Novel Indanone Derivatives as Potential Imaging Probes for β-Amyloid Plaques in the brain

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Research question and background

Although great progress towards understanding the disease mechanisms has been made in the last three decades, there remains no cure for AD. Senile plaques (SPs) is one of the main pathological feature of Alzheimer's disease that composed of β-amyloid (Aβ) protein aggregates. Noninvasive detection of SPs is an effective method for the early diagnosis of Alzheimer's disease. In the last few years, some of small molecules have been labeled with 11C, 18F, or 123I, and have been evaluated in PET or SPECT studies in AD patients to test their abilities to detect SPs in vivo (Scheme 1). The most widely studied amyloid probe to date— [11C]PIB—is limited for routine clinical use by the radioactive decay half-life of 11C (20 min). To overcome the limitation, there are now several amyloid probes labeled with 18F (110 min radioactive decay half-life) under clinical development, such as [18F]BAY94-9172, [18F]Florbetapir ([18F]AV- 45), and [18F]3'-F-PIB.

Methods and tissues used

Radioligand competition binding assays with human AD brain homogenates and use of [125I]1 as the radioligand were performed to determine the binding affinities of the synthesized compounds. Fluorescent staining of human AD brain tissue slices was used to visualize the abilities of ligands binding to SPs. The partition coefficients (P) of the two radiolabeled ligands [125I]2i and [125I]2j were measured by conventional octanol/buffer partitioning. All the samples used from NBB were listed below.

Results and conclusion

In in vitro binding studies, compound 2e exhibited a Ki value of 16 nm with a human AD brain homogenate. Although they displayed relatively low affinities for 2i and 2j—with Ki values of 99 and 237 nm, respectively—the SPs in AD brain sections were positively stained by 2j. A method for in situ micro-autoradiography of AD brain was developed in this study and showed clear labeling of SPs by [125I]2i and [125I]2j. Both [125I]2i and [125I]2j had suitable lipophilicities and displayed high initial uptake and rapid clearance from the mouse brains. Furthermore, [125I]2i and [125I]2j were more stable in human brain homogenates than in mouse brain homogenates. These data suggest that such indanone derivatives might represent potential amyloid imaging agents for the detection of SPs in AD.