# Neuroprotection by GLP-1 class drugs correlates with BBB penetration


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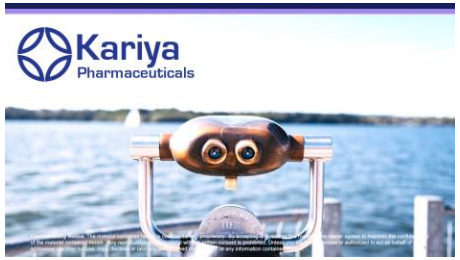
Copenhagen, Denmark

# Conflicts of interest:




- Dr. Hölscher is a named inventor on patents covering the use of GLP-1 and GIP as novel treatments in AD and PD
- He is the CSO of Kariya Pharmaceuticals Ltd.
- He has been a consultant for NovoNordisk, Pfizer, GSK, Sanofi, Roche

# GLP-1: Novel strategies for CNS treatments

- Glucagon-like peptide 1 is a growth factor
- GLP-1 normalizes energy utilisation in the brain
- GLP-1 reduces chronic inflammation
- Neuronal survival and synaptic activity is greatly enhanced

- Preclinical studies show good effects in AD and PD animal model
  - Liraglutide showed good effects in the APP/PS1 model of AD (McClean et al. 2011, J Neurosci).

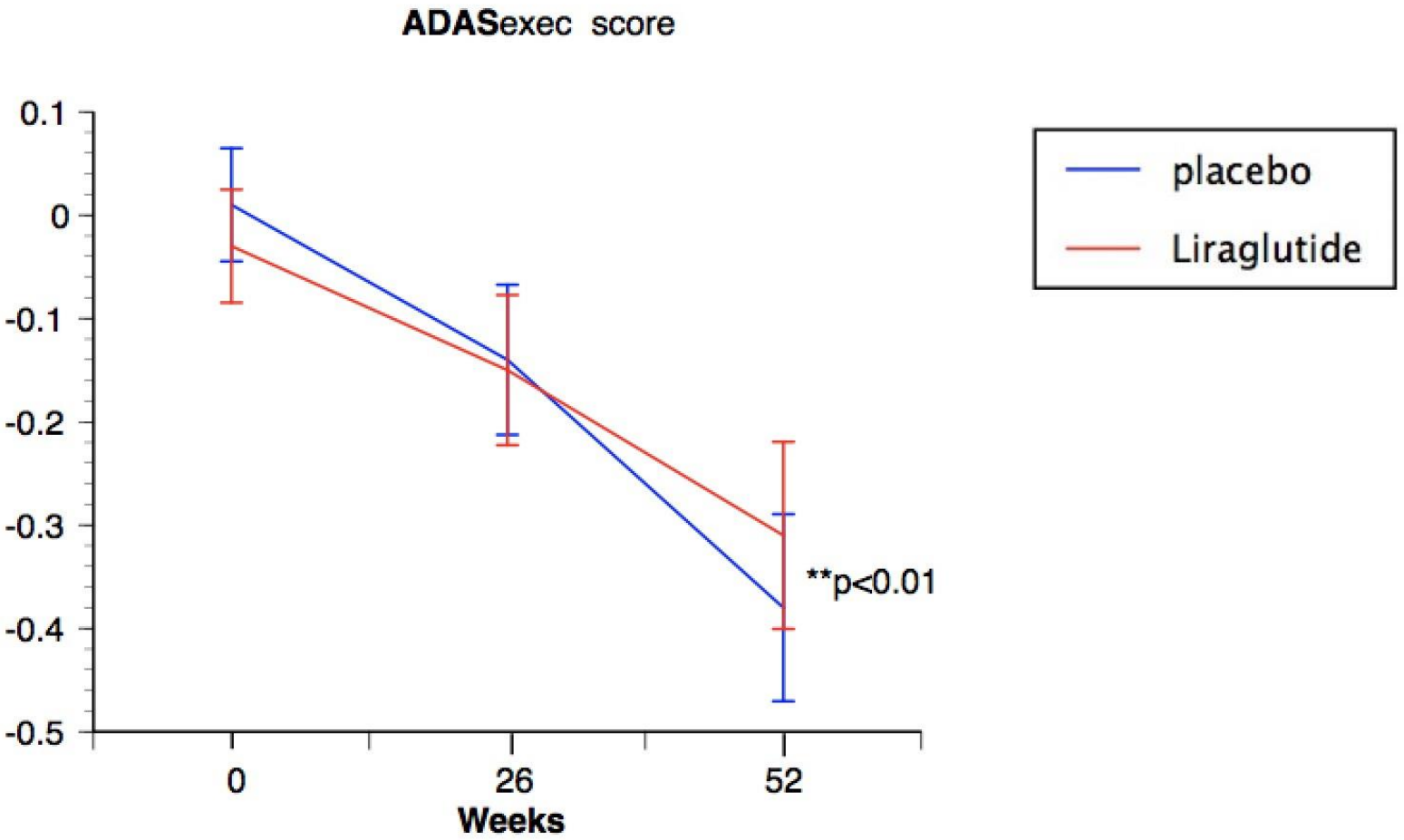
# Testing liraglutide in Alzheimer patients

We conducted a phase II clinical trial (ELAD study)

- 204 AD patients, double-blind, placebo controlled study,
- 12 months duration,
- PET imaging of $^{18}$FDG uptake, ADAS-exec cognitive test battery,
- MRI brain scans to measure brain shrinkage

