

Age-related undercarboxylated-osteocalcin loss may heighten dopaminergic vulnerability to α -synuclein pathology in Parkinson’s Disease

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Introduction

- Parkinson’s disease (PD) causes progressive dopaminergic (DA) neuron loss.
- α -synuclein aggregation drives early neurite degeneration.
- Undercarboxylated-osteocalcin (ucOCN), a bone derived hormone, supports neuronal resilience through GPR158 signalling.



- Ageing increases vulnerability, suggesting other biological systems are involved, such as ucOCN decline may heighten susceptibility to PD pathology.

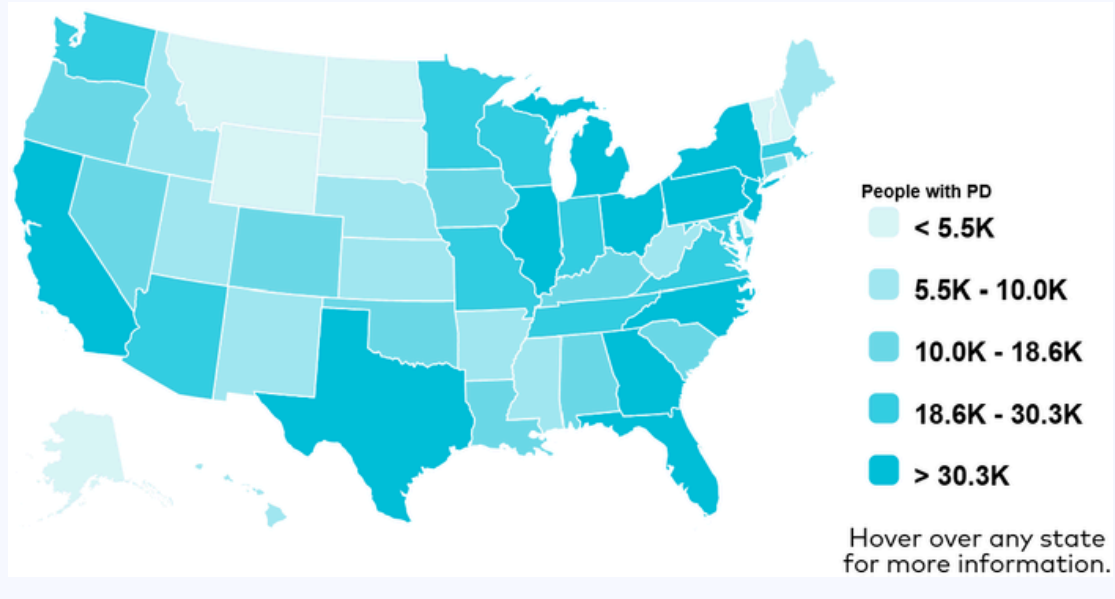


Figure 1. U.S. map displaying state-by-state Parkinson’s disease prevalence. (Parkinson’s Foundation)

Research Question

Does ucOCN protect DA neurons from α -syn-induced degeneration?

Hypothesis

- Reduced ucOCN increases DA neuron vulnerability
- ucOCN addition protects neurons via GPR158

Method

The methods will be split into three phases:

Phase 1

- SH-SY5Y neuroblastoma cells are differentiated using retinoic acid to produce dopaminergic-like neurons which express GPR158 receptors.
- The cells will be assigned to three groups of 1) Saline control, 2) α -synuclein preformed fibrils (PFFs) only, and 3) PFFs plus undercarboxylated osteocalcin (ucOCN).
- The final group will contain 5–100 ng/mL ucOCN in intervals; 5, 10, 25, 50, 75, 100 ng/mL in order to assess dose dependence.
- After 72 hours, neurite morphology is analysed by the Sholl analysis. Neurite intersections from the soma are measured, producing a dose-response curve – determining whether ucOCN has a protecting effect against PFF-induced neurite degeneration.

