DOI 10.18699/SBB-2022-429

Oral trehalose intake as an experimental therapy for Alzheimer's disease in a mouse model induced by the central administration of amyloid-β

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Key words: Alzheimer's disease, amyloid-beta, trehalose, autophagy

Motivation and Aim: Disaccharide trehalose with flexible α-1-1'glycoside bond (O-α,-D-glucopyranosyl-[1→1]-α-D-glucopyranoside) has the ability to inhibit neurodegeneration via several mechanisms, the main of which are chaperone-like activity, inhibition of protein aggregation, attenuation of oxidative stress, and activation of reparative autophagy through the mTOR-independent signaling pathways [1]. The drug has a promising translational potential in therapy for Alzheimer's disease (AD). In preclinical studies using animal models, trehalose dosages vary within a range of 1–5 % (usually 2 %) solution of the drug for drinking *ad libitum*. The degrees of autophagy induction and therapeutic effects vary either [2]. For the translational transition, it is of interest to define the optimal conditions and dosage for the use of the drug. Here we studied the therapeutic effect of oral intake of trehalose solution of 2 or 4 % concentration in drinking as well as an intermittent regimen of the drug treatment using a mouse model of AD induced by the central administration of the fragment of amyloid-β 25-35 (Aβ25-35).
Methods and Algorithms: C57BL6 mice were bilaterally strereotaxically injected with an aggregated amyloid fragment Aβ25-35 at a dose of 5 μg into lateral ventricles of the brain [3]. 2 days after the surgery, trehalose treatment started. Mice have been given 2 % or 4 % trehalose solution as drinking for 14 days or 4 % trehalose solution as drinking for 14 days in an intermittent regimen (every other day). In the hippocampus, the mRNA levels of the autophagy-related genes (*Atg8, Park2*, and *Becn1*) were studied. Using immunohistochemical analysis of the brain cryosections, we evaluated Aβ deposition, the expression of markers of autophagy (LC3-II) or neuroinflammation (IBA1), and neuronal density with the expression of neuronal marker NeuN or Nissl staining in the frontal cortex and hippocampus. Inflammatory markers (leukocyte elastase and α1-proteinase inhibitor) were measured in the serum samples. Recovery of cognitive function was assessed in the passive avoidance test.
Results: Treatment of the AD model with trehalose increased autophagy activity in the hippocampus, as measured by an increase in the expression of LC3-II. The maximal effect was achieved by the daily treatment with 4 % trehalose solution for two weeks. Trehalose elevated mRNA levels of autophagy-related genes *Atg8, Becn1,* and especially *Park2*. Trehalose intake reduced the Aβ load in the frontal cortex and hippocampus with a maximal effect of every day treatment with the 4 % drug solution. A therapeutic effect was also obtained for the inhibition of neuroinflammation as estimated by the expression

of a microglial marker IBA1 and the restoration of neuronal density estimated by the NeuN expression or Nissl staining. The main therapeutic effect was revealed for the restoration of cognition in the passive avoidance test with a maximal effect of daily intake of 4 % drug solution; the effect of daily intake of 2 % trehalose solution was similar to the consumption of 4 % trehalose solution in the intermittent mode.

Conclusion: The AD model induced by injection of the Aβ25-35 fragment into the brain of mice demonstrated a coordinated response of hippocampal neurons to autophagy activation by trehalose, which included a decrease in Aβ accumulation, inhibition of neuroinflammation, restoration of neuronal density, and repair of cognitive activity related to learning and memory. In general, the most prominent therapeutic effect was produced by the daily intake of 4 % trehalose solution.

Acknowledgements: The study was supported by budgetary funding for basic scientific research of the Scientific Research Institute of Neurosciences and Medicine (AAAA-A21-121011990039-2). The studies were partially implemented using the Unique scientific installation “Biological collection – Genetic biomodels of neuro-psychiatric disorders” (No. 493387) at the Scientific Research Institute of Neurosciences and Medicine.

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