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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- More than 50 million people suffer from Alzheimer's disease (AD).
- There are no radical cures for the disease.

Trehalose is a disaccharide O-α-D-gluranosyl-[1→1]-α-D-glucopyranoside consisting of two glucose residues linked by a flexible α-1-1'glycoside bond.

Trehalose appears to be a multi-targeted anti-AD drug as it has:
- chaperone-like activity
- ability to induce autophagy (as part of proteostasis control)
- antioxidant activity
- anti-inflammatory activity
**Aim:** to evaluate the dose-dependence of the therapeutic effect of oral trehalose intake and the effect of its intermittent administration.

**Modeling of AD** was performed by means of intracerebroventricular (i.c.v.) injection of neurotoxic fragment Aβ25-35.

**Trehalose treatment:** C57BL/6 mice received 2 or 4% trehalose solution as drinking for 2 weeks or 4% trehalose solution as drinking for 14 days in an intermittent regimen (every other day).

### Results

Trehalose induced autophagy according to immunohistochemical expression of the LC3-II marker in the CA1 area of the hippocampus. The highest outcome was achieved with 4% trehalose.
According to the amyloid concept, the accumulation of amyloid-β (Aβ) is a key pathogenic factor in AD. In the AD model, Aβ was sharply elevated in the CA1 region of the hippocampus. All regimens of trehalose administration reduced the level down to the control values.

*** - p<0.001 vs. H2O; # - p<0.05, ## - p<0.01 vs. Aβ.
**Iba1**, a marker of **neuroinflammation** (microglia activation), was elevated in the AD model and markedly reduced in all trehalose treatment regimens.

Although trehalose treatment had a **positive impact** on the **density** of hippocampal **neurons** (according to **Nissl staining**), the effects of both Aβ and trehalose on the parameter were **not pronounced** (data not shown).
The main therapeutic effect was revealed for the **restoration of cognition** in the behavioral testing (**the passive avoidance test**). The treatment effects of 2% trehalose and 4% trehalose in intermittent mode were high and almost identical. The **highest result**, close to control, was obtained for **4% trehalose**, that is similar to the effects on the activation of autophagy (shown above).
Conclusion

● Modeling of AD by acute damage to hippocampal neurons by the neurotoxic fragment Aβ25-35 causes mild alterations in the hippocampal neuronal density, Aβ accumulation, neuroinflammatory responses, and cognitive dysfunctions.

● Two weeks of treatment of the model with various regimens of oral trehalose resulted in a slight positive effect on hippocampal neurons and a marked recovery in cognitive behavior, most notable for 4% trehalose, which should be recommended for future studies.

● The effect on cognition was similar to that on autophagy stimulation in the hippocampus. Other mechanisms of the therapeutic activity of trehalose studied (influence on the Aβ level and neuroinflammation) were less concordant with the behavioral outcomes.

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