ASTROCYTES AND ALZHEIMER'S DISEASE: THE AMYLOID-β CLEARANCE

Sara Compte Sancerni
Degree in Biochemistry
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Universitat Autònoma de Barcelona

INTRODUCTION

- **Alzheimer's disease** (AD) is a neurodegenerative disorder, being considered the most prevalent cause of dementia leading to cognition decline.
- One of the major neuropathological hallmarks of Alzheimer's disease include the extracellular accumulation of **amyloid-β** (Aβ) in the brain.
- The amyloid hypothesis states that Aβ accumulation could result in alterations in synaptic functions and other molecular and cellular events that lead to neuronal degeneration responsible for the cognitive deficits in AD.
- **Astrocytes** are the major cell type in the SNC that maintain brain homeostasis. They have been considered important mediators of Aβ clearance helping to maintain a balance between its production and clearance.

OBJECTIVES

- Understanding the role of astrocytes in Aβ clearance.
- Knowing which mechanisms are involved in Aβ uptake by astrocytic cells.
- Analyzing which molecules participate in Aβ internalization and are important in this process.
- Describing the influence of apolipoprotein E in Aβ clearance, which is known to affect in Alzheimer's disease.
- Considering if Aβ internalization causes alterations of astrocytic metabolism and has consequences in neuronal viability.
- Contemplating astrocytes as a possible target in Alzheimer's disease therapy.

ASTROCYTES IN Aβ CLEARANCE

- Although it was thought that astrocytes are attracted by amyloid plaques through chemoattractant molecules, recent studies show that astrocytes do not migrate to Aβ [1,2].
- Studies *in vivo* and *in situ* in adult mouse astrocyte demonstrate that they can take up and degrade $A\beta_{1-42}$ (*Figure 1).*
- Experiments with primary human astrocytes also show Aβ internalization *in vitro* [4].
- It is suggested that size and aggregation state of Aβ is important in Aβ clearance, where oligomers are taken up more easily than larger fibrillar forms [4, 5].

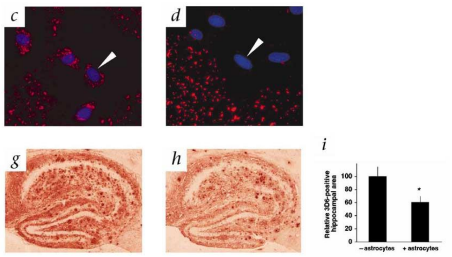

Figure 1: Adult mouse astrocytes cultivated on Cy3-$A\beta_{1-42}$ for 24h (c) and 48h (d). Red, Cy3-$A\beta_{1-42}$ signal; Blue, nuclei stained with DAPI. (i) Decrease of Aβ-immunostained with 3D6 antibody in hippocampal area of mouse expressing human APP, after incubation without (g) or with adult astrocytes during 24h (h) [4].

Mechanisms and molecules

- Macropinocitosis and endocitosis clathrin-dependent has been proposed as an important mechanism involved in Aβ clearance by astrocytes [3].
- Several studies suggest that *scavenger* receptors and LDL receptor (LDLR) family participate in Aβ internalization [4,3].
- In particular, it has been demonstrated that low-density lipoprotein receptor protein 1 (LRP-1) play a major role in Aβ uptake [4].

INFLUENCE OF APOE

- ApoE is a lipoprotein that mediates the transport and delivery of cholesterol and other lipids.
- It has been shown that ApoE influences Aβ metabolism in the brain, although the mechanism remains unclear [4,5]:
  - Some studies suggest that it facilitates Aβ clearance.
  - Recent studies indicate that ApoE influences this process by competing for the same receptors and clearance pathways within the brain.
- It is thought that these controversies depend on (1) ApoE concentrations; (2) ApoE isoform and lipidation state; (3) Aβ aggregation form; and (4) expression pattern of the receptors on astrocyte surface.

ASTROCYTE METABOLISM AND NEURONAL VIABILITY

- In experiments *in vitro* it has been proposed that Aβ accumulation inside mouse astrocytes can cause disruption of their metabolism, such as increasing glucose utilization and stimulating reactive oxygen species production [1].
- This effects demonstrated to have consequences and end with loss of neuronal viability.
- However, more studies are needed to understand the mechanisms of astrocytes metabolic dysfunction in front of Aβ effects.

CONCLUSIONS

Astrocytes have an important role in Aβ clearance by taking up and degrading Aβ peptides in the brain. If Aβ uptake breaks down could lead in an increase and aggregation of amyloid plaques. For this reason, they are being studied as a possible target for new therapeutic strategies in Alzheimer's disease. However, further studies are needed in order to know exactly the mechanisms and molecules involved, as well as the consequences in astrocytes metabolism and function.

References

[1] Allaman I, Gavillet M, Bélanger M, Laroche T, Viertl D, Lashuel HA and Magistretti PJ. Amyloid-β aggregates cause alterations of astrocytic metabolic phenotype: Impact on neuronal viability. *J Neurosci.* 2010; 30: 3326-3338

[2] Galea E, Morrison W, Hudry E, Arbel-Ornath M, Bacskai BJ, Gómez-Isla T, Stanley HE and Hyman BT. Topological analyses in APP/PS1 mice reveal that astrocytes do not migrate to amyloid-β plaques. *Proc Natl Acad Sci USA.* 2015; 112: 15556-61

[3] Lee SK, Seo BR and Koh JY. Metallothionein-3 modulates the amyloid β endocytosis of astrocytes through its effects on actin polymerization. *Mol Brain.* 2015; 8:84

[4] Mulder SD, Nielsen HM, Blankenstein MA, Eikelenboom P and Veerhuis R. Apolipoproteins E and J interfere with Amyloid-beta uptake by primary human astrocytes and microglia *in vitro*. *Glia.* 2014; 62: 493-503

[5] Nielsen HM, Veerhuis R, Holmqvist B and Janciauskiene S. Binding and uptake of Aβ1-42 by primary human astrocytes *in vitro*. *Glia.* 2009; 57: 978-988

[6] Wyss-Coray T, Loike JD, Brionne TC, Lu E, Anankov R, Yan F, Silverstein SC and Husemann J. Adult mouse astrocytes degrade amloid-β *in vitro* and *in situ*. *Nat Med*. 2003; 9: 453-457