to the medication. Currently, we are evaluating Borsantrazole's efficacy in SOD1-G85R, SOD1-A4V, and TDP43 overexpression models.

Methods

SOD1:

We use the UAS-GAL4 system to induce transgene expression of either human SOD1-G85R or SOD1-A4V variants pan-neuronally in the fly. These flies are reared on medicated food containing Borsantrazole, Edaravone, or DMSO as a control. Motor function is tested 4 times, every 5 days, to obtain data on motor control over time. Female and male flies are tested separately, allowing for the analysis of sex-specific differences.

TDP43:

We use the UAS-GAL4 system to induce transgene expression of human TDP43 in motor neurons. These flies are treated and tested identically to the SOD1 flies.

Results

Preliminary results indicate slowing of motor function loss with Borsantrazole (BSZ) compared to DMSO, in both the SOD1-G85R and SOD1-A4V groups, at a rate comparable to Edaravone (EDR). In the preliminary TDP43 overexpression model experiments, BSZ reduces progressive motor function decline and outperforms EDR.

Conclusion

Our preliminary findings support further investigation of Borsantrazole as a potential therapeutic approach targeting oxidative stress in ALS. Importantly, the use of *Drosophila* models allows rapid comparison of treatment responses across different ALS-associated mutations, which may ultimately contribute to a more personalized approach to treatment. Further studies are needed to confirm these findings and determine whether Borsantrazole can provide meaningful therapeutic benefit across diverse forms of ALS, including juvenile-onset disease.