Научно-исследовательский институт нейронаук и медицины

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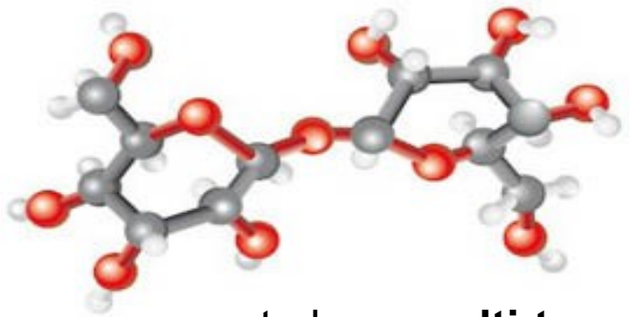
- More than 50 million people suffer from Alzheimer's disease (AD).
- There are no radical cures for the disease.



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:

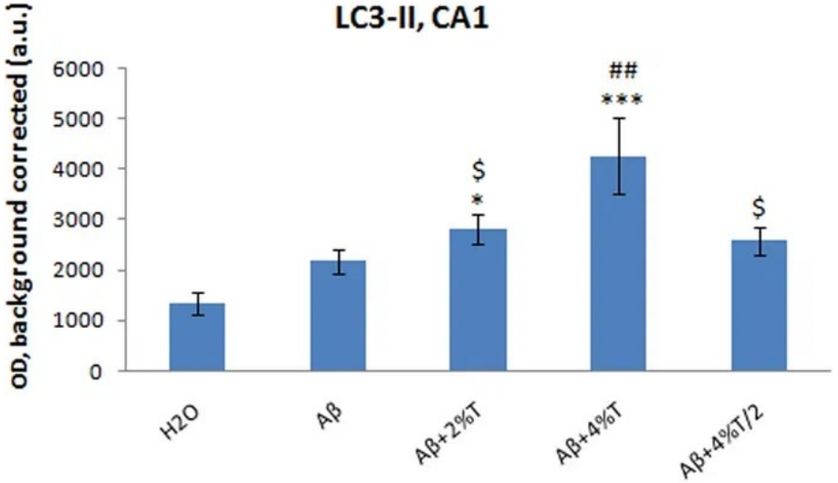
- chaperone-like activity
- ability to **induce autophagy** (as part of proteostasis control)
- antioxidant activity
- anti-inflammatory activity

**Aim:** to evaluate the dose-dependence of the therapeutic effect of of oral trehalose intake and the effect of its intermittent administration.

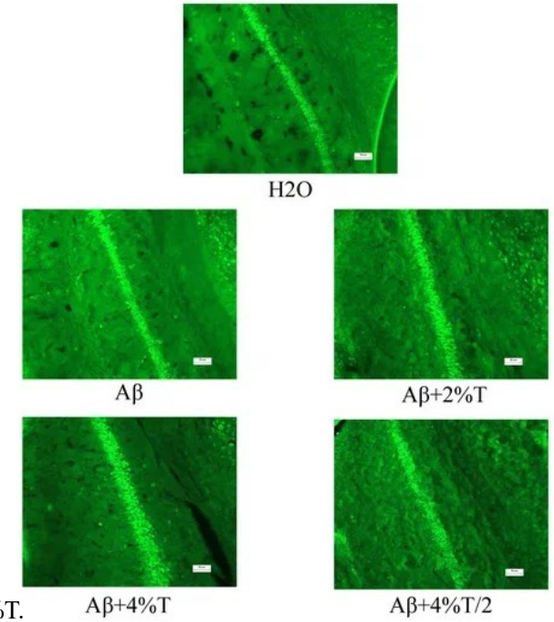
**Modeling of AD** was performed by means of intracerebroventricular (i.c.v.) injection of neurotoxic fragment Aβ25-35.