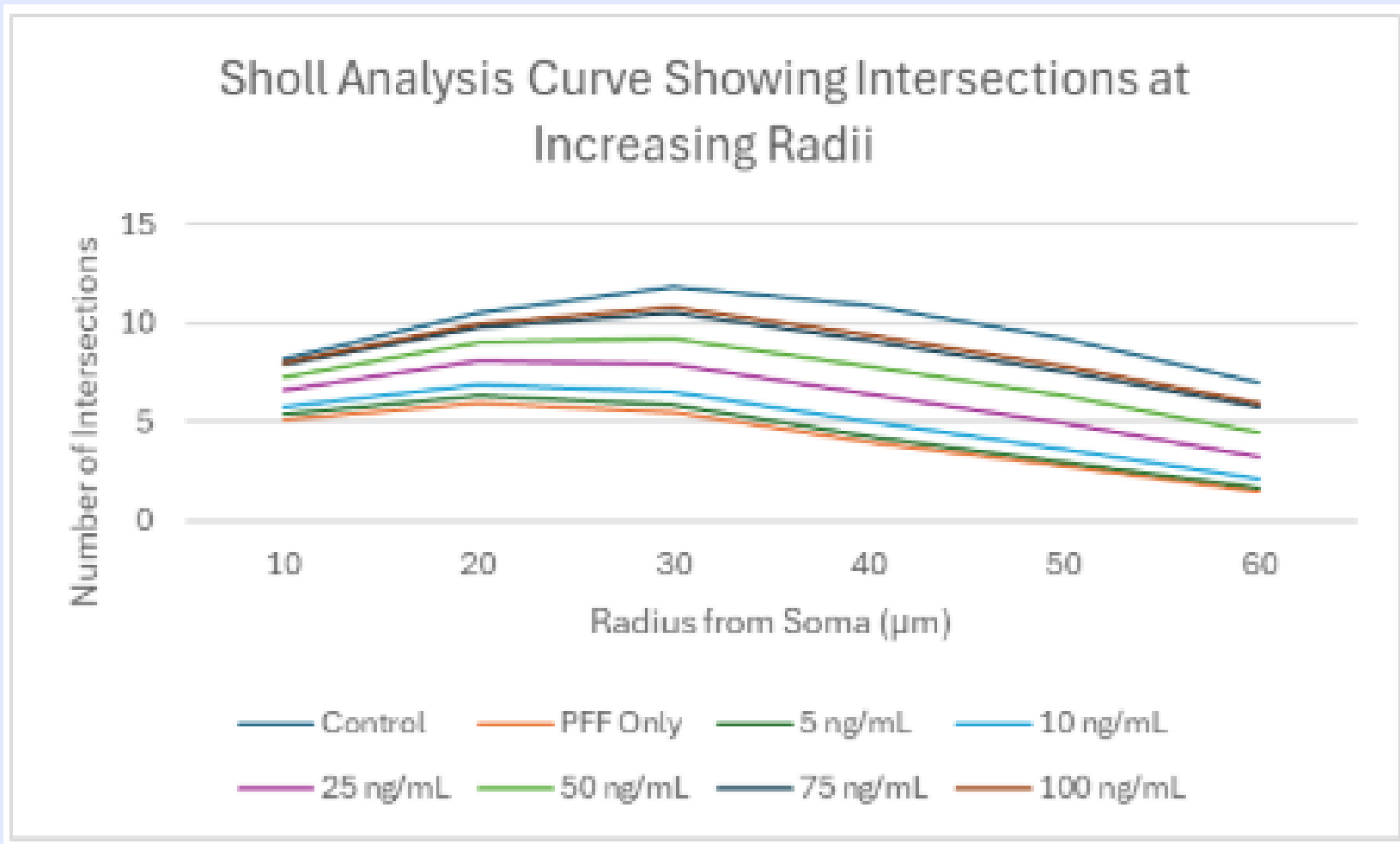
Phase 2

- Initiate exposure of primary DA neurons from E14.5 mouse embryos to 5 μ g/mL α -syn PFFs, treat with 100 ng/mL ucOCN.
- Then use double-label ICC to stain acetylated α -Tubulin, as stable microtubules, and total tubulin.
- Measure stable:total tubulin fluorescence (ratio) and axonal blebbing density (blebs/100 μ m axon) using Confocal microscopy.
- If there is a higher ratio and lower blebbing density in ucOCN-treated neurons, microtubule stabilisation and protection against neurodegeneration is indicated.