*See Femminella et al., 2019, Trials 20:191pp*

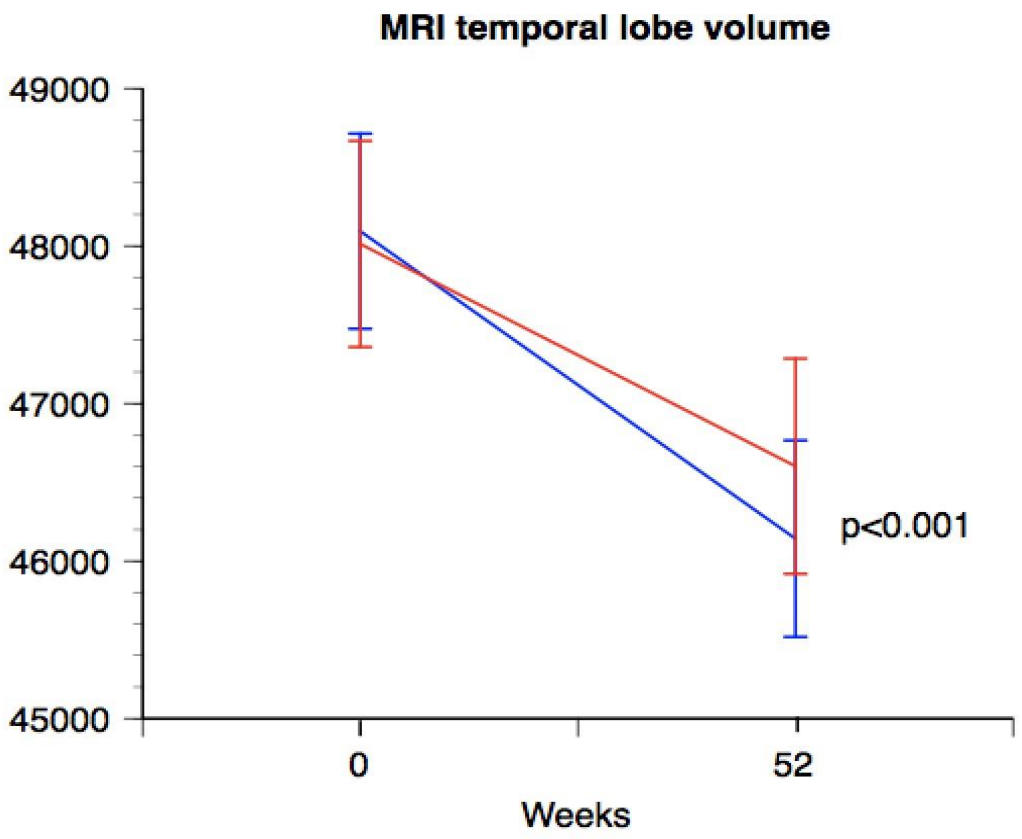
# Cognition improved

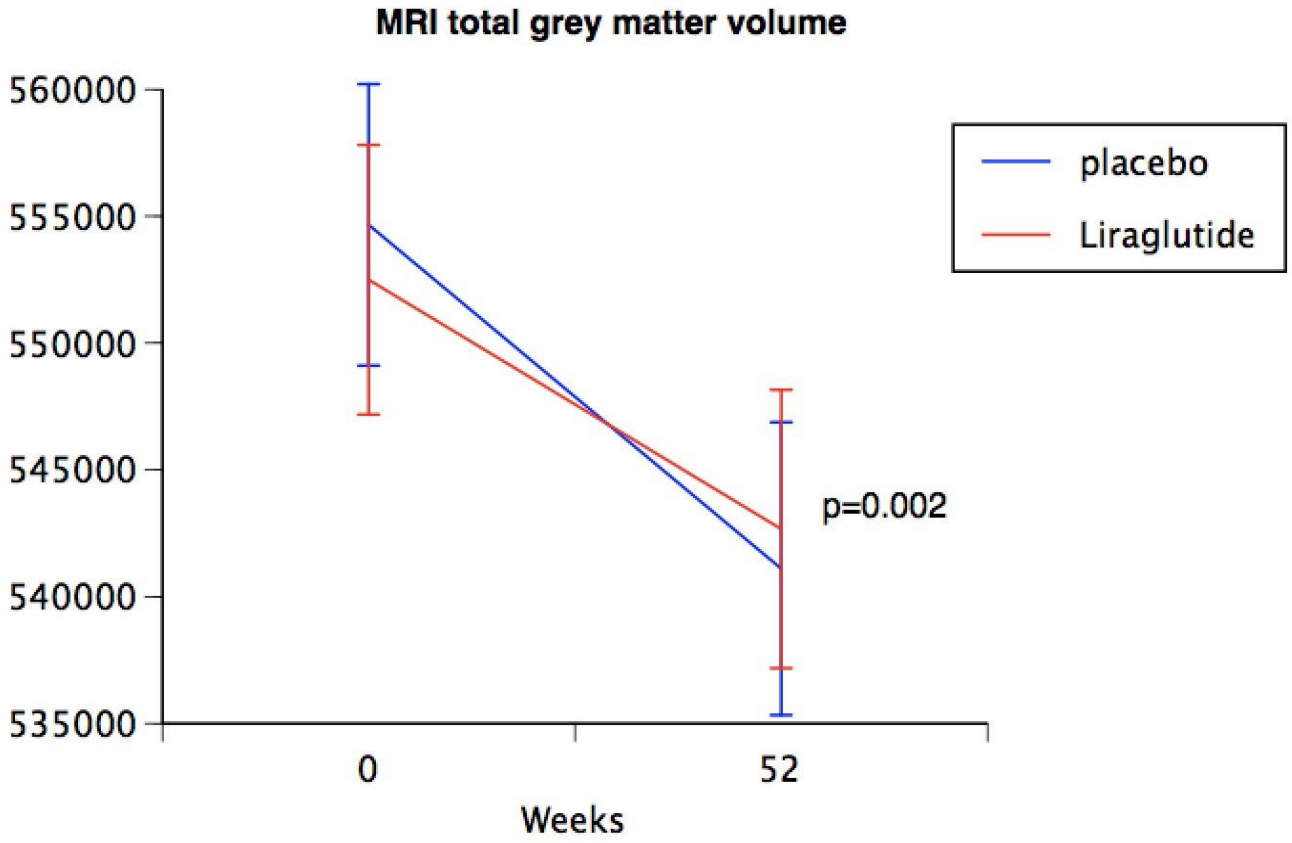



N=102 per group, results shown are means±SEM

*Edison et al. 2024*

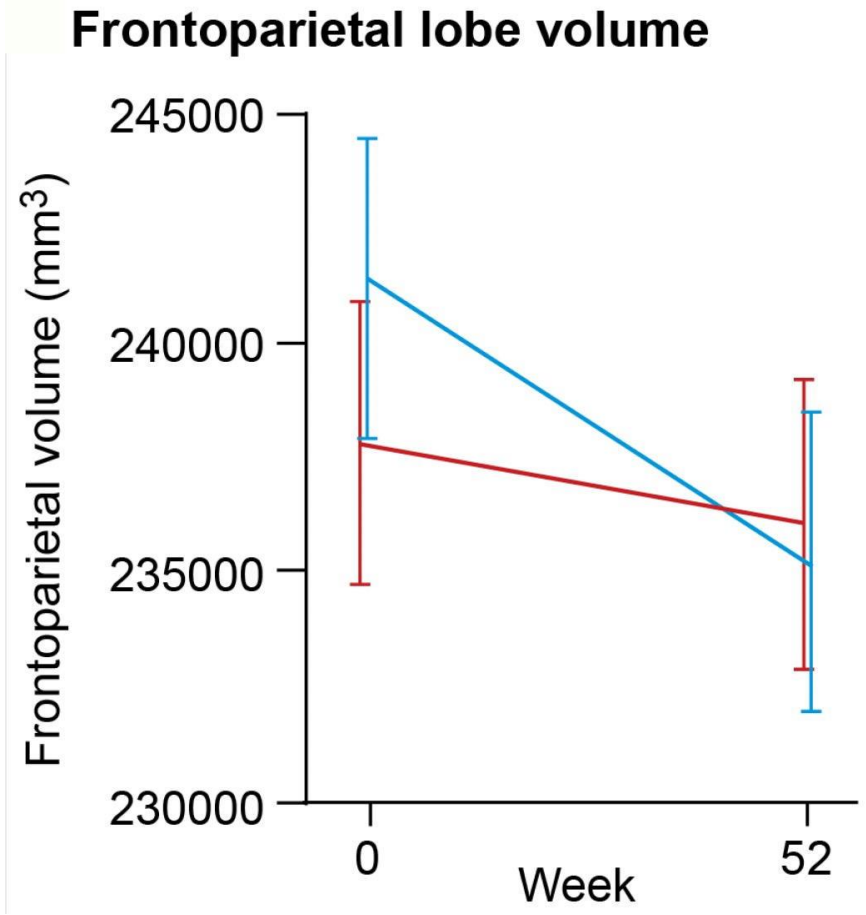
