DO ANTIDIABETIC AGENTS IMPROVE COGNITIVE FUNCTION IN ALZHEIMER'S DISEASE MODELS VIA INSULIN MODULATION OR NEUROINFLAMMATION REDUCTION?

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PRECLINICAL RESEARCH

Introduction / Background

- **Alzheimer's disease** (AD) and **type 2 diabetes mellitus** (T2DM) frequently co-occur, with over 80% of AD patients exhibiting T2DM or abnormal glycemia.
- Shared mechanisms such as insulin resistance and neuroinflammation have been implicated in the pathophysiology of both conditions.
- Antidiabetic agents may offer therapeutic benefits in AD by targeting these mechanisms:
  - **Semaglutide:** A glucagon-like peptide-1 (GLP-1) receptor agonist acting as an insulin secretagogue.
  - **Metformin:** An insulin sensitizer with potential anti-inflammatory properties.
- This study evaluates the cognitive benefits of Semaglutide and Metformin in preclinical models of AD-related memory deficits.

Methods

Animal Models

1 **Aβ-Induced memory Impairment** (Rats):
Memory impairment induced by intracerebroventricular injection of fibrillated **amyloid-beta (Aβ) peptide**.

2 **LPS-Induced Neuroinflammation** (Mice):
Cognitive deficits induced by a non-septic dose (0.25 mg/kg) of **lipopolysaccharide (LPS)**.

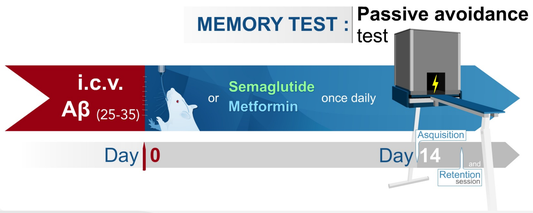
Drug Treatments

Semaglutide and Metformin were orally administered once daily following Aβ or LPS induction.

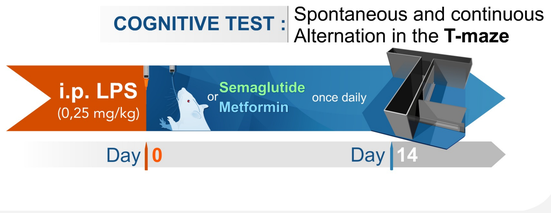
Cognitive Assessments

- **Passive Avoidance Test** (Rats): Evaluates memory retention by measuring avoidance behavior in Aβ-treated rats.
- **T-Maze Spontaneous Alternation Task** (Mice): Measures spatial working memory in LPS-treated mice.

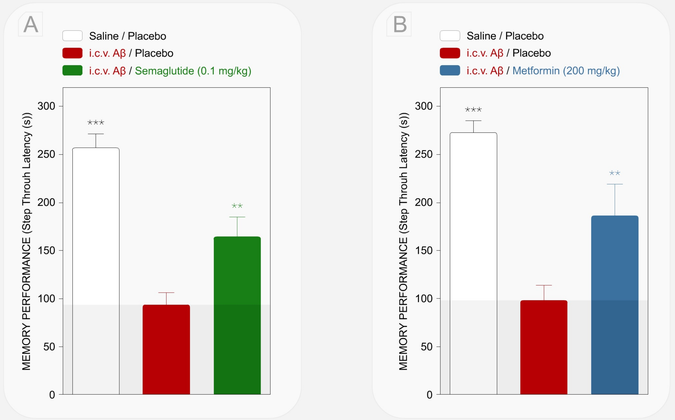
Timeline of Aβ - induced memory deficit model



Timeline of LPS - induced cognitive deficit model

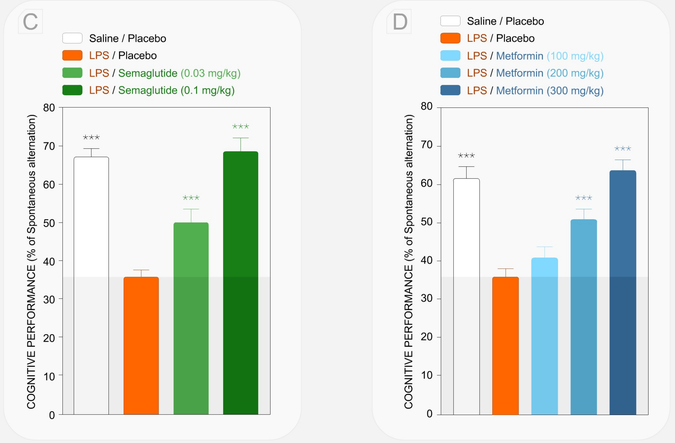


Results



Semaglutide and metformin significantly alleviated memory deficits in Aβ-treated rats.

Statistical significance: **, ***: $p \leq 0.01$ and $p \leq 0.001$, respectively, compared to the Aβ / Placebo group.



Semaglutide and metformin markedly restored cognitive performance in mice with LPS-induced neuroinflammation.

Statistical significance: ***: $p \leq 0.001$ compared to the LPS / Placebo group.

Key points

Shared Benefits Across Mechanisms:

Despite differing primary modes of action (insulin secretagogue vs. insulin sensitizer), both Semaglutide and Metformin showed comparable cognitive improvements.

Potential Mechanisms:

- Modulation of insulin signaling pathways?
- Reduction of neuroinflammation?

Conclusion:

- **Semaglutide** and **Metformin** improve cognitive performance in preclinical models of **AD-related cognitive impairment**.
- Further research is needed to elucidate whether these effects are driven by **insulin modulation**, **neuroinflammation reduction**, or both.
- These results support the potential **use of antidiabetic agents as adjunctive therapies in AD**.