DEPLETION OF sAPPα AS A PRIMARY TOXIC EVENT IN ALZHEIMER'S DISEASE MODELS

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1. Alzheimer's disease (AD)

AD is the leading form of dementia

Causes progressive decline in memory and cognition, leading to death

700,000 informal carers in the UK [1]. **63.5%** claim to not have enough support

Costs the UK **£34.7 billion** per year, projected to increase to **£94.1 billion** by 2040 [2]

It is the only condition in the top 10 causes of death without a treatment to prevent, cure or slow its progression.

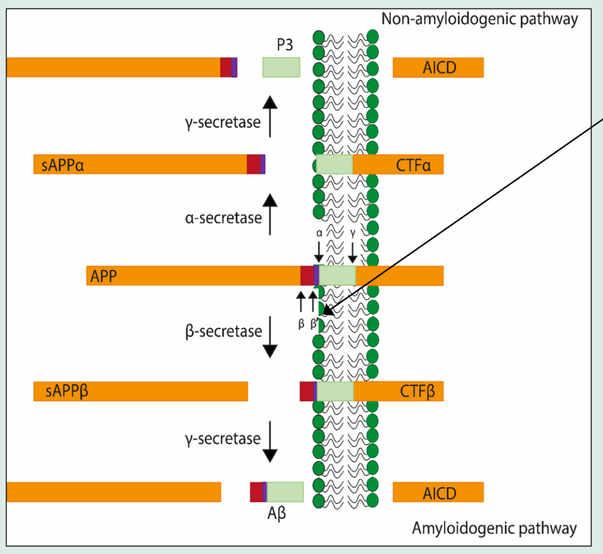
2. Introduction

- One hallmark observed in the brain of AD patients is amyloid plaques which contain toxic amyloid-β peptides derived from the larger Amyloid Precursor Protein (APP).
- **The good:**

APP can be cut by enzymes called α-secretases within its Aβ region. This prevents the formation of toxic Aβ-peptides and produces a beneficial protective fragment called sAPPα [3].

- **The bad and the ugly:**

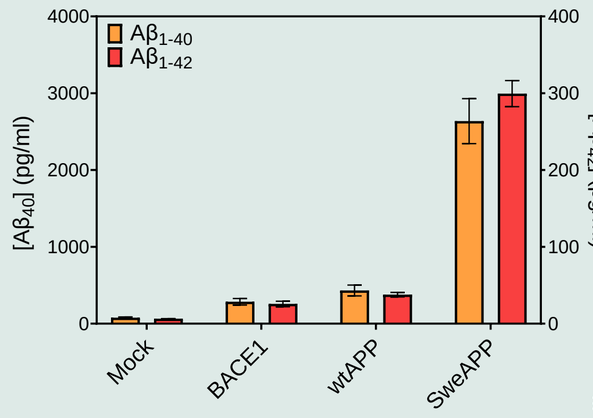
Aβ-peptides are snipped out of APP by two enzymes called β-secretase (or BACE1) and γ-secretase.



3. Our project

- We used **four versions** of human neuroblastoma cells (a cell model of AD):
  - Mock (no increased levels of protein)
  - Increased levels of BACE1
  - Increased levels of APP
  - Increased levels of mutant APP (SweAPP, associated with genetic form of AD)
- We were originally investigating the hypothesis that Aβ-peptides would cause toxicity (decreased viability) in these cells.
- **However**, we noticed that, although three of the cell lines had elevated Aβ-peptide levels, only one had decreased viability.

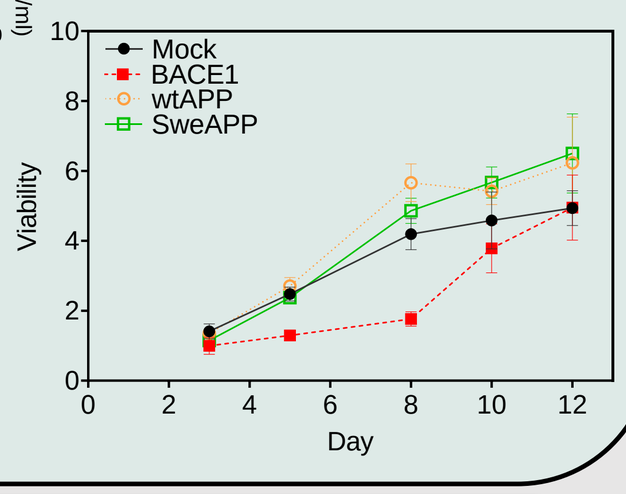
4. Cell viability lacks correlation with Aβ-peptide levels



BACE1, APP and SweAPP all had increased Aβ-peptide levels.