# Brain shrinkage was reduced over time

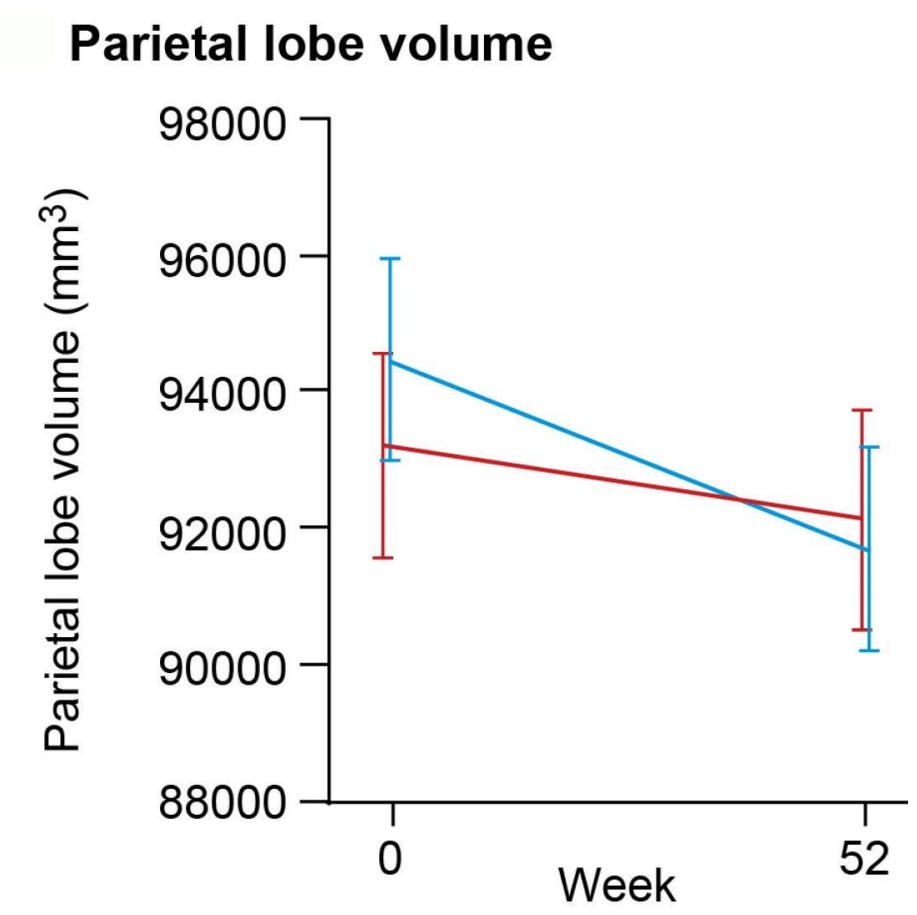



*Edison et al. 2024*

# Brain shrinkage was reduced over time




*Edison et al. 2024*

# Conclusion:
# Liraglutide reduced disease progression in AD

A proof of concept that GLP-1 analogues are effective in the clinic.

