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THERAPEUTIC POTENTIAL OF REPURPOSED DRUG FOR THE TREATMENT OF C9ORF72 AMYOTROPHIC LATERAL SCLEROSIS IN AN ANIMAL MODEL

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a fatal and incurable neurodegenerative disease characterized by the degeneration of motor neurons, resulting in symptoms such as loss of muscle strength and coordination, difficulty with breathing, swallowing and other symptoms that eventually lead to death. Among the genetic causes, studies demonstrated that abnormally expanded regions of G4C2 repeats (HRE's) located in the human 9th chromosome (C9orf72) cause progressive neurodegeneration and account for most familial ALS cases. HRE's lead to an accumulation of RanGTPases and a pathological nuclear/cytoplasmic gradient, characteristic of the disease. Sigma receptor mutant form (SiR-E102Q) is associated with ALS cases, and it was demonstrated that the overexpression of the receptor on model animals can rescue the defective nucleocytoplasmic transport and reverse neurodegeneration. Therapies available for the ALS treatment act only by preventing neuronal damage but are ineffective in improving the patient's condition. Thus, drugs that can simulate Sigma´s action by repelling G4C2 repeats represent innovative therapeutic strategies to ALS. A virtual screening based on the receptor structure was conducted to select drugs capable of modulating its action and rescuing defective nucleocytoplasmic transport. The aim of this study was to evaluate the therapeutic potential of a repurposed drug for the treatment of C9orrf72-ALS in an animal model. Using the UAS-GAL4 system, we assessed the biocompatibility and exposure effect of Sigma Targeted Molecule #2 (STM2) in Drosophila melanogaster strains that recapitulate the disease phenotype by expressing transgenes containing the toxic G4C2 repeats in motor neurons and the eye retina. Transgene expression led to high ocular toxicity, due to the disruption of the ommatidium structure, and severe motor neuron degeneration, with significant reductions in lifespan and impaired adult and larval motility. In vivo model results demonstrate the neuroprotective properties of Sigma targeted molecule and its role in reducing toxicity caused by ALS transgenes, increasing the lifespan and locomotor capacity of flies compared to untreated animals. These findings suggest the therapeutic potential of the drug through possible modulation of Sigma activity, positioning it as a promising candidate for drug repurposing in the search for effective treatments for ALS.