

Neurodegeneration and diabetes; positive effect of trehalose in behavior of db/db mice, model of diabetes

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Diabetes development is associated with neurodegeneration development, and new approaches for prevention and treatment of neurodegeneration development are important [1, 2]. Autophagy suppression was shown in aging, diabetes. Db/db mice is a model of diabetes, related to leptin receptor deficiency, was used in experiments [3, 4]. Our topic was to study the effect of an autophagy inducer, trehalose, on brain autophagy and behavior in a genetic model of diabetes with signs of neuronal damage (db/db mice). In experimental models of neurodegenerative diseases, the correction of autophagy in the brain reverses neuronal and behavioral deficits and hence seems to be a promising therapy for neuropathologies. Our aim – to evaluate effect of autophagy inducer trehalose on autophagic activity in brain of db/db mice, and behavioral changes. The study was carried out on a specific pathogen-free mice of db/db strain, 3 months old (SPF-vivarium of the Institute of Cytology and Genetics, SB RAS, Novosibirsk). Mice were subdivided into following groups: 1) WT mice + H₂O; 2) WT mice drinking 2 % trehalose (24 days); 3) db/db mice + H₂O; 4) db/db mice drinking 2 % trehalose (24 days). Expressions of markers of autophagy (LC3-II), neuroinflammation (IBA1), redox state (NOS), and neuronal density (NeuN) in the brain were assessed by immunohistochemical analysis. For behavioral phenotyping, the open field, elevated plus-maze, tail suspension, pre-pulse inhibition, and passive avoidance tests were used. It was shown that treatment by trehalose reduced weight of db/db mice, improved glycemic profile and behavioral characteristics of db/db mice. Immunohistochemical analysis revealed significant decrease of LC3-II expression in hippocampal areas in db/db mice compared to the control WT mice, while trehalose treatment significantly increased this index. We have shown positive effect of trehalose in liver and heart of db/db mice, revealing activation of lipophagy by trehalose. Trehalose can restore the suppressed autophagy induced by high glucose *in vivo* in db/db mice. Autophagy activation may be useful for treatment of diabetes, regulating the balance between apoptosis and autophagy by inhibiting mTOR signaling. Mechanism of protective effect of trehalose includes activation of hepatic transcription factor EB (TFEB), increasing TFEB nuclear translocation, elevating level of LC-3-II (marker of autophagosome) in mouse liver. These findings provide the basis for trehalose usage in pathology. Trehalose exerted some beneficial peripheral and systemic effects and partially reversed behavioral alterations in db/db mice. Thus, trehalose as an inducer of mTOR-independent autophagy is effective at alleviating neuronal and behavioral disturbances accompanying experimental diabetes.

References

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