The effect was only limited, and better drugs are needed.

# Two phase 3 clinical trials in AD are ongoing, testing semaglutide

**Novo Nordisk to enter phase 3 development in Alzheimer's disease with oral se...**

## Novo Nordisk to enter phase 3 development in Alzheimer's disease with oral semaglutide

December 16, 2020 08:08 ET | Source: Novo Nordisk A/S

**Bagsværd, Denmark, 16 December 2020** – Novo Nordisk today announced the decision to enter phase 3 development in Alzheimer's disease with 14 mg oral semaglutide, a once-daily oral

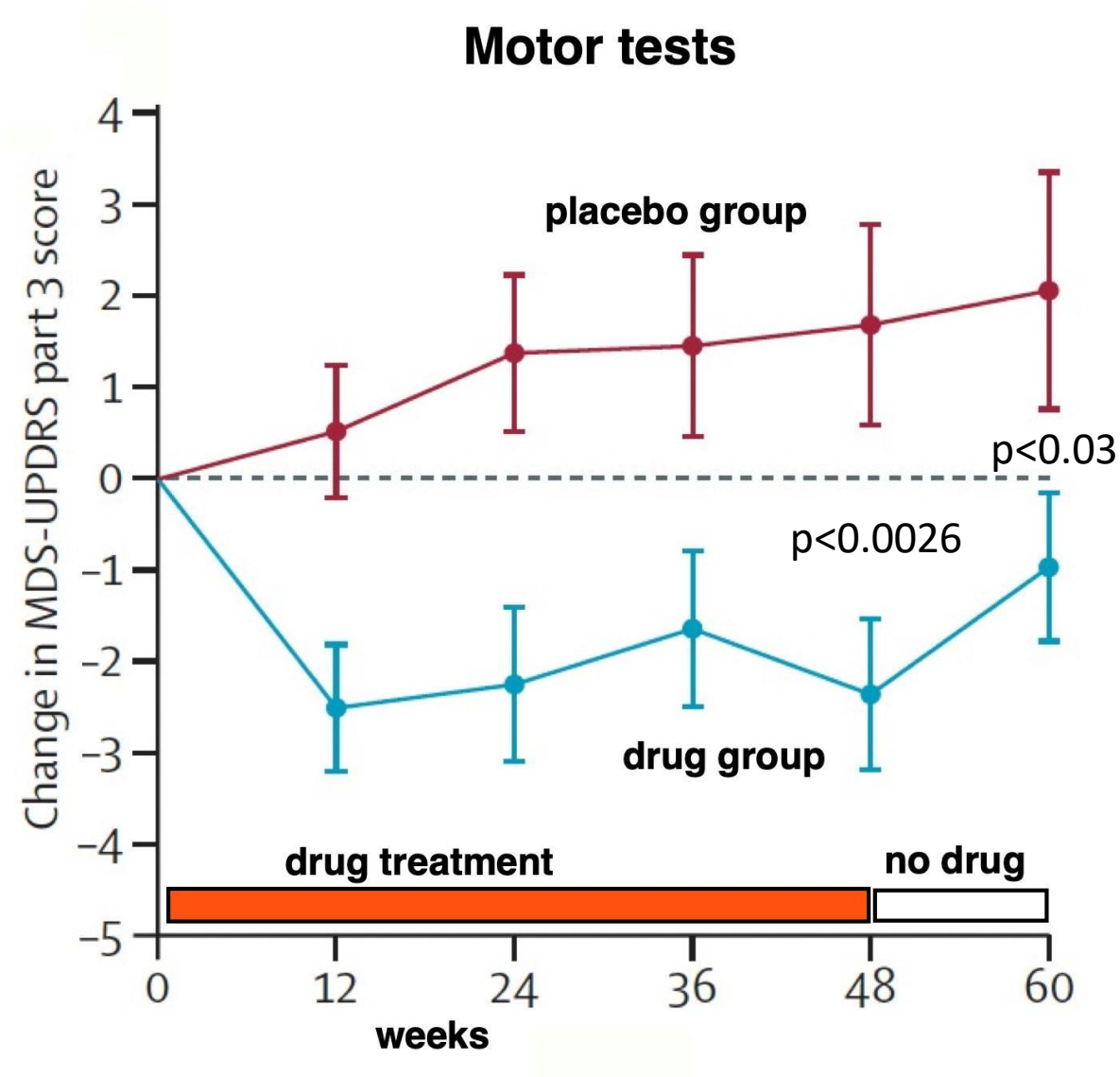
# The importance of BBB penetration

# Phase II trial testing exenatide in PD

- 62 patients,
- Bydureon® - once-weekly formulation of exendin-4
- Double blind, placebo controlled
- 7 months treatment
- Re-testing 3 months after the treatment had stopped
- All patients took L-Dopa

