P-039 - IN VITRO EVALUATION OF BROMOCRIPTINE AS A POTENTIAL PHARMACOLOGICAL CHAPERONE FOR MORQUIO A DISEASE

Cepeda J, Olarte-Avellaneda S, Salazar LM, Alméciga-Diaz CJ

(1) Instituto de errores innatos del metabolismo, Pontificia Universidad Javeriana. Bogotá - Colombia, (2) Universidad Nacional de Colombia, Bogotá D.C., Colombia. cjalmeciga@javeriana.edu.co.

INTRODUCTION: Morquio A syndrome (mucopolysaccharidosis IVA, MPS IVA), is a lysosomal storage disorder caused by deficiency of the enzyme N-acetylgalactosamine-6-sulfate sulfatase (GALNS). This enzyme hydrolyzes the sulfate bonds of the glycosaminoglycans chondroitin-6-sulfate and keratan sulfate. Currently, MPS IVA treatment is mainly based on enzyme replacement therapy (ERT), which has shown some clinical improvements. Nevertheless, it has limited effects on skeletal, corneal and heart valvular complications along with issues of immunogenicity, short half-life, and high cost. In this sense, it is necessary to develop new therapies that improve the therapeutic efficacy for MPS IVA patients.

OBJECTIVE: In this study, we describe the characterization of a GALNS pharmacological chaperone identified by virtual screening.

MATERIALS AND METHODS: Bromocriptine was identified using the crystal structure of human GALNS and molecular docking-based virtual screening against a subset of ZINC. Bromocriptine was evaluated using a recombinant GALNS and Morquio A skin fibroblasts.

RESULTS: Computational analysis suggested that Bromocriptine binds to the active cavity of GALNS in a similar position of natural GALNS substrates. In-vitro evaluation using recombinant GALNS produced in Pichia pastoris showed that bromocriptine inhibits enzyme activity to 24.4% at 10 μM. These results suggest a competition with the fluorogenic substrate for the active cavity of the enzyme, which confirmed the computational models. We observed a 54% increase in GALNS activity during production of recombinant GALNS in HEK293 compared to control cells. Finally, MPS IVA GM00593 fibroblasts (p.R386C/p.F285del) treated with 10 μM bromocriptine allowed an increase of 60% in GALNS activity, while MPS IVA GM01361 fibroblasts (p.R61W/p.W405_T406del) treated with 0.1 μM bromocriptine, generated a 14.2% increase in GALNS activity. Finally, GALNS activity in GM00958 fibroblasts (p.A393S), was not improved in any treatment with bromocriptine.

CONCLUSIONS: Overall, the results suggest that bromocriptine is a competitive inhibitor of GALNS and might has a positive impact in the production of recombinant GALNS. In addition, this drug increase activity of mutated GALNS in a mutation-based manner. These novel GALNS pharmacological chaperone should has potential to be further developed to improve the treatment for MPS IVA.