Introduction

Alzheimer’s Disease (AD) is a degenerative disease characterized by loss of cognitive function, representing the most common cause of dementia in the elderly.

- Aβ is formed by secretase cleavage from its precursor (APP). Its accumulation is supposed to trigger the other events in AD.
- Glial response to Aβ could lead to:
  - A pro-inflammatory state, detrimental for the disease.
  - Struggle to maintain brain homeostasis.
- The aim of this work is to carry out a review in which:
  1. Microglial response to Aβ is studied.
  2. Effects of pro-inflammatory interleukin-1β (IL-1β) are reviewed.
  3. Treatments targeting neuroinflammation are mentioned.

Methods

- Scientific literature search on PubMed database: using as keywords Microglia + Alzheimer’s Disease + IL-1β or derived combinations. Articles cited in articles or reviews were also consulted. Papers were sorted by relevance.

Results

1. Microglial response to Aβ

- Microglia are essential glial cells for brain homeostasis. They can be found around Aβ (Fig 2) and are able to recognize and phagocyte it. The exact receptors involved in the process are still in debate.
- They can have different activated phenotypes, being able to secrete both anti- and pro-inflammatory proteins (such as IL-1β) depending on the context. Mechanisms driving each type of activation are poorly understood.
- The NOD-, UNR- and pyrin domain-containing 3 (NLRP3) inflammasome is required for caspase-1 activation, which leads to maturation of pro-IL-1β to IL-1β. It can be assembled in microglia after exposure to Aβ, but the precise mechanisms are also still discussed.

2. IL-1β effects

- Besides its debatable role in Aβ accumulation, IL-1β has other effects that could increase neurodegeneration.
- IL-1β can inhibit brain-derived neurotrophic factor (BDNF) signaling, impairing spine formation and synaptic plasticity.
- It can also activate kinases that will phosphorylate protein tau. This precedes formation of NFT and neuronal dysfunction.
- Moreover, it can increase inducible Nitric Oxide Synthase (NOS) levels, enhancing Nitric Oxide production. This also increases oxidative stress, propitiating neurotoxicity.
- In addition, it can induce S100P production in astrocytes. This protein can further increase NFT formation, neurodegeneration and oxidative stress.

- Finally, it can activate its own expression, creating a neurodegenerative cycle, as summarized in the scheme (Fig 4).

3. Treatment approaches

- Peptides that shift microglial activation towards an anti-inflammatory cycle have been tried, but was less effective than expected.
- Treatment with non-steroidal anti-inflammatory drugs has also been tried, and improve cognitive deficits.
- Anti-IL-1 antibodies decreased IL-1β signaling and improved cognitive behavior in AD mouse models.
- Aβ immunization showed similar results.
- Application in patients is controversial due to possible side effects.

- Calorie restriction (CR) in rats has been shown to decrease IL-1β levels and improve cognitive deficits.
- CR can also decrease pro-inflammatory cytokines in AD mouse models, and to reduce the levels of pTau.

Conclusions

- Glial cells are actively implicated in the pathogenesis of AD. Precise mechanisms are still unclear, but it is now accepted that microglia becomes activated after Aβ exposure, they can both promote and secrete proinflammatory proteins in response.
- Initial function of IL-1β is still in debate while other, negative effects for AD pathogenesis are in a more general agreement.
- Consensus is needed in the models used: when carried out in different models and IL-1β treatment conditions, studies generate controversial results. Drawing conclusions would be easier if studies were carried out in equal conditions and results were reproduced.
- More in vivo experiments are lacking to deeply study if IL-1β effects, where involvement of other cytokines may interfere.
- New treatments trying to reduce overall neuroinflammation are being studied. Translation into applications for real patients must be regarded carefully due to possible adverse effects.

References