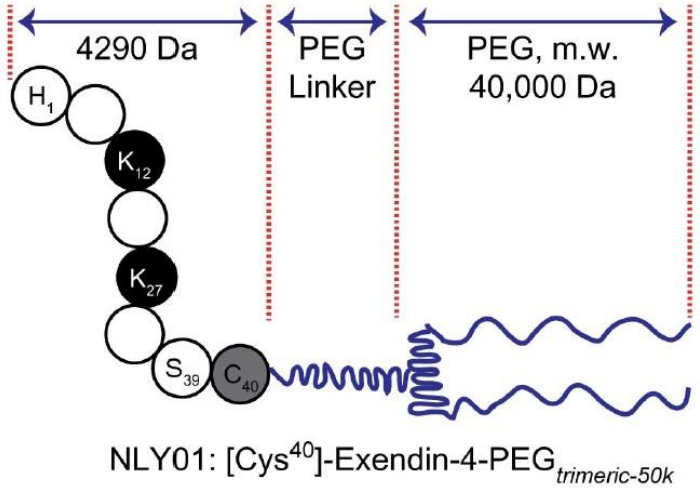
*Athauda et al., 2017*

# MDS-UPDRS III motor score




*Athauda et al., 2017*

# Testing NLY01 in Parkinson's patients

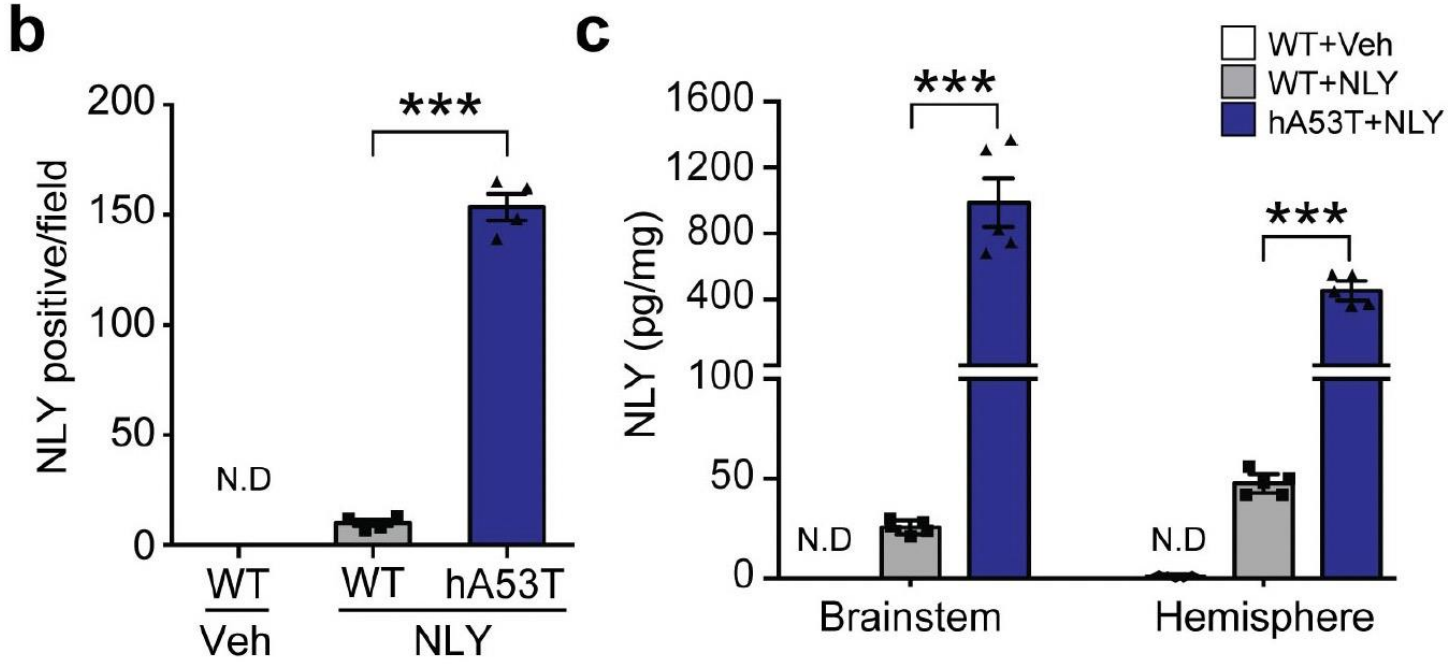



- NLY01 is a pegylated form of exendin-4
- 36 weeks trial duration
- 85 patients per group, 3 groups (5.mg, 2.5mg, placebo)
- Drug groups did not differ from placebo in sum scores on MDS-UPDRS parts II and III

- NO EFFECT!

*McGarry et al., Lancet Neurol, 2024*

# NLY01 does not enter the brain




Testing BBB penetration in WT mice and in the hA53T tg mouse model, which has a leaky BBB

*Yun et al., Nat Med, 2018*

# Designing novel drugs that enter the brain

- Current GLP-1 drugs are designed to treat type 2 diabetes
- Most do not enter the brain well and are designed to stay in the blood stream
- We designed novel peptide drugs that are designed to cross the blood-brain barrier faster
- These peptides activate the GLP-1R and a second receptor, the glucose-dependent insulinotropic (GIP) receptor

# Glucose-dependent Insulinotropic Polypeptide

- A peptide hormone that acts as a growth factor similar to GLP-1
- GIP analogues have neuroprotective effects in AD and PD animal models
- A dual GLP-1/GIP agonist is on the market to treat diabetes and weight loss (Tirzepatide, Mounjaro®, Eli Lilly)

