DEVELOPMENT OF RADIOLABELED PROBES FOR IN VIVO MOLECULAR IMAGING WITH PET/SPECT

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Molecular imaging by radiolabeled probes for PET/SPECT enables noninvasively quantitative evaluation of physiological function, gene expression, pharmacokinetics of proteins and peptides and distribution of receptors with high sensitivity. Together with recent development of imaging equipments, molecular imaging by PET/SPECT is expected to contribute to elucidation of physiological and pathological functions, medical sciences and clinical diagnoses.

Currently, the development of radiotracers for *in vivo* imaging β-amyloid plaques in Alzheimer's disease (AD) brains is an important and active area of molecular imaging. Postmortem brains of AD patients reveal neuropathological features; the presence of β-amyloid plaques and neurofibrillary tangles, which contain β-amyloid proteins (Aβ) and highly phosphorylated tau proteins. Increases in the concentration of Aβ in the course of the disease lead to gradual increase in the load of β-amyloid plaques, which is thought to be an initial neuropathological change in AD brains. Thus, when used in combination with PET/SPECT, β-amyloid imaging agents could serve as surrogate markers in early diagnosis and neuropathogenesis studies of AD. Furthermore, quantitative evaluation of β-amyloid plaques in the brain could allow facilitate the evaluation of the efficacy of anti-amyloid therapies that are currently being investigated.

As part of an effort to develop ^{11}C labeled tracers for PET imaging of β-amyloid plaques in AD, we have evaluated a series of simple molecular probes. Minimum requirements for a successful Aβ-plaque-specific imaging agent include: small and neutral molecules, sufficient but moderate lipophilicity, good brain penetration, low non-specific binding in regions of brain with no β-amyloid plaques. To meet the challenges of designing such molecules we have investigated several series of core structures. Two of them are the stilbene and phenylbenzofuran derivative, which are relatively simple and readily amenable for structural modification. In the search for β-amyloid imaging agents, we have developed the stilbene derivative ([^{11}C]SB-13) and the phenylbenzofuran derivative ([^{11}C]HMBZF) as useful PET probes for *in vivo* imaging of β-amyloid plaques in the brain.

More recently, we have reported additional compounds such as flavone, chalcone and aurone derivatives to be useful β-amyloid imaging agents for SPECT. The combination of relatively high binding affinity to Aβ and high brain uptake and good clearance in mice of these flavonoid derivatives provides a series of potential β-amyloid imaging agents for SPECT.

This presentation will review our research on the development of PET/SPECT imaging agents for *in vivo* detection of β-amyloid plaques in Alzheimer's brains.