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 Aβ [3], (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 [3,5].

Mechanisms and molecules

- Macropinocytosis and endocytosis clathrin-dependent has been proposed as an important mechanism involved in Aβ clearance by astrocytes [5].
- Several studies suggest that scavenger receptors and LDL receptor (LDLR) family participate in Aβ internalization [4,5].

In particular, it has been demonstrated that low-density lipoprotein receptor protein 1 (LRP-1) play a major role in Aβ uptake [6].

ASTROCYTE METABOLISM AND NEURONAL VIABILITY

- In experiments in vitro it has been proposed that Aβ accumulation inside mouse brains 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 astrocytic metabolic dysfunction in front of Aβ effects.

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 [6,8]:
  - 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.

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

[3] van HL, van RL and Heyn H. Macrophagocytosis regulates the amyloid β-endocytosis of astrocytes through its effects on actin polymerization. Mol Brain. 2011; 84