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Review

Diagnostic imaging of Alzheimer's disease with copper and technetium complexes

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Contents

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ABSTRACT

The most common form of dementia is Alzheimer's disease, a progressive neurodegenerative disease that leads to synaptic failure and neuronal death. This review discusses the development of copper and technetium coordination complexes designed as radiopharmaceuticals to assist in the diagnosis of Alzheimer's disease using positron emission tomography or single photon emission computed tomography. Technetium complexes used to image regional brain perfusion are discussed as well as copper and technetium complexes specifically designed to bind to amyloid-β plaques that are associated with the onset of symptoms of the disease.

1. Alzheimer's disease

The most common form of dementia is Alzheimer's disease (AD), a progressive neurodegenerative disease that leads to synaptic failure and neuronal death. These symptoms can initially manifest as mild forgetfulness but progress to complete loss of cognition and ultimately death [1,2]. The condition is more prevalent in older people and an ageing population means its prevalence is set to increase. Characteristic pathological hallmarks in the brains of those suffering with the disease include the presence of extracellular senile plaques, intracellular neurofibrillary tangles and altered levels of neurotransmitters. Amyloid plaques are composed of an insoluble aggregated peptide called amyloid-β (Aβ), a 39–43 amino acid peptide derived from the amyloid precursor protein (APP). The precipitation of Aβ plaques proceeds through various stages involving the formation of fibrillar aggregates (Aβ fibrils) and finally plaques (Fig. 1). These Aβ plaques do not consistently correlate with cognitive impairment and some argue that smaller soluble oligomeric species are the toxic species responsible for neuronal death. However, oligomers and plaques are thought to be in equilibrium and although the exact role of Aβ plaques in the onset of dementia is controversial, what is certain is that

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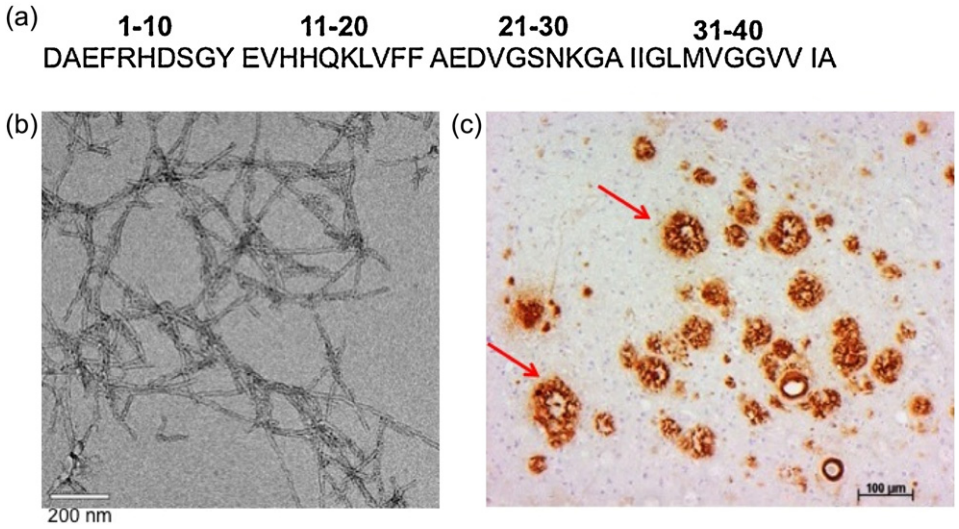

Fig. 1. (a) The amino acid sequence for $A\beta_{1-42}$; (b) TEM image of $A\beta_{1-42}$ fibrils; (c) a section of the cortex region of human brain tissue from a subject with diagnosed AD, the Aβ plaques have been stained using a 1E8 antibody.

histopathological studies show extensive cortical Aβ deposition in post-mortem analysis of AD sufferers [1,3–7]. Neurofibrillary tangles (NFTs) consist of a hyper-phosphorylated form of a microtubule-associated protein called tau and are initiated with the formation of bundles of paired helical filaments that accumulate in the neuronal cytoplasm. The hyper-phosphorylation of tau results in its detachment from microtubules that consequently lose structural integrity with concomitant impaired axonal transport and compromised synaptic function [8,9].