However:

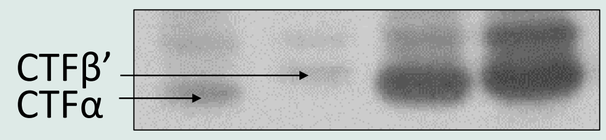
Only BACE1 cells exhibited a decrease in viability relative to Mock (normal) cells.

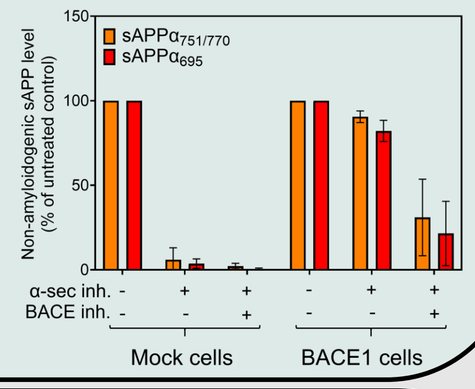


5. sAPPα is replaced by β' cleavage in BACE1 cells

- In BACE1 cells, CTFα (a fragment produced alongside sAPPα) was entirely replaced by a slightly larger fragment, CTFβ':
- CTFβ' (and therefore sAPPβ') is formed when BACE1 cuts APP at a different site to the one that forms Aβ-peptide.
- Inhibiting α-secretase in BACE1 cells didn't reduce sAPP production, however inhibiting BACE1 did.

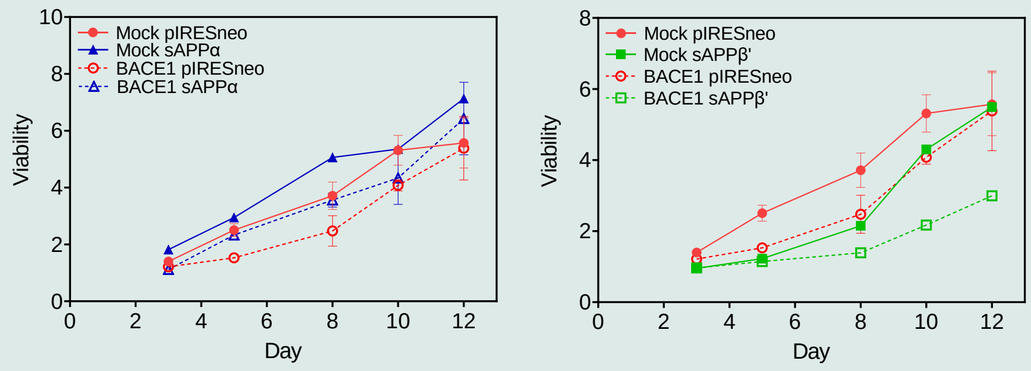
These findings suggest that sAPPα is lost in BACE1 cells in lieu of sAPPβ'.





6. sAPPα restores viability in BACE1 cells

We repeated analysis of viability in mock and BACE1 cells also containing sAPPα and sAPPβ':



sAPPα increased viability of mock and BACE1 cells whilst sAPPβ' decreased viability.

7. Conclusions

- Many experimental treatments aimed at reducing the accumulation of Aβ-peptide have entered clinical trials and failed.
- Our research suggests that the toxic event in the AD models used is either sAPPα depletion and/or an increased ratio of sAPPβ' to sAPPα.
- This may provide evidence for increasing sAPPα, as opposed to (or in addition to) reducing Aβ-peptides, to potentially treat AD.
- We are currently developing a system to increase levels of sAPPα in a brain-specific and reversible manner.

References

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[3] Tan VTY, Mockett BG, Ohline SM, Parfitt KD, Wicky HE, Peppercorn K, et al. Lentivirus-mediated expression of human secreted amyloid precursor protein-alpha prevents development of memory and plasticity deficits in a mouse model of Alzheimer's disease. Molecular Brain. 2018;11(1):7.

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Defying Dementia

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