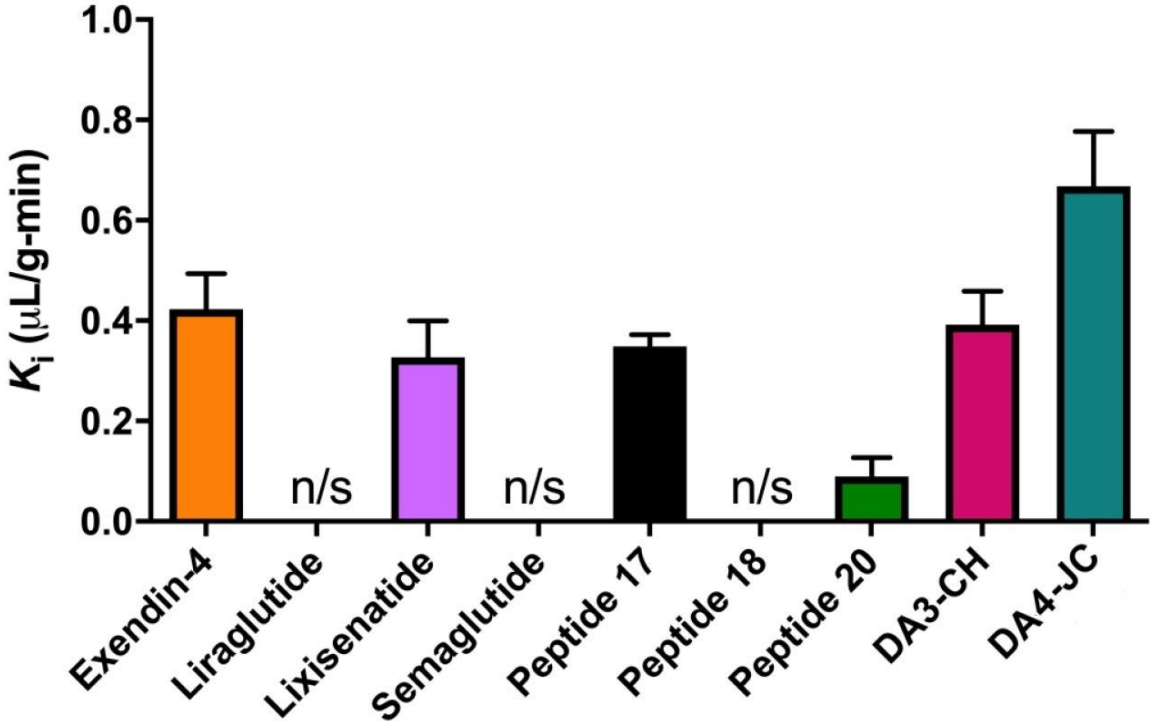
# Dual GLP-1/GIP dual agonists cross the BBB

