TREHALOSE REVERSES THE PHENOTYPE OF MACHADO-JOSEPH DISEASE MODELS

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Machado–Joseph disease (MJD), also known as spinocerebellar ataxia type 3, is the most common of the dominantly inherited ataxias worldwide and is characterized by mutant ataxin-3 misfolding, intracellular accumulation of aggregates and neuronal degeneration. No treatment able to modify the disease progression is available. In the present study, we evaluated whether trehalose, a natural occurring alpha-linked disaccharide, could rescue the disease phenotype of cell and mouse models of MJD. N2A cells, stably expressing human mutant ataxin-3, were treated with trehalose (1 mM and 10 mM) for 24h, 48 h and 72 h. By western blot, we observed a clearance of mutant ataxin-3 protein after 48h and 72 h treatment with trehalose (10 mM). Furthermore, MJD transgenic mice were orally treated with 2% trehalose for a period of 30 weeks. Motor behavior was measured at different time points during lifetime and neuropathological features were evaluated after sacrifice. We observed that trehalose treatment significantly improved the motor and coordination behavior in both males and females MJD transgenic mice. Moreover, trehalose effects on behaviour were associated with a reduction of the MJD-associated neuropathology as MJD transgenic mice treated with 2% trehalose presented a reduced atrophy of cerebellar layers and a decrease in the size of protein aggregates in Purkinje cells.

In conclusion, we show that trehalose induces the clearance of mutant ataxin-3 in N2A cells and alleviates motor impairments and neuropathological features in a mouse model of MJD, suggesting that trehalose is a promising pharmacological drug for therapy of this disease.