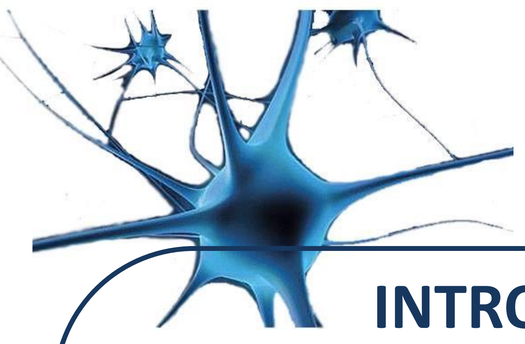
Astrocytes influence on the Aβ pathogenesis of the Alzheimer Disease drived by ApoE



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INTRODUCTION

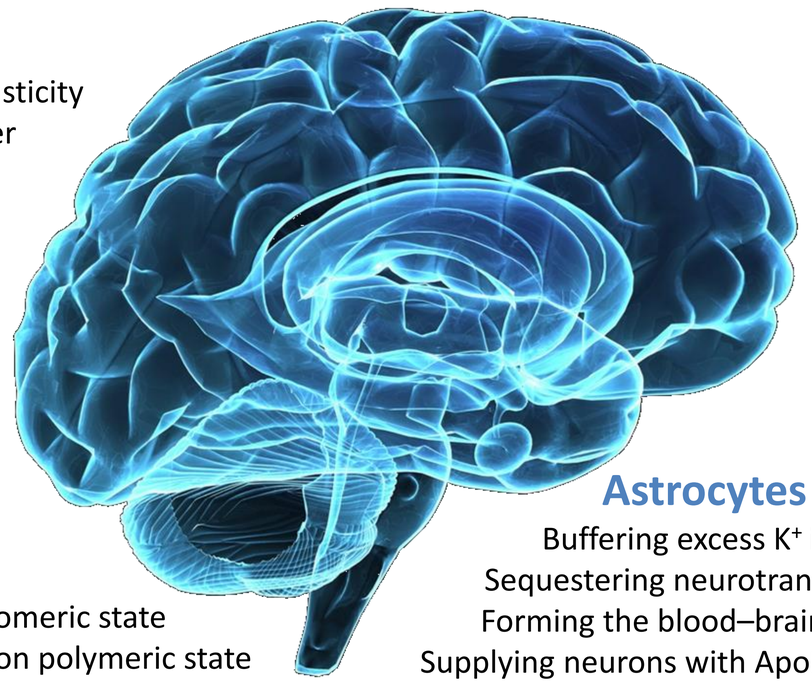
The **Alzheimer Disease** is the most frequent cause of dementia in the elderly. Is caused by the loss of specific neuronal circuits in the neocortex, hippocampus, and basal forebrain cholinergic system. The neurodegeneration is consequence of **β-amyloid** (Aβ) peptides accumulation. Individuals who inherit the **ApoE4** allele have a 16-fold increased risk of developing the disease. **Astrocytes** accumulate and degrade substantial amounts of Aβ and undergo astrogliosis.

OBJECTIVES

- Explain the physiological roles of ApoE, Aβ and astrocytes in the central nervous system.
- Describe the different proposed ways by which ApoE drive the Aβ pathogenesis and determine how this is influenced by astrocytes.
- Describe an AD treatment based on astrocytes.

PHYSIOLOGICAL ROLES

ApoE
Facilitates synaptic plasticity
Cholesterol carrier



Aβ
Antioxidant on monomeric state
Neurodegenerative on polymeric state

Astrocytes
Buffering excess K^+ ions
Sequestering neurotransmitters
Forming the blood–brain barrier
Supplying neurons with ApoE and lactate

HOW DOES APOE INFLUENCE ON Aβ AGGREGATION?

