Modelling Parkinson's disease in the retina

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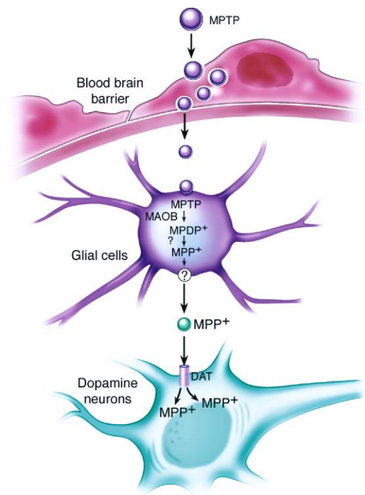
Introduction

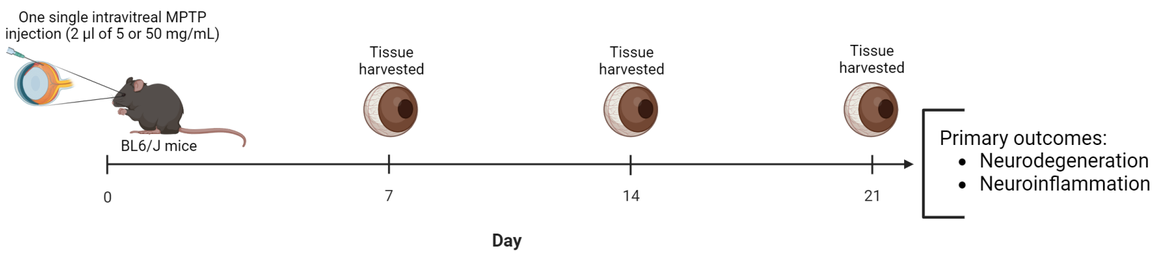
- **Parkinson's disease** (PD) is a neurodegenerative disease in which symptoms include rigidity, bradykinesia and tremor.
- **PD is hard to research** because only post-mortem human brains are available, and animal models have a severe phenotype.
- **PD has a retinal phenotype** characterised in mice by loss of visual function, retinal thinning, loss of dopaminergic amacrine cells, neuroinflammation and metabolic dysfunction[1].
- By **intravitreally injecting MPTP,** we aimed to produce a **retina-specific model of PD in mice.**

MPTP

- **Neurotoxin** specifically targeting dopaminergic neurons.
- Crosses the **blood-brain-barrier**.
- Metabolised by **glia** to toxic **MPP+** the **enzyme MAOB**.
- Taken up by **dopaminergic neurons** through the **dopamine transporter**.
- MPP+ inhibits the **mitochondrial Complex I**, resulting in the death of dopaminergic neurons[2].