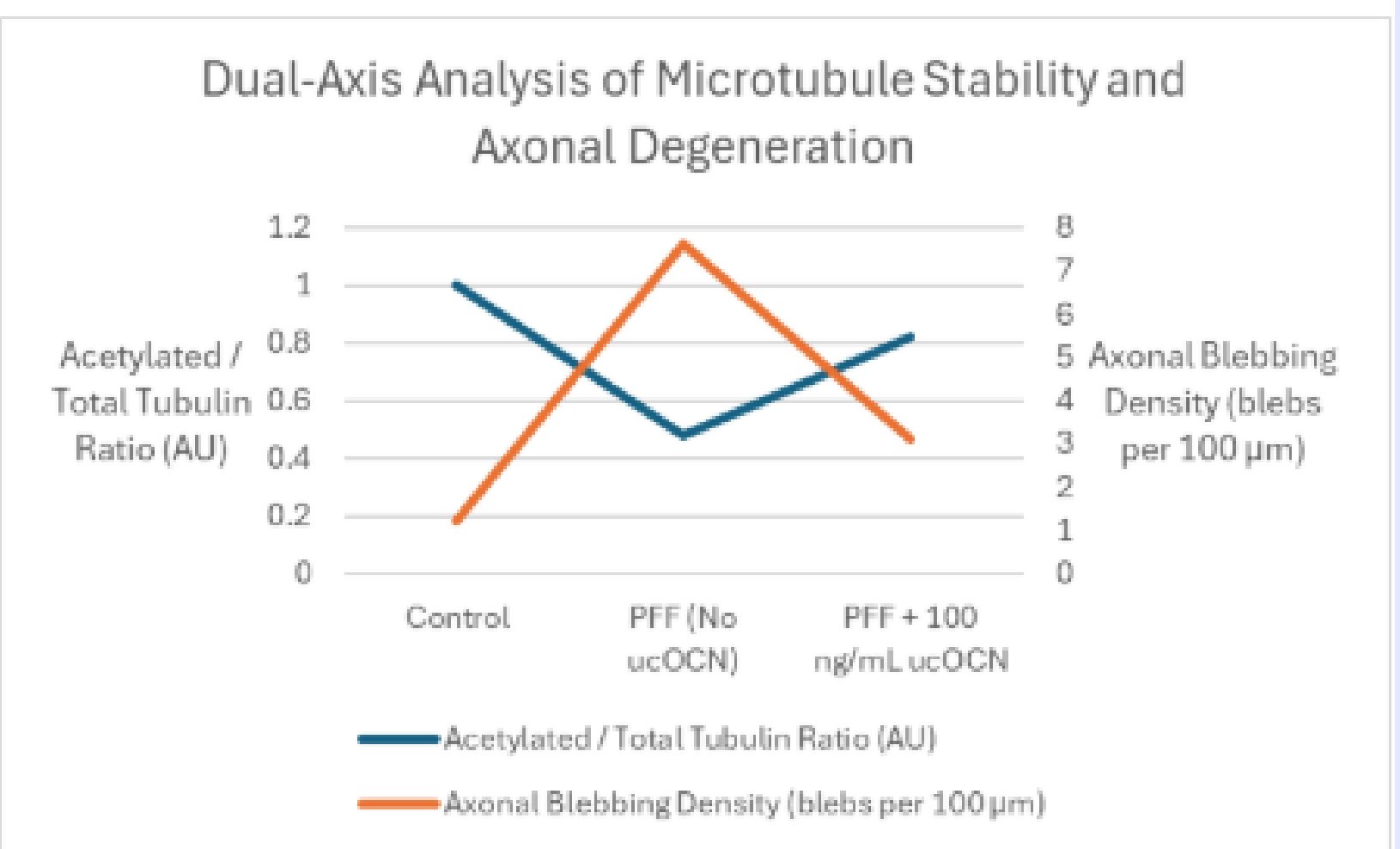
Phase 3

- Uses 3-month-old mice across three groups: WT + PFFs (baseline decay), OCN-KO + PFFs (ucOCN deficiency), and OCN-KO + PFFs + daily ucOCN (treatment rescue).
- Mice receive a microinjection of 5-syn PFFs into the right SNc to induce structural decay.
- At 8 weeks post-injection, mice undergo the Cylinder Test to measure left-paw motor defects caused by right-side SNc damage
- Golgi-Cox staining visualizes the 3D structure of dopaminergic neurons.
- Tyrosine Hydroxylase (TH) IHC identifies intact neurons (dark brown), with terminal loss quantified via Optical Density rather than manual fiber counts.