ApoE **competes** with Aβ for the same cellular clearance pathway with **minimal interaction**

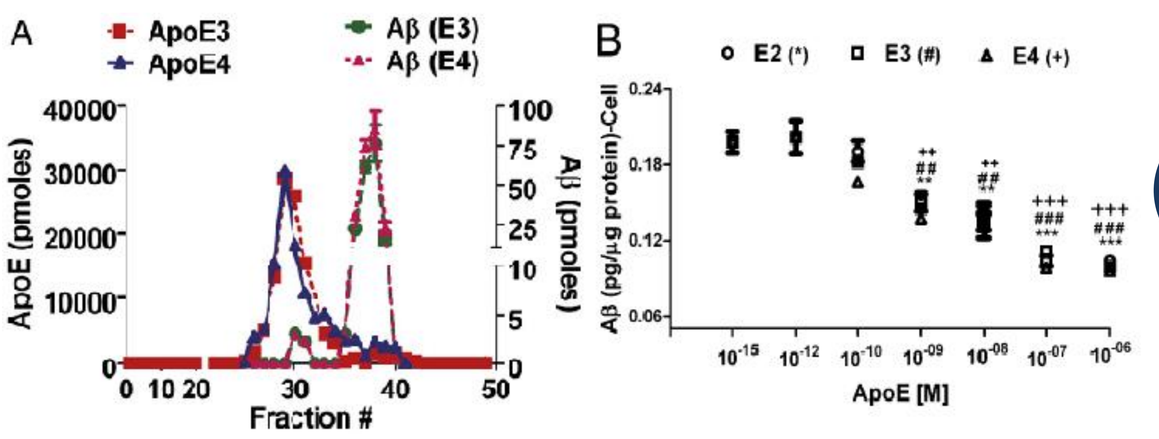


Fig. 1. (A) SEC performance to human APOE e3/e3 and APOE e4/e4 CSF previously incubated with Aβ peptide shows minimal ApoE/Aβ association **(B)** Cellular Aβ quatification of ApoE-KO astrocytes under growing concentrations of the three ApoE isoforms shows that ApoE particles significantly inhibit the cellular clearance of Aβ by astrocytes.

The ApoE/Aβ **binding facilitates** Aβ intraneuronal accumulation and reduces Aβ degradation

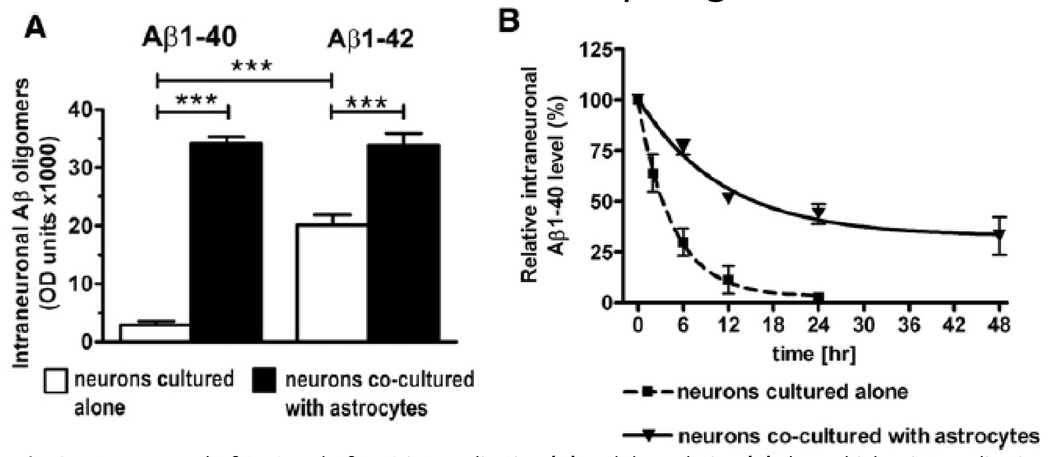
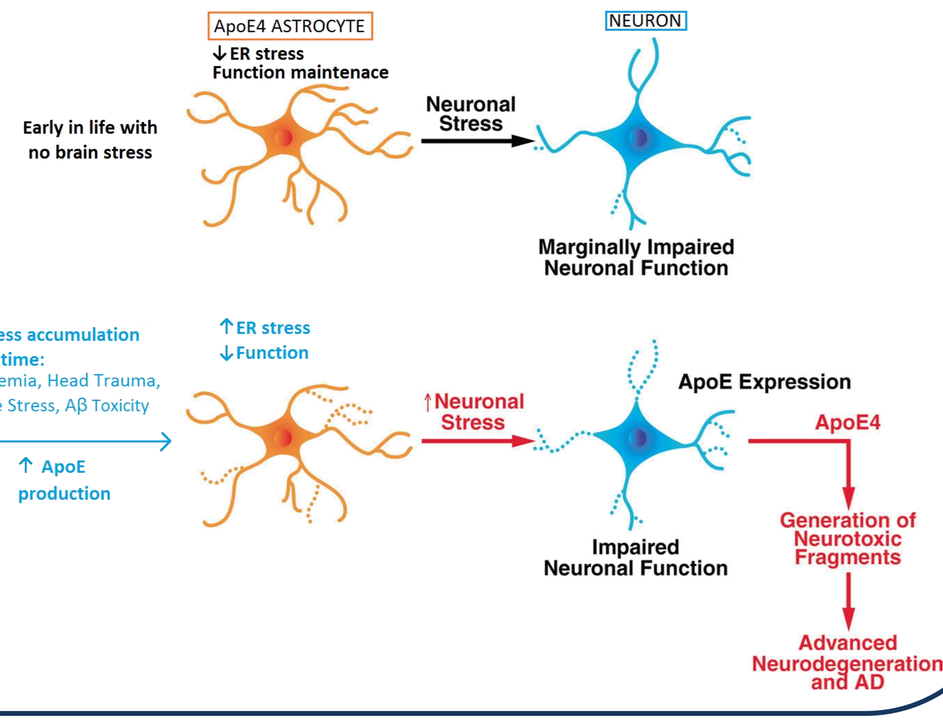