**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

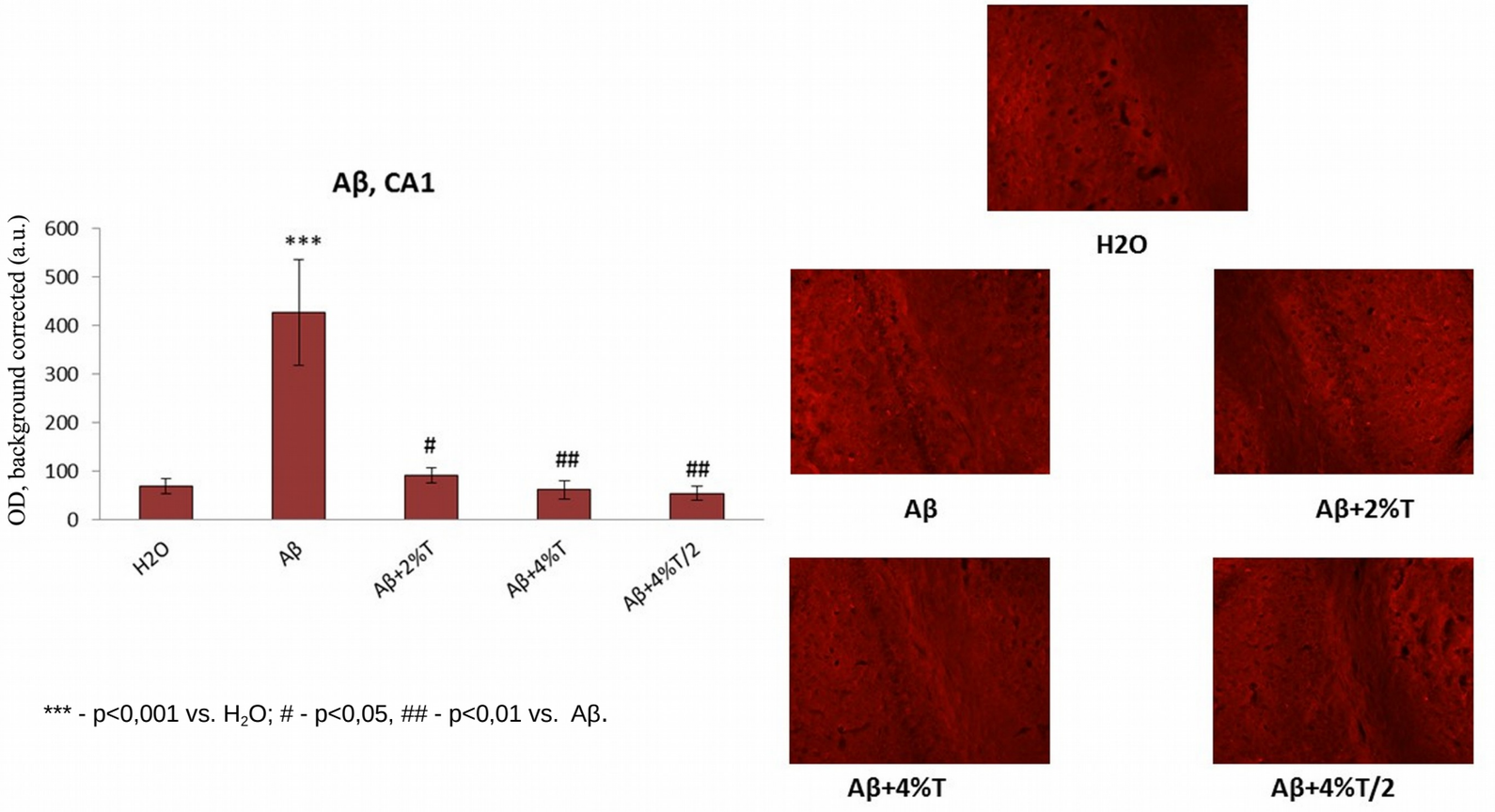



* - p<0,05; *** - p<0,001 vs. H2O; ## - p<0,01 vs. Aβ; $ - p<0,05 vs. Aβ+4%T.