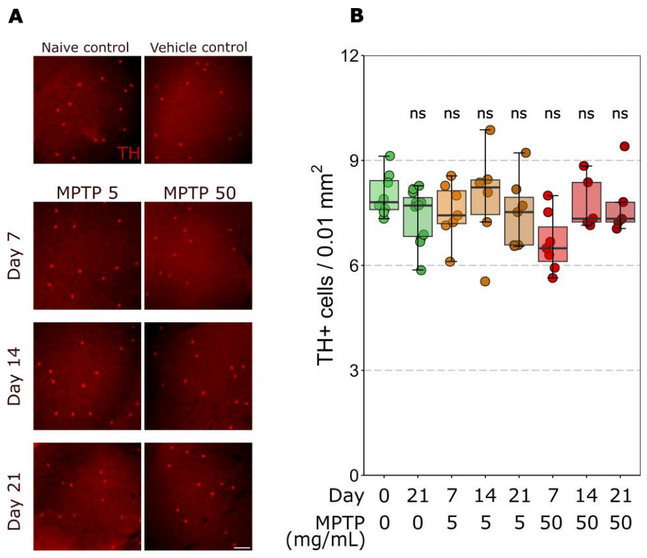


Experiment set-up

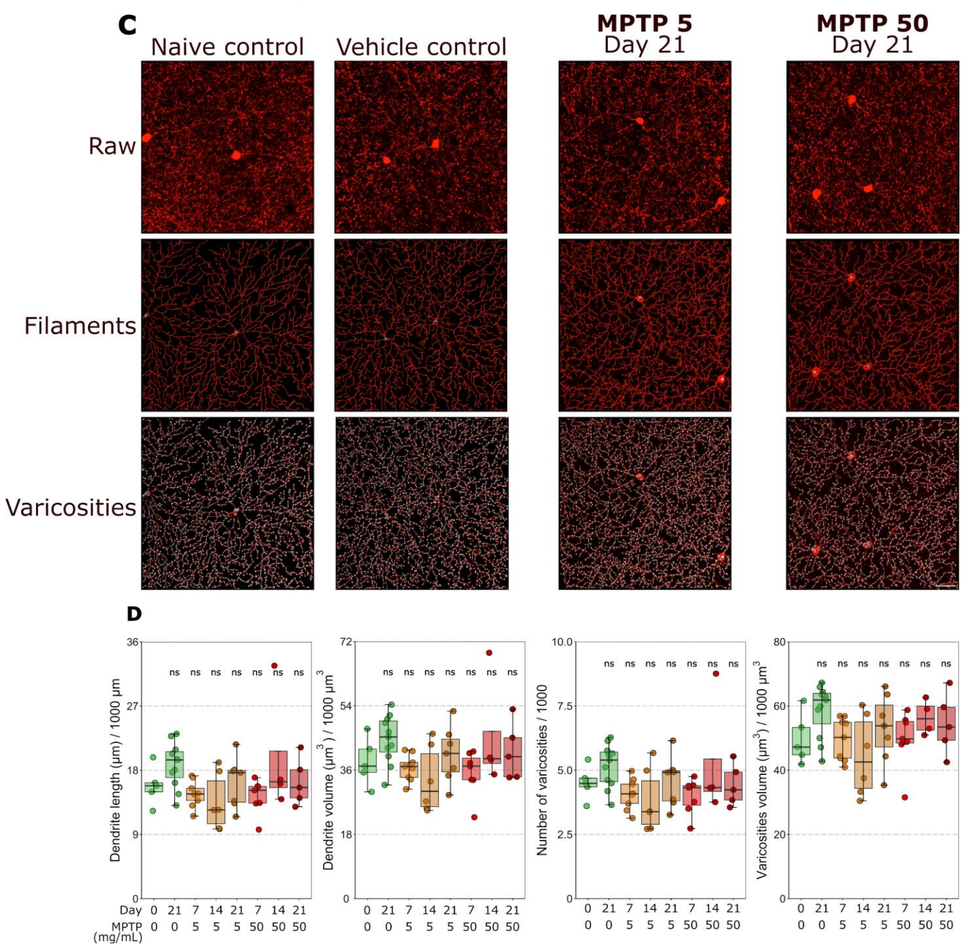


Results

Dopaminergic neurons are the primary affected cell type in PD. In the retina, a subset of **amacrine cells**, **tyrosine hydroxylase (TH) positive**, are dopaminergic. After MPTP injections we fluorescently labelled TH, (A, C) to investigate whether the **number of TH+ cell somas** (B) or the **integrity of TH+ dendrites** (D) was affected.