- Using radio- labelled peptides show BBB penetration

*Salameh et al. (2020) , Rhea et al., (2023)*

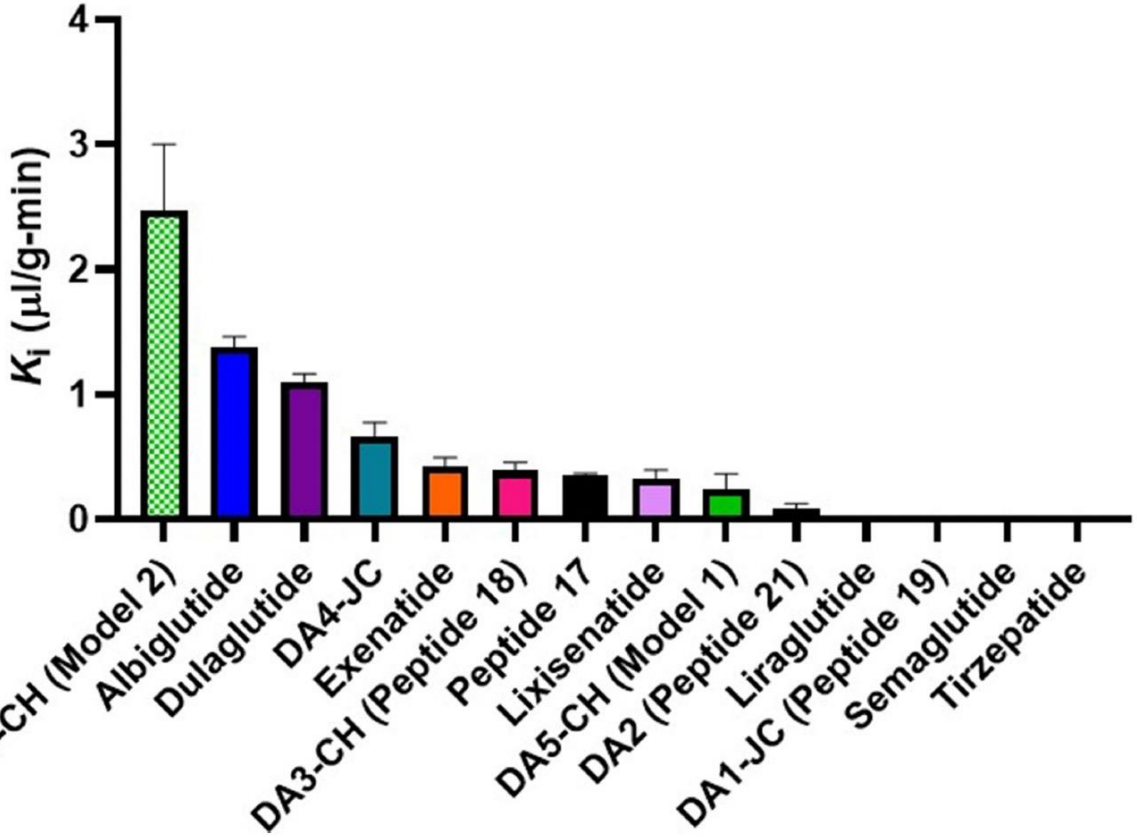
# BBB penetration test

**Rate constants of $^{125}$I-labeled peptides into whole brain after 10 min**



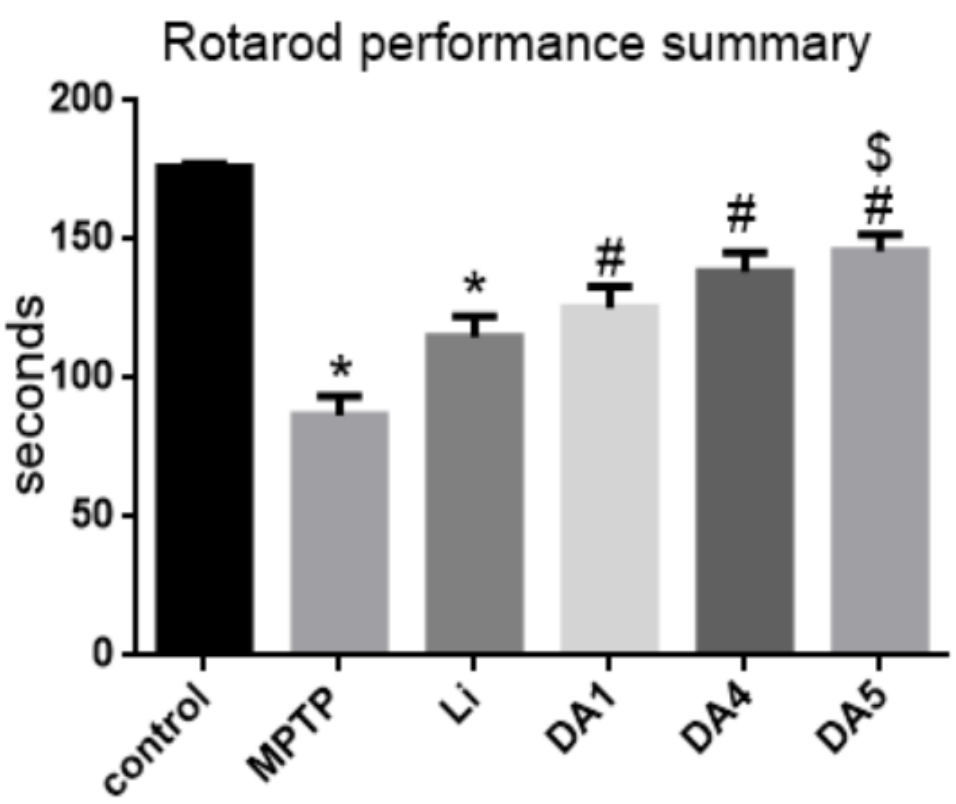

*Salameh et al., 2020*

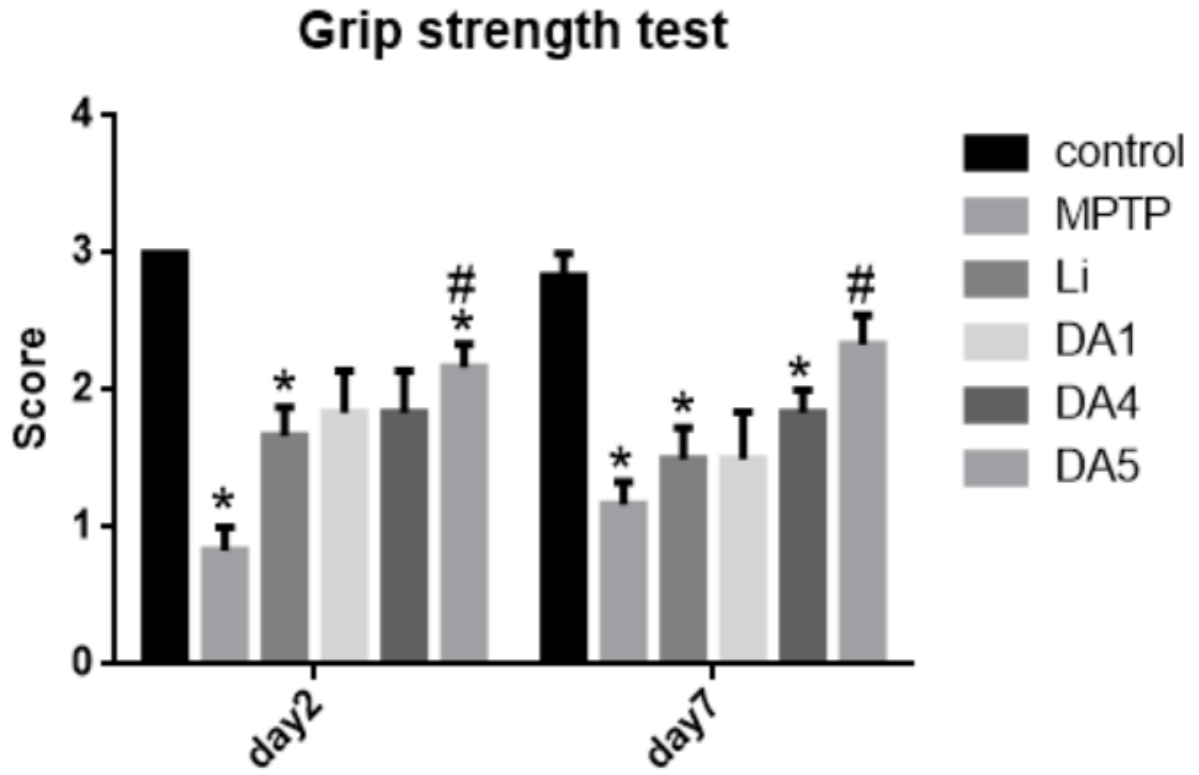
**after 1 h**




*Rhea et al., 2023*

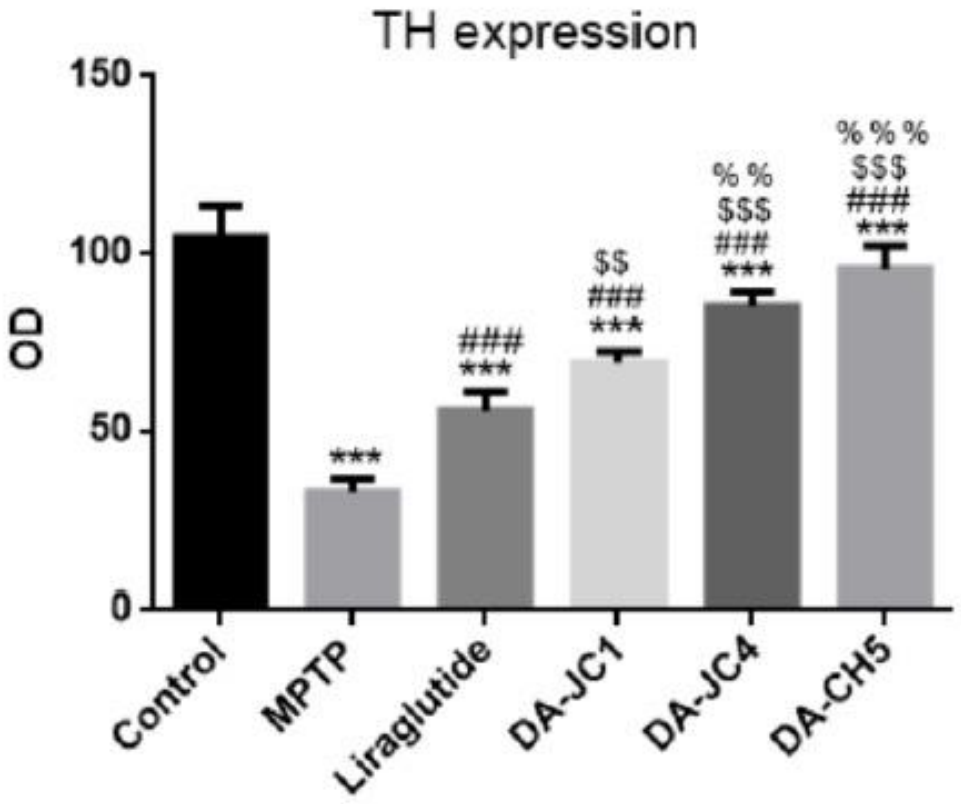
# Testing liraglutide and dual agonists in the MPTP model

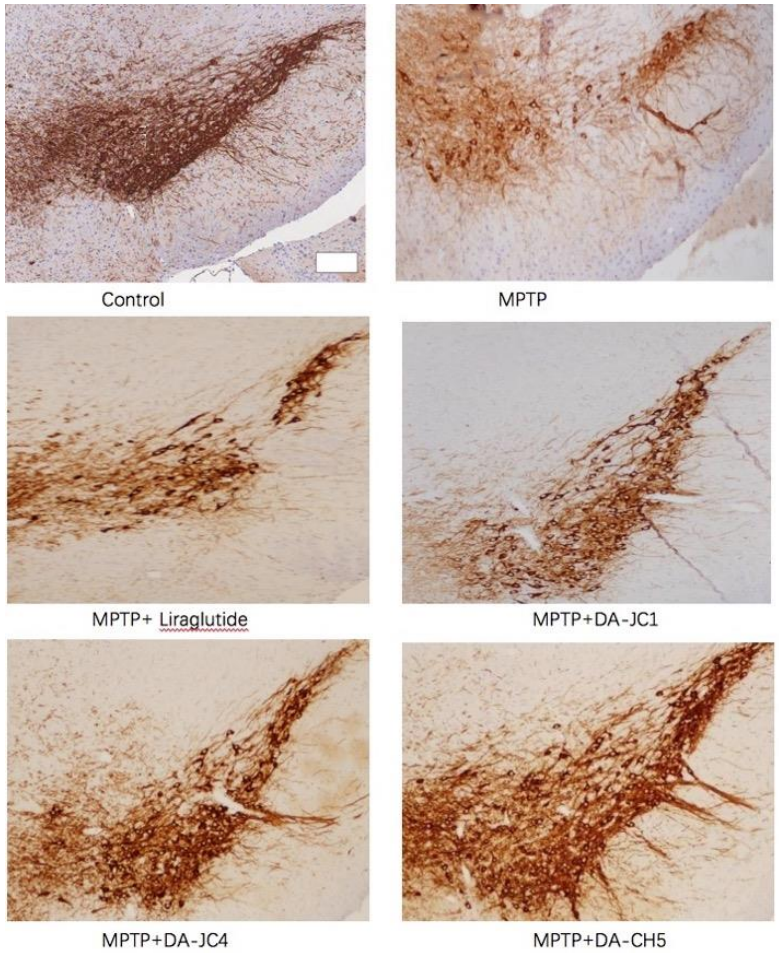



*Feng et al., 2018*

# Dopaminergic neurons in the SN are protected



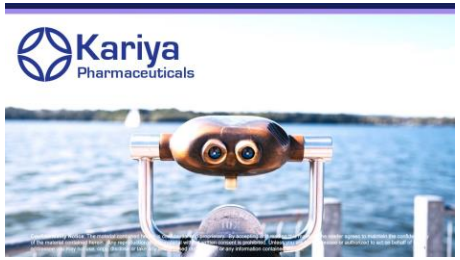




*Feng et al., 2018*

# Conclusion:

- GLP-1 mimetics have shown protective effects in AD/PD: proof of concept
- Our dual agonists can cross the BBB better than older GLP-1 drugs
- In animal studies, our dual agonists are superior to older GLP-1 drugs in protecting the brain
- These dual agonists may be superior drug treatments for AD/PD patients than standard GLP-1 mimetics
- Our dual agonist DA5-CH (KP405) has entered phase 1 clinical trials

# Thanks to:

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