Fig. 2. Intraneuronal Aβ1-40 and Aβ1-42 internalization **(A)** and degradation **(B)** shows higher internalization levels and a reduced Aβ clearance rate of neurons co-cultured with astrocytes. Neurons co-cultured with astrocytes are in presence of ApoE, while neurones cultured alone not.

APOE4 DOMAIN INTERACTION IMPAIRS ASTROCYTE FUNCTION

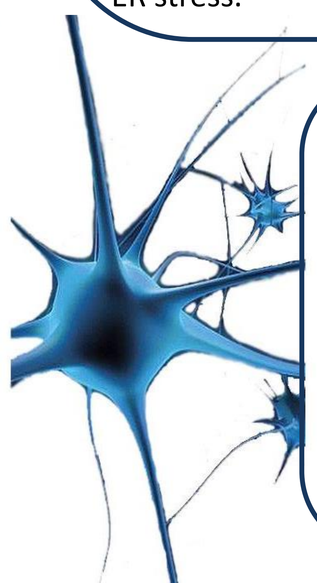
ApoE4 isoform can be structural distinguished from ApoE2 and ApoE3 by the **domain interaction**:

- In the absence of brain stress, **early in life**, ApoE4 domain interaction exert a **low** level of **ER stress** response on astrocytes. Thus, young astrocytes can support neuronal function.
- Effects of stress accumulate **over time** causing neuronal damage, and astrocytes express additional ApoE4 domain interaction increasing the ER stress. **Astrocyte support** of neurons becomes **less effective** and stressed neurons begin to express ApoE4 and try to support themselves. In consequence, neurons become more susceptible to neurodegeneration.



THERAPY

Reduction of the interaction domain levels by converting the ApoE4 to an ApoE3 like particle, summed to an inhibition of the unfolded protein response pathways to reduce the ER stress.



CONCLUSIONS

- The physiological function of Aβ and ApoE within the brain is unclear.
- Despite the great investigation done, it remains to be elucidated the mechanism involved in Aβ plaque formation and which role has ApoE.
- Alzheimer Disease neurodegeneration could be consequence of atrocyte disfunction.
- Further investigation aimed to discover the cause of Alzheimer Disease, must consider astrocytes role.
- Astrocytes are a good target for Alzheimer Disease treatment.

REFERENCES

Fig.1 Verghese, P. B. *et al.* ApoE influences amyloid-β (Aβ) clearance despite minimal apoE/Aβ association in physiological conditions. *Proc. Natl. Acad. Sci. U. S. A.* **110,** E1807–16 (2013).

Fig.2 Kuszczyk, M. a. *et al.* Blocking the interaction between apolipoprotein e and Aβ reduces intraneuronal accumulation of Aβ and inhibits synaptic degeneration. *Am. J. Pathol.* **182,** 1750–1768 (2013).

Fig. 3. Zhong, N., Ramaswamy, G. & Weisgraber, K. H. Apolipoprotein E4 domain interaction induces endoplasmic reticulum stress and impairs astrocyte function. *J. Biol. Chem.* **284,** 27273–80 (2009).