Alzheimers Disease Diagnostic Imaging Agent

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Technology description

Copper radiopharmaceuticals that target Aβ plaques: diagnostic imaging agents for Alzheimer’s Disease
Non-invasive diagnostic
Rapid and simple incorporation of radio-metal into a specific targeting ligand
Monitor therapeutic intervention
Elucidate the role of Aβ plaques in the progression of amyloid related diseases
Backgroun
Alzheimer’s disease (AD) is a progressive neurodegenerative disease that leads to synaptic failure and neuronal death. AD accounts for 50–70% of all dementias. One of the major characteristic pathological hallmarks of the disease is the presence of extracellular senile plaques in the brain. The plaques are comprised of insoluble aggregated peptide amyloid-β (Aβ), a 39-43 amino acid peptide derived from the amyloid precursor protein (APP). Histopathological studies show extensive cortical amyloid-β deposition in post-mortem analyses in Alzheimer’s disease patients which is the current accepted definitive diagnosis for AD. Researchers at The Bio21 Research Institute at the University of Melbourne have been investigating non-invasive method using radiopharmaceutical compounds that provide early intervention AD diagnosis and the ability to monitor the Aβ plaque burden in AD patients.
The Problem
At present, clinical diagnosis of AD is based on psychological tests that probe progressive impairment of memory and cognitive decline; whilst definitive diagnosis of AD generally relies on post-mortem histological analysis.
Currently there are two compounds offering limited information of the plaque burden and role of Aβ in AD, Benzothiazole and stilbene compounds radiolabelled with carbon-11 ([11C]-PIB, Pittsburgh compound B) and more recently, fluorine-18 ([18F]-AV45, florbetapir). Most research into PET tracers to target Aβ plaques has centred on organic dyes radio-labelled with either carbon-11 or fluorine-18. Both isotopes are handicapped by relatively short half-lives (C-11 = 20.4 min, F-18 = 109.7 min) and must be attached covalently, which complicates synthetic manipulations.
Technology
Positron emission tomography (PET) provides the opportunity for non-invasive imaging to enhance diagnosis and monitor therapeutic intervention of AD patients. PET is a molecular imaging technique with exquisite sensitivity readily detecting concentrations in the picomolar range.

The family of ligands known as bis(thiosemicarbazones) derived from 1,2-diones show considerable potential as delivery vehicles for radioactive copper isotopes as they form stable and neutral membrane permeable copper complexes. The stable, neutral complexes can diffuse into cells, which provide a reducing environment, where upon the complexes are susceptible to intracellular reduction, CuII to CuI.
Moreover, hybrid thiosemicarbazonato-pyridylhydrazine (THYNIC) bifunctional chelators for copper-64 labelling of Aβ plaques have been synthesised and exemplified.
Fig 1. Hybrid thiosemicarbazonato-pyridylhydrazine (THYNIC) bifunctional chelator for copper Fig 2. (top) AD human brain sections with 1E8 antibody stained Aβ plaques x 20 magnification; (bottom) epi-fluorescence of CuIIL25 3 binding selectively to Aβ plaques x 20 magnification, collated images measured at lex = 359 nm, lem = 461 nm; lex = 420 nm, lem = 470 nm; and lex = 430 nm, lem = 476 nm; overlaid.

Advantages

Non-invasive diagnostic
Ligand is prepared and can be formulated into kits analogous to technetium kits (GMP kit)
Radiolabeling is merely involves adding a Cu2+ to a solution of the ligand
Monitor therapeutic intervention and further elucidate the role of Aβ plaques in the progression of amyloid related diseases
Ligand can be used with the full selection of copper radioisotopes
Potential use with other amyloid related diseases, Diabetes mellitus type 2 (amylin); Alzheimer's disease (Ab 39-42); Parkinson's disease (alpha-synuclein); Huntington's disease (huntingtin); Creutzfeldt-Jakob disease (PrP in cerebrum); congestive heart failure (PrP or transthyretin) 20 and Bovine spongiform encephalopathy (PrP). Age related Macular Degeneration (AMD).
Choice of Cu
64Cu - 12.7 h half-life, allows PET imaging at site remote from the cyclotron facility, across country
62Cu - very short half life, nuclear med. depts. of hospitals can manage the generator for this
61Cu - 3 h half-life, cyclotron generated, cheap easy

Institution

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