Disaccharide trehalose in experimental therapies for neurodegenerative disorders: Molecular targets and translational potential

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Abstract

Induction of autophagy is a prospective approach to the treatment of neurodegeneration. In the recent decade, trehalose attracted special attention. It is an autophagy inducer with negligible adverse effects and is approved for use in humans according to FDA requirements. Trehalose has a therapeutic effect in various experimental models of diseases. This glucose disaccharide with a flexible α-1-1’-glycosidic bond has unique properties: induction of mTOR-independent autophagy (with kinase AMPK as the main target) and a chaperone-like effect on proteins imparting them natural spatial structure. Thus, it can reduce the accumulation of neurotoxic aberrant/misfolded proteins. Trehalose has an anti-inflammatory effect and inhibits detrimental oxidative stress partially owing to the enhancement of endogenous antioxidant defense represented by the Nrf2 protein. The disaccharide activates lysosome and autophagosome biogenesis pathways through the protein factors TFEB and FOXO1. Here we review various mechanisms of the neuroprotective action of trehalose and touch on the possibility of pleiotropic effects. Current knowledge about specific features of trehalose pharmacodynamics is discussed. The neuroprotective effects of trehalose in animal models of major neurodegenerative disorders such as Alzheimer’s, Parkinson’s, and Huntington’s diseases are examined too. Attention is given to translational transition to clinical trials of this drug, especially oral and parenteral routes of administration. Besides, the possibility of enhancing the therapeutic benefit via a combination of mTOR-dependent and mTOR-independent autophagy inducers is analyzed. In general, trehalose appears to be a promising multitarget tool for the inhibition of experimental neurodegeneration and requires thorough investigation of its clinical capabilities.
Keywords: Clinical trial; Multitarget therapy; Neurodegenerative disorder; Neuroprotection; Trehalose; mTOR-independent autophagy.

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