Exploring the Vulnerability of Myelination of GABAergic Interneuron Axons in the Hippocampus in a Mouse Model of Alzheimer's Disease.

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Introduction

- **Alzheimer's disease (AD):** a neurodegenerative disease that causes cognitive decline and death characterized by amyloid-β plaques & neurofibrillary tangles containing hyperphosphorylated tau[1].
- **Observed phenotype in AD models and patients**: Neuronal hyperexcitability in excitatory pyramidal neurons due to deficit of inhibitory synaptic transmission.
- **Animals used:** APP/PS1 mice, a model of amyloidopathy, display an early decrease in inhibitory, but not excitatory neurotransmission in the hippocampus during pre-plaque pathology[2].

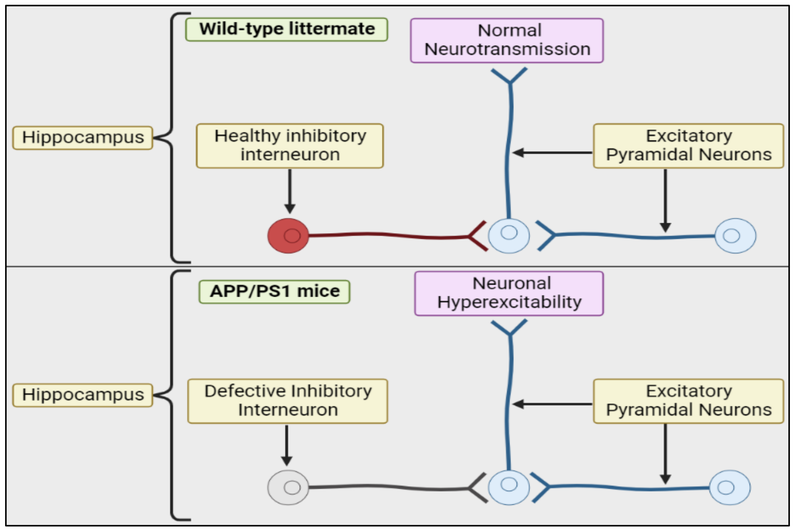

Figure 1: *Neurotransmission in the hippocampus in APP/PS1 and wild-type littermate mice. Inhibitory interneurons have impaired function in AD animal models and patients.*

Hypothesis & Aim

Hypothesis: The deficit of inhibitory synaptic transmission onto excitatory pyramidal neurons observed in the model of APP/PAS1 is due to demyelination of GABAergic inhibitory neurons, which in turn impair inhibitory synaptic transmission in the hippocampus.

Aim: To quantify co-localization of the myelin marker MBP and parvalbumin, to reveal myelination properties of parvalbumin-positive inhibitory interneurons of old (6-10 months) APP/PS1 mice compared to wild-type littermates.