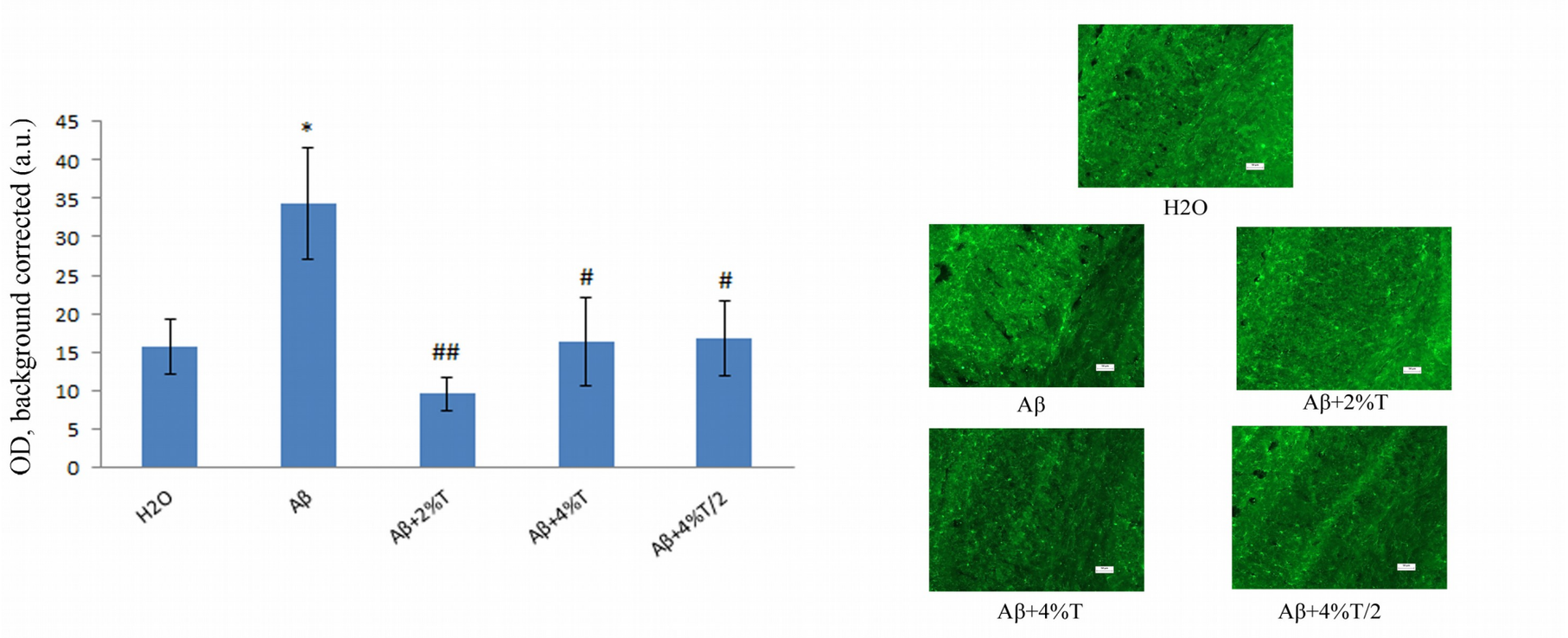

Trehalose induced autophagy according to immunohistoche-mical expression of the LC3-II marker in the CA1 area of the hippocampus. The highest outcome was achieved with 4% trehalose.

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. $H_2O$; # - p<0,05, ## - p<0,01 vs. Aβ.

