Chapter 25
Noninvasive Detection of Misfolded Proteins in the Brain Using [^{11}C]BF-227 PET

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ABSTRACT

Alzheimer's disease (AD) and many other neurodegenerative disorders belong to the family of protein misfolding diseases. These diseases are characterized by the deposition of insoluble protein aggregates containing an enriched β-sheet structure. To evaluate PET amyloid-imaging tracer [^{11}C]BF-227 as an agent for in vivo detection of various kinds of misfolded protein, a [^{11}C]BF-227 PET study was performed in patients with various protein misfolding diseases, including AD, frontotemporal dementia (FTD), dementia with Lewy bodies (DLB), sporadic Creutzfeldt-Jakob disease (sCJD) and Gerstmann-Sträussler-Scheinker disease (GSS). BF-227 binds to β-amyloid fibrils with high affinity. Most of the AD patients showed prominent retention of [^{11}C]BF-227 in the neocortex. In addition, neocortical retention of BF-227 was observed in the subjects with mild cognitive impairment who converted to AD during follow-up. DLB patients had elevated [^{11}C]BF-227 uptake in the neocortex. However, FTD and sCJD patients showed no cortical retention of [^{11}C]BF-227. Patients with multiple system atrophy had elevated BF-227 binding in the putamen. Finally, GSS patients had elevated BF-227 uptake in the cerebellum and other brain regions. This chapter confirms that BF-227 can selectively bind to α-synuclein and prion protein deposits using postmortem brain samples. Based on these findings, [^{11}C]BF-227 is not necessarily specific for β-amyloid in AD patients. However, this tracer could be used to detect various types of protein aggregates in the brain.

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INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia in the elderly. AD currently affects 4 million people in the United States and 15 million people globally. This disease begins insidiously with mild memory problems and progresses to the development of functional impairment in multiple cognitive domains within a few years. It is important to develop diagnostic methods that have adequate sensitivity and specificity to distinguish those who are likely to develop AD from those memory-impaired individuals who will not. The pathological hallmarks of AD are the deposition of senile plaques (SPs) and neurofibrillary tangles (NFTs) (Vickers et al., 2000). SPs and NFTs are mainly composed of β-amyloid (Aβ) protein and hyperphosphorylated tau protein, respectively. Aβ is a 4 kDa 39–43 amino acid metalloprotein product derived from the proteolytic cleavage of the amyloid precursor protein (APP) by β- and γ-secretases. The abnormal accumulation of SPs has been implicated as a central event in the etiology and the pathogenesis of AD and precedes the cognitive deterioration observed in AD (Okamura et al., 2008). Tau proteins accumulate in the neuronal cytoplasm and form NFTs with age. The initial lesions leading to NFTs occur in the transentorhinal cortex, followed by involvement of the entorhinal cortex and hippocampus, progressing to the neocortex. In vivo detection of SPs and NFTs in the brain enables the detection of AD patients in the pre-symptomatic stage. Noninvasive measurement of the amount of Aβ and tau deposits in the living brain is desirable for preventive interventions and assessment of therapeutic effects.

The density of SPs in brain tissue can be measured by molecular imaging techniques using positron emission tomography (PET) and a specific radiotracer. As Aβ deposits in the AD brain generally include the β-sheet fibrillar structure, many β-sheet binding agents have been developed as Aβ binding radiotracers for PET imaging. Currently, the most successful amyloid-binding agent is N-methyl-[^{11}C]2-(4'-methylaminophenyl)-6-hydroxybenzothiazol (PIB), which has been shown to possess a high affinity for Aβ fibrils. PIB-PET studies in human subjects have shown a robust difference between the retention pattern in AD patients and healthy controls, with AD cases showing significantly higher retention of PIB in the neocortical areas of the brain affected by Aβ deposition (Klunk et al., 2004). PIB retention in the neocortical areas is correlated with the Aβ plaque load (Ikonomovic et al., 2008). Benzoxazole derivatives are also promising alternatives for amyloid-imaging probes (Okamura et al., 2004; Furumoto et al., 2007). A PET study using ^{11}C-labeled 2-(2-[2-dimethylaminothiazol-5-yl]ethenyl)-6-(2-[fluoro]ethoxy) benzoxazole (BF-227) demonstrated retention of this tracer in the cerebral cortices of AD patients but not in those of normal subjects. AD patients were clearly distinguishable from normal individuals using neocortical uptake of [^{11}C]BF-227 (Kudo et al., 2007). Neocortical retention of BF-227 was observed in the subjects with mild cognitive impairment (MCI). BF-227 PET showed higher specificity and sensitivity than FDG-PET and voxel-based morphometric analysis of MRI for differentiating between AD patients and normal controls, and between MCI converters and non-converters (Waragai et al., 2009; Furukawa et al., 2010). A voxel-by-voxel analysis demonstrated a higher retention of [^{11}C]BF-227, mainly in the posterior association cortex of AD patients and MCI converters. This distribution pattern corresponds well with the distribution of neuritic plaque deposits in postmortem AD brains. These findings suggest that [^{11}C]BF-227 is a promising PET probe for in vivo detection of dense amyloid deposits in AD patients.

AD and many other neurodegenerative disorders, including frontotemporal dementia (FTD), progressive supranuclear palsy, corticobasal degeneration, Parkinson's disease (PD), dementia with Lewy bodies (DLB), multiple system atrophy,