PET Imaging of Misfolded Proteins in Alzheimer’s disease
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In the protein misfolding diseases, the progressive accumulation of protein aggregates causes neuronal loss and functional disturbance. In Alzheimer’s disease, the two major pathological protein deposits (senile plaques and neurofibrillary tangles) are composed of amyloid-β and tau proteins. The measurement of amyloid-β and tau concentrations in the living brain will contribute to the early, accurate and differential diagnosis of dementia, tracking disease progression and evaluating the efficacy of disease-specific therapies. Currently, several amyloid PET tracers are commercially available in the United States and the European countries. On the other hand, tau PET tracer is still in the process of clinical development. About ten years ago, we screened more than 3,000 of small molecules and discovered novel quinoline derivatives with high binding selectivity to tau deposits in Alzheimer’s disease brain. After compound optimization, we developed three 18F-labeled PET tracers, [18F]THK-5105, [18F]THK-5117 and [18F]THK-5351, which showed high binding affinity to tau protein fibrils and high binding selectivity to tau over amyloid-β in Alzheimer’s disease brain samples. Recent PET studies have demonstrated these radiotracer retention in sites with predilection for the deposition of tau pathology in Alzheimer’s disease, and distinctly differentiated from aged normal individuals. Furthermore, tracer retention was closely associated with the clinical severity of dementia and the atrophy of the brain. In this symposium, we will show the progress in the development of tau-selective PET tracer and recent results of first-in-man PET studies.

References