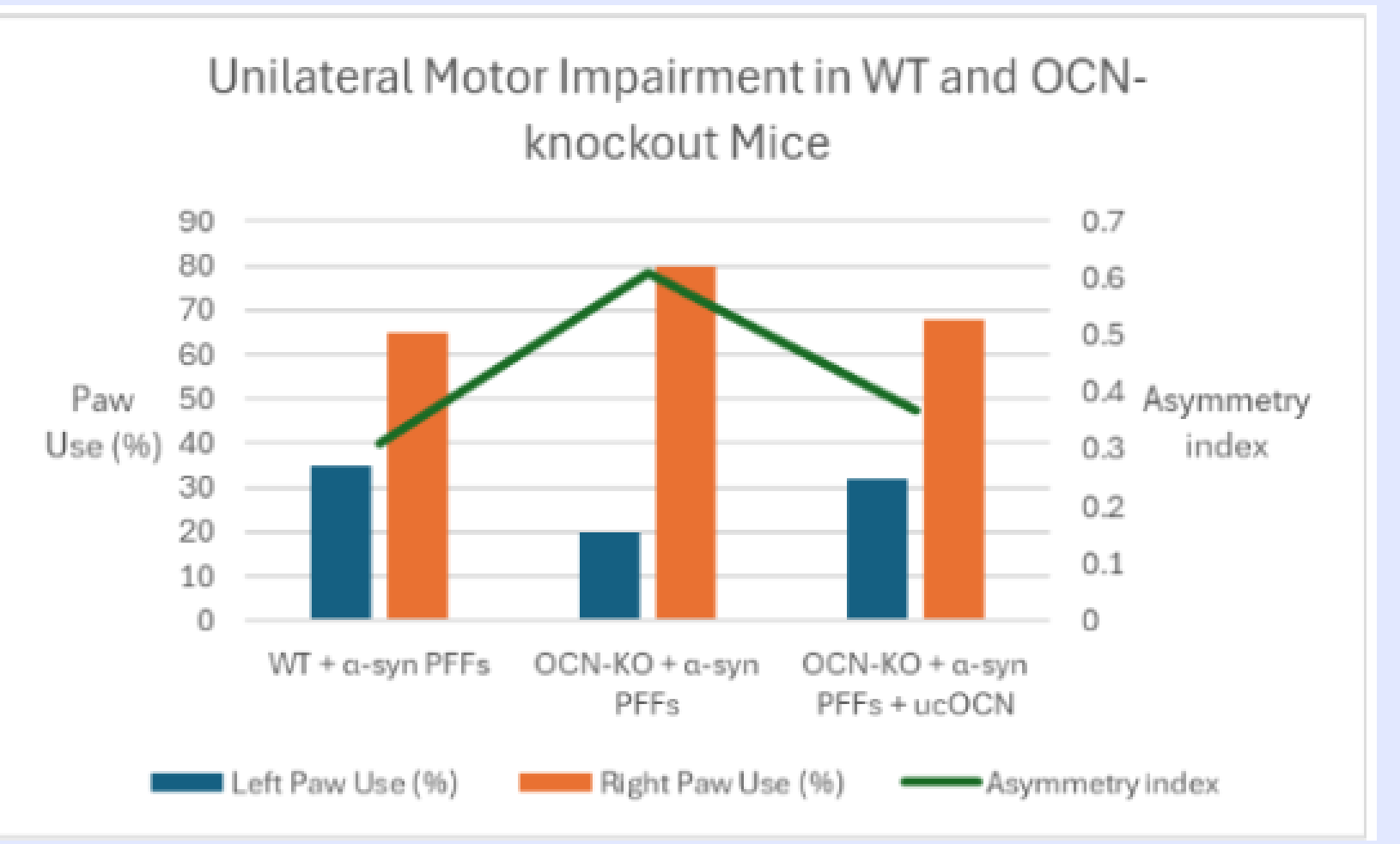
Results



- ucOCN progressively increased neurite preservation from low to high doses.
- High doses (75–100 ng/mL) restored structure to control levels without hyper-growth.



- ucOCN (100 ng/mL) restored microtubule stability and reduced α -syn PFF-induced axonal blebbing.
- Lack of direct rescue suggests neuroprotection requires whole-body/non-neuronal signaling.



- ucOCN supplementation partially prevented α -syn PFF-induced motor asymmetry in OCN-KO mice.
- Persistent asymmetry despite treatment suggests chronic ucOCN absence causes permanent structural changes.

Discussion

Key Findings:

- ucOCN protects DA neurons from α -syn damage
- ucOCN stabilises microtubules

Biological Significance:

- Supports the bone-brain axis concept
- Age-related decline in ucOCN may increase neuronal stability
- ucOCN could serve as a biomarker for dopaminergic resilience