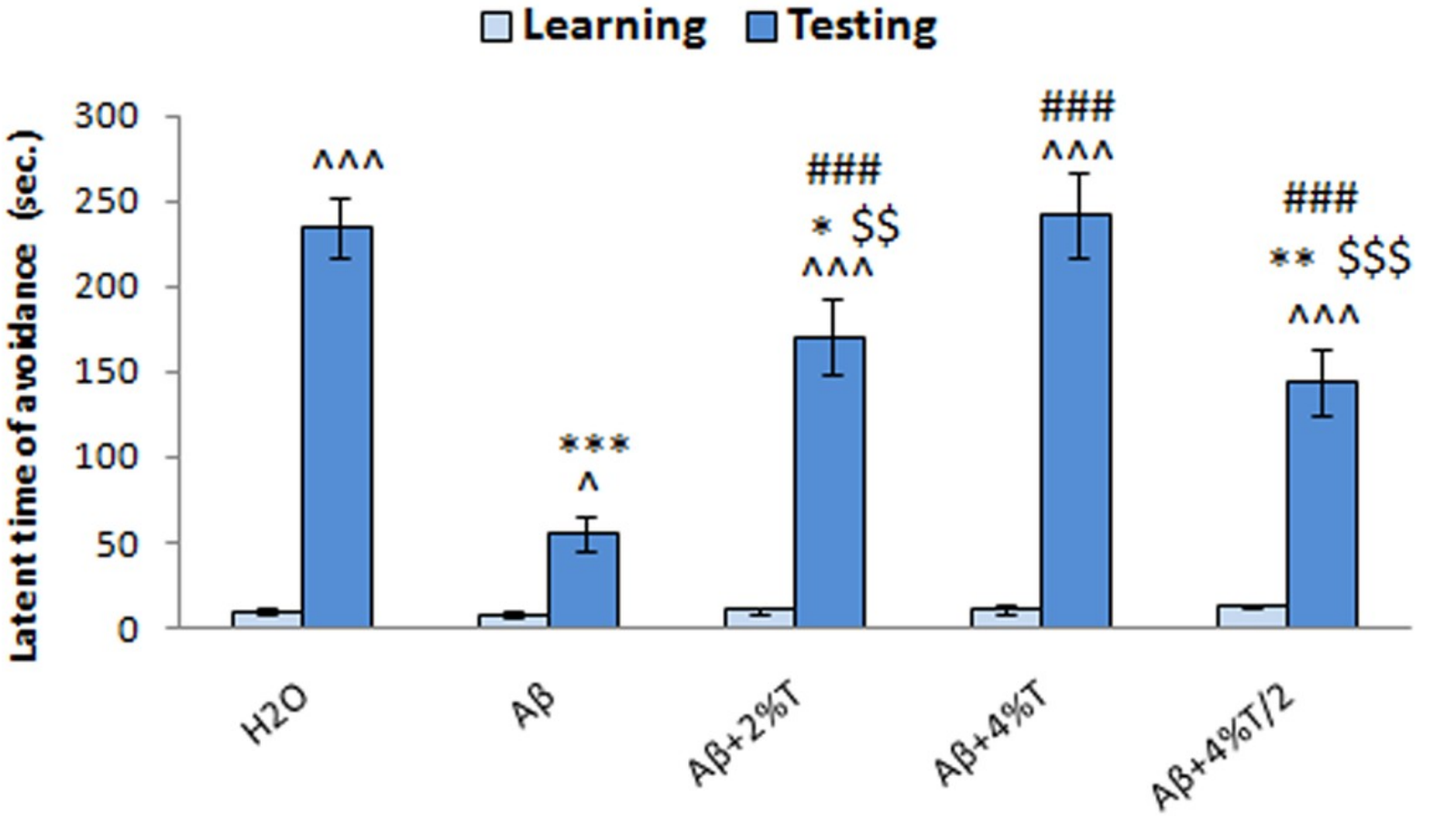
**Iba1**, a marker of **neuroinflammation** (microglia activation), was elevated in the AD model and markedly reduced in all trehalose treatment regimens.




* p<0,05 vs H2O; # p<0,05; ## p<0,01 vs Aβ.

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).




^ - p<0,05, ^^^ - p<0,001 vs. Learning; * - p<0,05; ** - p<0,01, *** - p<0,001 vs. H2O; ### - p<0,001 vs, Aβ; $$ - p<0,01, $$$ - p<0,001 vs. Aβ+4%T.

# 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.

**Acknowlegements**

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