Effect of Alzheimer Familial Chromosomal Mutations on the Amyloid Fibril Interaction with Different PET Tracers: Insight from Molecular Modeling Studies.

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Abstract: Alzheimer's disease (AD) is the most common neurodegenerative disorder. Along with an increasing number of elderly worldwide, it poses a great challenge for the society and health care. Although sporadic AD is the common form of AD, 2-3% of the AD cases are expected to be due to mutations in the ? region of the amyloid precursor protein, which is referred to as autosomal dominant AD (ADAD). These mutations may cause changes in the secondary structure of the amyloid ? fibrils and may alter the fibrillization rate leading to changes in the disease development and could also affect the binding to tracers used in diagnosis. In particular, from some recent clinical studies using PET tracers for detection of fibrillar amyloids, it is evident that in ADAD patients with Arctic mutation no amyloid plaque binding can be detected with the (11)C-Pittsburgh Compound B ((11)C-PIB). However, for in vitro conditions, significant binding of (3)H-PIB has been reported for the amyloid fibrils carrying the Arctic mutation. The aim of the present study is to investigate if there is any mutation specific binding of commonly used amyloid tracers, namely, florbetaben, florbetapir, FPIB, AZD4694, and AZD2184, by means of molecular modeling techniques. Other than Arctic, ADAD mutations, such as the Dutch, Italian, Iowa, and Flemish mutations, are considered in this study. We report that all tracers except florbetapir show reduced binding affinity toward amyloid ? fibrils with the Arctic mutation when compared to the native type. Moreover, florbetapir is the only tracer that binds to all mutants with increased affinity when compared to the native fibril. The results obtained from these studies could increase the understanding of the structural changes caused by mutation and concomitant changes in the interaction pattern of the PET tracers with the mutated variants, which in turn can be useful in selecting the appropriate tracers for the purpose of diagnosis as well as for designing new tracers with desirable properties.

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