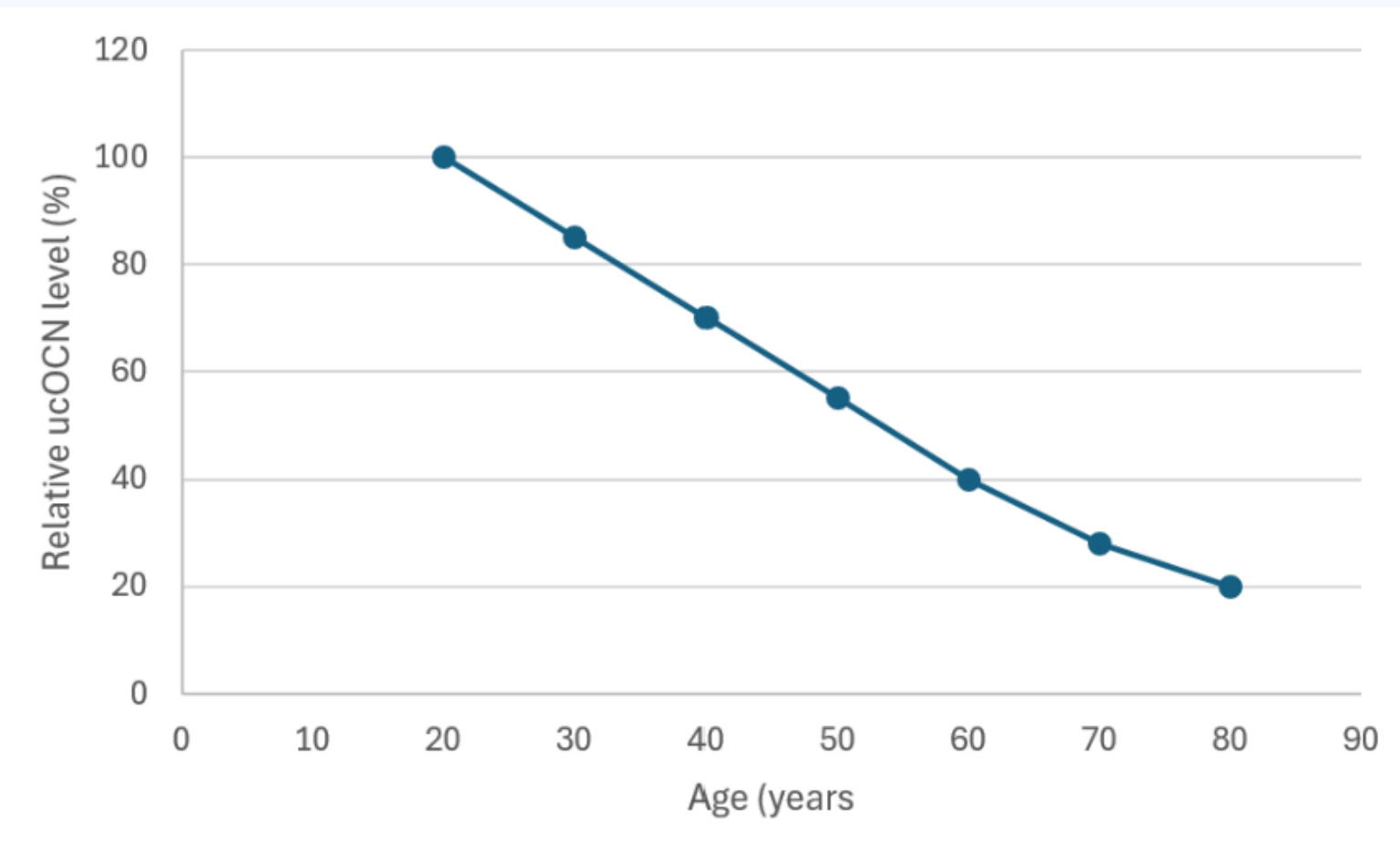


Figure 5: Conceptual illustration of age-related decline in circulating ucOCN levels.

⚠ Limitations:

- 🧪 High ucOCN doses may not be achievable in vivo
- ⌚ ucOCN has a short half-life
- 🐭 Mouse models don’t fully mimic human PD

🔗 Future Work:

- 🔗 Explore GPR158, PI3K/Akt and related signalling routes
- 🧬 Test ucOCN effects in human iPSC-derived DA neurons
- 🧪 Explore delivery strategies to extend ucOCN’s half-life

Conclusion

This study suggests that age-related declines in ucOCN may increase DA neuron vulnerability in PD. Our predicted results indicate that ucOCN helps maintain neurite structure and microtubule stability under α -syn-induced stress, highlighting its role in early neuronal protection. Overall, ucOCN may serve as a useful biomarker for age-related susceptibility and a potential target for future therapeutic strategies.

References

1. Parkinson’s Foundation. Statistics on Parkinson’s disease in the United States. 2026. Available from: www.parkinson.org/understanding-parkinsons/statistics



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