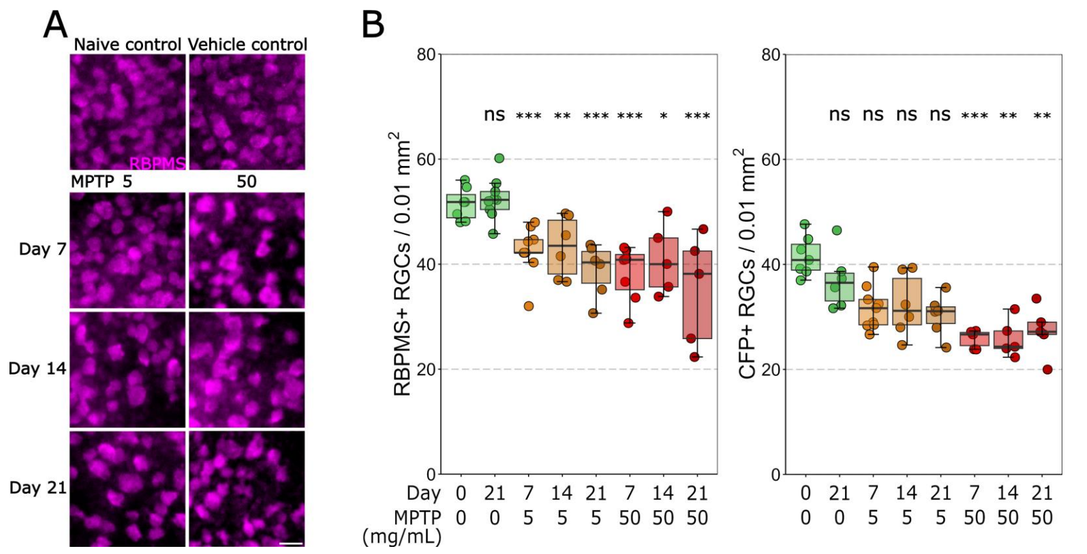


Intravitreal MPTP injection did not lead to death of TH+ amacrine cells.



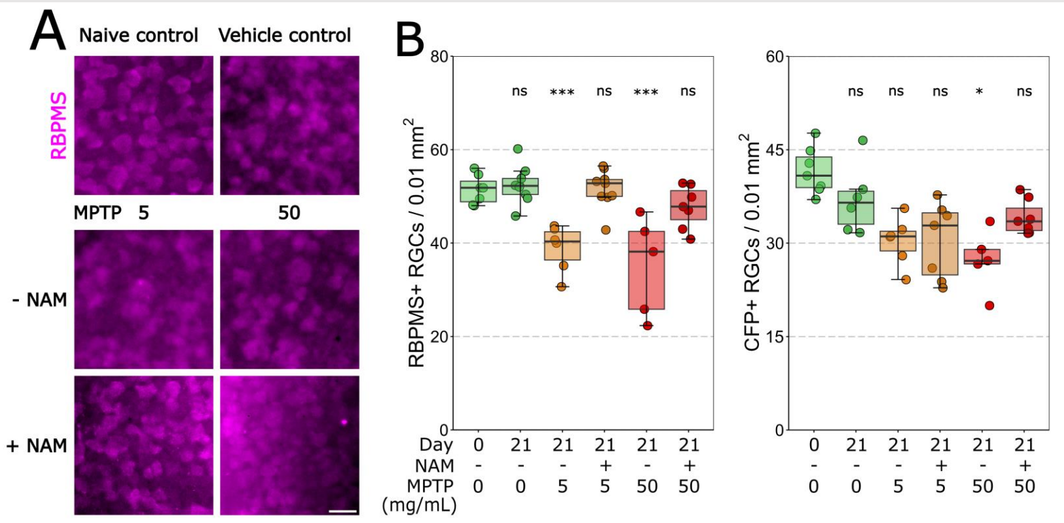
Intravitreal MPTP injection did not affect the integrity of TH+ dendrites.

MPTP targets dopaminergic neurons by blocking **mitochondrial Complex I**. Since **retinal ganglion cells** (RGCs) are specifically metabolically vulnerable[3], we fluorescently labelled the **RGC marker RBPMS** (A) to assess the effects of MPTP on the **number of RGCs** (B).



Intravitreal injection of MPTP results in a significant death of RGCs compared to naive controls.

Our group has established a **neuroprotective role for nicotinamide** (NAM) in glaucoma animal models[4]. To assess whether NAM would have the same effect on RGCs in this intravitreal MPTP model, we **added NAM to the drinking water of mice one week before MPTP injection**. We then assessed the **number of RGCs** again by RBPMS labelling.

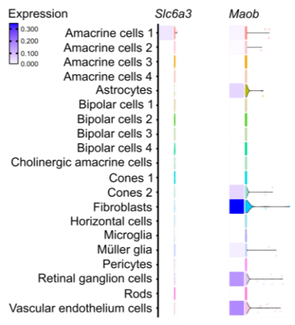


Treatment with NAM prevents RGC death following MPTP injection.

Discussion

Why are RGCs affected by MPTP, and not dopaminergic amacrine cells?

RGCs express *Maob*, allowing RGCs to directly metabolise MPTP to MPP+. The concentration of MPP+ that reaches the dopaminergic amacrine cells is too low to cause cell stress.



Conclusion

- The intravitreal injection of MPTP does not result in a perfect replication of the retinal PD phenotype.
- However, the observed degeneration of RGCs makes this model a **useful tool to study RGC degeneration and mitochondrial dysfunction**. Therapies such as the shown NAM treatment could be tested in this model.

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