Methods

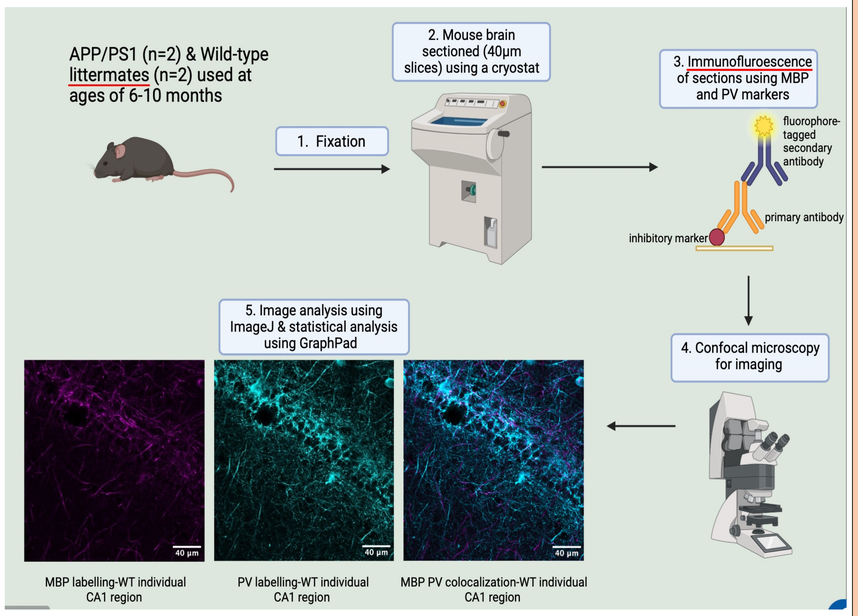

Figure 2: *Overall project workflow. Step 1 was carried out before this project started. 40µm sections were used for detecting myelination properties and colocalization of myelin protein marker (MBP) and parvalbumin (PV) in the CA1 region (cell body layer and dendritic area separately) and in the dentate gyrus.*

Method steps

1. **Fixation of mouse brain tissue (done before project started)**
2. **Cryosectioning of brain slices.** 40µm sagittal slices were used for further steps.
3. **Immunohistochemistry labelling of slices.** Slices were incubated with primary antibody (Myelin protein marker and parvalbumin marker simultaneously) first and secondary antibody after, specific to each primary antibody.
4. **Imaging using confocal microscopy.** Localization of the hippocampal areas of interest (CA1 dendritic and cell body layers, and dentate gyrus)
5. **Quantification of each marker and their colocalization using ImageJ.** The percentage of positive area was quantified for the CA1 cell body and dendritic layers separately, and for the dentate gyrus for comparison.
6. **Statistical analysis and interpretation of results using GraphPad Prism.**

Results

Image Analysis of PV

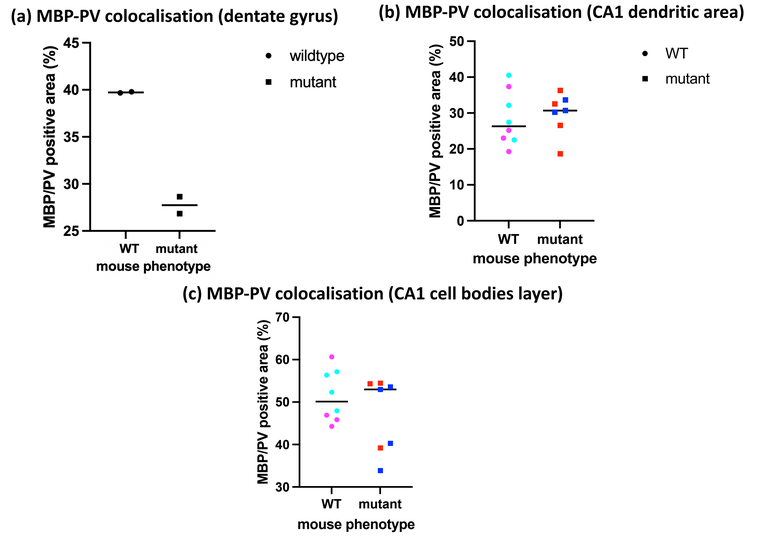

Figure 4: *Graphs representing the analysis of MBP and PV colocalization in the (a) dentate gyrus (b) CA1 dendritic area and (c) CA1 cell body layer. The x axis represents the 2 mouse phenotypes that were analysed (wildtype being the control). The y axis represents the % of positive area in the image in which MBP and PV were colocalised. A significant difference was found in (a) but not in (b) nor (c).*

Conclusion & Future Directions

- Successful labelling of parvalbumin and myelin protein marker was achieved.
- A significant difference between the colocalization of parvalbumin and myelin protein marker between wildtype and mutant individuals was not observed in the CA1, but was observed in the dentate gyrus (to be confirmed with more replicates). Further experiments with young individuals (2-3 months), and other areas such as the CA3 will be performed and analysed in the future.

Acknowledgements

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References

1. van der Kant *et al.,* 2020. *Nat Rev Neurosci* 21: 21-35.
2. Unpublished data from Dr Jian Gan's lab.