Big Hope from Small Particles: Challenges in Alzheimer's Disease

Houshang Amiri[1,2], Morteza Mahmoudi[3], Valerio Zerbi[1,4], and Arend Heerschap[1]

[1]Department of Radiology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Department of Tumor Immunology, Nijmegen Centre for Molecular Life Sciences, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [3]National Cell Bank, Pasteur Institute of Iran, Tehran, Iran, [4]Department of Anatomy, Donders Centre for Neurosciences, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Purpose Giving a comprehensive overview of the current developments in Alzheimer's disease (AD) together with the advances in the nanao-theranostics systems, to detect AD in very early stages, by MRI technique.

Outline

- General background of Alzheimer disease (AD)
- Clinical aspects of AD
- Macroscopic and microscopic changes in AD brain
- Synaptic dysfunction in AD
- The amyloid precursor protein (APP) family of genes
- Intracellular trafficking of APP
- Biological functions of APP
- The etiology of Alzheimer's disease (AD)
- Aβ aggregates and their role in AD
- Multivalent cationic signaling pathways
- The Importance of nanoscience and nanotechnology in AD
- Magnetic nanoparticles (MNPs)
    - MNPs as MRI contrast agent
    - MNPs for molecular imaging of amyloid beta
    - MNPs against amyloid fibrillation
    - MNPs and homeostasis
- Limitations and challenges
- Conclusions

Summary

Alzheimer's disease (AD) is the most common form of dementia. There has been significant progress in defining the main pathology of AD, and whilst understanding of the progression is better understood, the underlying cause of AD remains elusive. One of the most widely accepted characteristic hallmarks of AD is the accumulation/aggregation of insoluble amyloid beta (Aβ) peptides in the brain. These Aβs, are produced in a soluble form from the amyloid precursor protein (APP), and form aggregations of various sizes and levels of solubility. Over time they fibrillise, which is the process by which misfolded (i.e. toxic folding) proteins form large linear aggregates or amyloid. These in turn form insoluble protein fibrils which go on to form senile plaques which contribute to neuronal cell death. Until recently, two of the molecular-hypothesizes believed to explain the pathology of AD are those that include the misfolding of some brain proteins/peptides (e.g. Aβ) and the effects of multivalent cations (e.g. Zn2+, Cu2+, Mn2+, Fe2+, Fe3+, and Al3+), in modulating the formation of plaques and tangles in the brain. During recent decade, nanoscience and nanotechnologies have been widely considered, as promising tolls, for theranosis (diagnosis and therapy) of AD. Due to their ultra-small size, nanoparticles (NPs) have distinct properties compared with the bulk form of the same materials. NPs are recognized also as powerful tools to fight against the AD. For instance, they are capable to inhibit protein fibrillation process, which is a building block of AD. The recent results confirmed that not only the molecular events could cause the fibrillation but also a number of intermediate oligomeric states of different association numbers and structures could interfere with fibrillation process. The use of some useful agents, which have interference effect with these processes, can elucidate the molecular mechanism of fibril formation. It is interesting that some strategies can have therapeutic potential for the treatment of amyloidosis. In this case, NPs can have significant effect on the fibrillation of proteins; for instance, their presence could lead to a shortening of the lag phase for nucleation of the fibrillation process. Targeted drug delivery to the central nervous system (CNS), for the therapeutic advancement of neurodegenerative disorders such as AD, is complicated by restrictive mechanisms imposed at the blood–brain barrier (BBB). To overcome this, there has been a remarkable progress over the past decade in the development of NPs as effective drug delivery systems. NP-based drug delivery systems are pharmacological agents that can be targeted to a specific area of the human body by adding nanoreceptors on their surface. These receptors specifically recognize the target tissue, bind to it, and release the drug molecules. Healthy tissues are not affected due to cytotoxic effects of drugs and drugs can be protected from degradation by encapsulating them with NP coatings. Another challenge is to be able to track such NPs over time by non-invasive techniques, e.g. MRI. In this review different MRI techniques, e.g. ^{19}F MRI, to perform molecular imaging of the NP-based drug delivery systems will be addressed.