Alzheimer’s disease (AD) is a progressive, neurodegenerative disorder that affects over 35 million people and leads to a severe loss of mental function. The cause of AD is unclear. However, research has revealed that the disease is characterized by the accumulation of amyloid beta (Aβ), a protein that can form toxic oligomers. While the cause of the accumulation of Aβ is not known, the “amyloid hypothesis” suggests it is due to an imbalance between Aβ production and clearance. Further evidence suggests that transport across the blood-brain barrier may have an important role in the observed reduced clearance of Aβ.

Recently, it has been suggested that P-glycoprotein (Pgp) is involved in the clearance of Aβ from the brain. Pgp is a membrane protein that has a protective role in the body, as it is expressed at barriers like the intestine, and also effluxes many xenobiotics. Pgp is highly expressed at the luminal (blood) side of the blood-brain barrier. There, it extrudes substances from the brain to the blood, including toxins. In this way, Pgp plays an important role in protecting the brain.

Studies have provided evidence that Pgp may clear Aβ from the brain to the blood. One study showed lower Aβ accumulation with higher Pgp expression. Available data suggests that Pgp is involved in the clearance of Aβ, and thus may be a significant factor in AD.

INTRODUCTION

METHODS

RESULTS

CONCLUSIONS

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We were able to successfully express mouse P-glycoprotein in yeast and purify the protein using various techniques. We also obtained crystals in conditions where Pgp was incubated with Aβ. We will verify if the crystals that appeared in these conditions are Pgp-Aβ co-crystals. If Aβ is present, we will obtain x-ray diffraction data towards generating a structural model of the Aβ-Pgp interaction. The structure would show how Pgp interacts with Aβ at the atomic level. Furthermore, this structure would show if any conformational changes occur, and with which residues in the drug-binding pocket Aβ interacts. The ultimate goal is using the co-crystal structure in order to further characterize Pgp-mediated transport of Aβ, which is a promising target in Alzheimer’s disease.

REFERENCES