VIII. 1. 2-(2-[2-Dimethylaminothiazol-5-yl]ethenyl)-6-(2-fluoroethoxy)-benzoxazole: A Novel PET Agent for In Vivo Detection of Dense Amyloid Plaques in Alzheimer’s Disease Patients

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Extensive deposition of dense amyloid fibrils is a characteristic neuropathologic hallmark in Alzheimer’s disease (AD)\textsuperscript{1-3}). Noninvasive detection of these molecules is potentially useful for early and precise detection of patients with AD. This study reports a novel compound, 2-(2-[2-dimethylaminothiazol-5-yl]ethenyl)-6-(2-fluoroethoxy) enzoxazole (BF-227, Fig. 1), for in vivo detection of dense amyloid deposits using PET.

Methods

The binding affinity of BF-227 to amyloid-β (Aβ) fibrils was calculated. The binding property of BF-227 to amyloid plaques was evaluated by neuropathologic staining of AD brain sections. Brain uptake and in vivo binding of BF-227 to Aβ deposits were also evaluated using mice. For clinical evaluation of \textsuperscript{11}C-BF-227 as a PET probe, 11 normal (healthy) subjects and 10 patients with AD participated in this study. Dynamic PET images were obtained for 60 min after administration of \textsuperscript{11}C-BF-227. The regional standardized uptake value (SUV) and the ratio of regional to cerebellar SUV were calculated as an index of \textsuperscript{11}C-BF-227 retention. The regional tracer distribution in AD patients was statistically compared with that of aged normal subjects on a voxel-by-voxel basis\textsuperscript{4}).
Results

BF-227 displayed high binding affinity to synthetic Aβ1-42 fibrils (Ki [inhibition constant], 4.36 ± 1.5 nM). Neuropathologic staining has demonstrated preferential binding of this agent to dense amyloid deposits in AD brain (Fig. 2). Moreover, a biodistribution study of this agent revealed excellent brain uptake and specific labeling of amyloid deposits in transgenic mice. The present clinical PET study using $^{11}$C-BF-227 demonstrated the retention of this tracer in cerebral cortices of AD patients but not in those of normal subjects (Fig. 3). All AD patients were clearly distinguishable from normal individuals using the temporal SUV ratio. Voxel-by-voxel analysis of PET images revealed that cortical BF-227 retention in AD patients is distributed primarily to the posterior association area of the brain and corresponded well with the preferred site for neuritic plaque depositions containing dense Aβ fibrils (Fig. 4).

Conclusion: These findings suggest that BF-227 is a promising PET probe for in vivo detection of dense amyloid deposits in AD patients.

References


Figure 1. Chemical Structure of $^{11}$C-BF-227.
Figure 2. Neuropathologic staining of human brain sections by BF-227. Amyloid plaques are clearly stained with BF-227 in AD temporal brain sections (A). BF-227 staining correlates well with Aβ immunostaining in adjacent sections (B, arrows). Bar = 50 μm.

Figure 3. Mean SUV images between 20 and 40 min after injection of $^{11}$C-BF-227 in aged normal subject (top, 70-y-old woman) and AD patient (bottom, 68-y-old woman). Coregistered MR images are shown below PET images.
Figure 4. Brain regions show significantly elevated SUVs in AD patients compared with data from aged healthy subjects (P < 0.001, uncorrected for multiple comparisons).