At present, clinical diagnosis of AD is based on establishing the presence of progressive impairment of memory as well as deficits in at least one other area of cognition. Definitive diagnosis of AD relies on post-mortem histological analysis. Accepted biomarkers for AD include characterisation of specific pathology through a cerebrospinal fluid assay of $A\beta_{1-42}$ [10] or total tau and phosphorylated tau as well as identification of biomarkers that indicate neuronal damage, such as brain atrophy as measured by magnetic resonance imaging, or changes in metabolism identified by radiolabelled glucose imaging using positron emission tomography [11]. Valuable insight into the mechanisms of disease progression and earlier more accurate diagnosis of AD is possible using specific radiolabelled tracers and 'molecular imaging' techniques to identify molecular aspects of the progression of the disease and in particular to characterise Aβ plaque burden.

2. Single photon emission computed tomography and positron emission tomography

The techniques of single photon emission computed tomography (SPECT) and positron emission tomography (PET) offer the opportunity of non-invasive imaging to enhance diagnosis and monitor therapeutic intervention. They involve the use of radiolabelled compounds (tracers) that are injected into a patient and an external detector detects the emitted radiation. SPECT relies on tracers that emit γ-radiation whereas PET relies on a tracer that emits a positron that annihilates, releasing two gamma photons travelling in opposite directions. In the case of PET, detection of the emitted photons can generate an image with a spatial resolution of 3–5 mm, with exquisite sensitivity readily detecting concentrations in the picomolar range. The biodistribution of the radiotracer is dependent upon the molecular detail of its interaction with the biological milieu. Diagnostic imaging of particular disease states is possible depending upon tracer design. A radiolabelled glucose analogue called FDG (^{18}F-fluoro-2-deoxy-D-glucose) is routinely used to probe glucose metabolism, central to many metabolic processes, but personalised and disease specific diagnosis requires fundamental research into radiotracers designed to target specific disease markers. Radiotracers labelled with positron-emitting or γ-emitting isotopes that effectively cross the blood–brain barrier and bind selectively with favourable pharmacokinetics to Aβ plaques in human brains in living patients are of considerable use to clinicians in their quest for early and accurate diagnosis and the monitoring of emerging therapies.

3. Diagnosis of Alzheimer's disease using positron emission tomography

A challenge in diagnostic imaging of AD is to achieve earlier diagnosis and differential diagnosis from other types of neurodegeneration. Early diagnosis is seen as a critical precursor to effective treatment and preventative strategies. Whilst new therapeutic strategies for the treatment of AD are under development, there is an urgent need for tools to monitor the progress of treatment [2,12]. Other causes of loss of brain function can complicate a definitive diagnosis of AD. Older people usually complain of increasing forgetfulness with age but not all progress to actual dementia. Clinicians refer to mild cognitive impairment (MCI) to describe people who are impaired beyond what is expected on the basis of their age and education. About 40–60% of all MCI patients progress to AD dementia within 3–5 years. Molecular imaging will assist clinicians in the accurate diagnosis of the underlying pathological process, allowing discrimination between MCI subjects with and without AD pathology. Further complications in the accurate diagnosis of AD arise from other neurodegenerative diseases including frontal temporal dementia, dementia with Lewy bodies and dementia in Parkinson's disease (PD). Dementia with Lewy bodies represents the second most frequent cause of neurodegenerative dementia and is associated with insoluble aggregates of a protein called α-synuclein. These aggregates of α-synuclein are known as Lewy bodies and are also present in PD. Most people with dementia Lewy bodies also have high cortical Aβ burden so amyloid imaging cannot always distinguish between AD and dementia Lewy bodies [13].

Unlike receptors and enzymes, Aβ plaques do not have a known specific function and lack a designated substrate binding site or binding domain. This presents considerable challenges to the development of specific probes. Aβ plaques adopt a cross-β-sheet