Biochemistry & Pharmacology: Open Access

Szymański et al., Biochem Pharmacol 2014, 3:2
DOI: 10.4172/2167-0501.1000e159

Editorial Open Access

Diagnosis of Alzheimer Disease – The Most Popular and Future Perspective Methods

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Abstract

Alzheimer disease (AD) is classified as a neurodegenerative age-related disease. Despite all efforts in research therapy, current pharmacotherapy is mainly based on symptomatic treatment. Unfortunately, brain damage caused by the pathophysiological mechanisms of Alzheimer disease is still irreversible. The first symptoms, observed as cognitive impairments, occur when the neurodegenerative process is in progress. This was one of the reasons why scientists found that early diagnosis could be a way to combat the disease, they concentrated on searching and improving methods of early detection of any brain lesions. Alzheimer disease is only one of the types of dementia and the first symptoms are similar to mild cognitive impairments which do not have to be developed to AD. These medical observations prove that there is a great need for accurate methods of diagnosis. These factors give the direction of present and future perspective methods of neuroimaging. This review is focused on current structural (MRI) and functional (PET) brain imagining as well as promising future ways of using biological markers.

Introduction

According to our knowledge of molecular pathogenesis of AD, neurodegenerative changes in the brain tissue are caused by the accumulation of the protein amyloid-beta (Aβ). This protein is produced in normal physiological conditions (it is released from the amyloid precursor protein - APP) [1- 4]. Over production or imbalance in clearance mechanisms causes its accumulation and aggregation to insoluble amyloid plaques– this state is defined as criteria for Alzheimer disease. Another specific hallmark of AD is the excessive accumulation of tau protein which normally isinvolved in the assembly of microtubules from tubulin subunits [5]. It is thought that these patho-mechanisms are responsible for neuron atrophy or damage and as a result learning and cognitive functions are impaired. Clinically this process is characterized by slowly progressive dementia which occurs even decades after structural changes take place. Many researchers suggest that β-amyloid aggregates are a major factor in AD development. Thus, it seems to be crucial to obtain diagnostic imaging agents (radio pharmaceuticals) targeting Aβ plaques [6]. Neuroimaging methods can detect functional and structural brain changes. To diagnose functional impairment local glucose metabolism or blood flow is measured. It is feasible to manage this by using nuclear medicine imagining devices: single photon emission computed tomography (SPECT) and positron emission tomography (PET). Structural abnormalities can be detected by usingmagnetic resonance imagining (MRI). Moreover, biological markers must be taken into consideration because are expected to play a key role in an early detection and accurate diagnosis of AD [3].

PET

PET images are obtained after intravenous injection of a radiotracer emitting a positron that subsequently annihilates with neighbouring electron and releases two gamma photons travelling in opposite directions at the same time this process is recorded by a scanner. Usage of different diagnostic agents enables the measurement of several properties [3,4].

[18F] FDG-PET

[18F] fluoro deoxyglucose is used as a radiotracer. This method allows us to estimate the level of tracer accumulation in a given area which is parallel to the amount of delivered nutrients and local glucose metabolism connected with neurosynaptic activity. These measurements provide information about cerebral tissue functionality, because any symptoms of disorders can be detected even though structural changes are imperceptible. The question is how can this test detect and confirm AD? Every type of dementia cause changes in different regions of cerebral structure. AD is characterized by cortical brain alterations that begin in the posterior cingulate and parietal regions, and then spread to the temporal and prefrontal cortices. Glucose hypometabolism is related to the decline in cognitive abilities, but additional assessment is recommended before final diagnosis [2,7,8].

Detection of β-Amyloid Plaques and Tau Tangles

This technique uses amyloid-binding radiopharmaceuticals to detect amyloid-β plaques and tau tangles. Cortical ligand concentration is incomparably greater in patients with AD than in controls.Research to find highly effective tracers are still ongoing, but there are several compounds available such as [11C]-labeled Pittsburgh compound B (PIB-PET) – which binds only to amyloid plaques or [18F] FDDNP-PET with ability to bind both – plaques and tau tangles. The last one has a longer half-life (11C T1/2=20 min; 18F T1/2=110 min) what makes it more useful in clinical conditions because of a possibility of off-site cyclotron preparation. Neuropathological post-mortem studies have confirmed high efficacy of AD diagnosis in patients who previously underwent this PET scanning [2,4,7].

In April 2012 the US Food and Drug Administration has approved [18F] florbetapir for clinical use. [18F] florbetapir PET enables highly

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Received March 24, 2014; **Accepted** March 25, 2014; **Published** Aprile 1, 2014

Citation: Szymański P, Pietrzak K, Olasik EM (2014) Diagnosis of Alzheimer Disease– The Most Popular and Future Perspective Methods. Biochem Pharmacol 3: e159. doi:10.4172/2167-0501.1000e159

specific detection of β-amyloid aggregates. 10 minutes scans are taking within 50-60 min after an injection, what makes this examination relatively comfortable for patients. Moreover, a 110 minute half-life is long enough to off-site preparation [9].

SPECT

This is the second type of nuclear medicine imaging device which uses single photon emission to measure local blood flow. SPECT is a useful device in diagnosis of AD and other kinds of dementia which are based on a particular pattern of up taking 99mTc-ECD (ethyl cysteinate dimer). Some studies have proved that decreases in perfusion in given areas correlate with special disorders and respectively temporoparietal hypoperfusion is associated with AD. Nevertheless SPECT is considered to detect Aβ amyloid plaques by using radiopharmaceuticals – there are researches on [123I] IMPY, but the approach of finding new radionuclides is more commonin PET [4,10].

MRI

Structural neuroimaging can be a preliminary assessment of cognitive disorders and provides information about brain structure (volume) – differentiation and atrophy of grey or white matter. However low sensitivity and specificity to diagnose AD is the reason why abnormalities detected on MRI should be evaluated by using more accurate tests [3].

fMRI

Functional MR imagining allows measuring the local concentration of deoxy-hemoglobin during memory or other cognitive tasks. Then the result is compared to the blood flow during the rest-time and how does it look like without any disorders. Several studies proved that among AD patients was observed lowered brain activity in parietal and hippocampal regions while higher activation in primary cortices unaffected by the disease. How can we interpret this result? There is a hypothesis which involves compensatory- recruitment idea, when greater cognitive effort is required to realize the same task when another brain structures are impaired. This theory requires more studies but may be an useful device in AD early diagnosis [5,7].

Biomarkers A-BETA (Aβ)

As mentioned before, presence of Aβ amyloid plaque is a specific hallmark of AD which appears even decades before visible symptoms of the disease. Amyloid plaque consists of the Aβ peptide components which may exist in solution until Aβ associates to aggregates. Vulnerability to self-association depends on primary sequence of the peptide. Variant Aβ42 occurs in a minority, but is highly prone to aggregation in comparison with the variant Aβ40. The ability to exist in solution allows detecting these peptides in cerebrospinal fluid (CSF).

The analysis of Aβ isoforms in CSF led to the conclusion that in AD patients the level of Aβ42 is significantly reduced to 50% in most of studies. This is obvious accordingly to the deposition of Aβ42 in senile plaques. Furthermore, a decrease in the ratio of Aβ42/ Aβ40 is believed to prove this theory while remembering differences in tendency of aggregation of these two isoforms. In addition to this many studies have found an undeniable correlation between the level of Aβ42, ratio of Aβ42/ Aβ40 and high retention of PIT in PET or numerous plaques in the neocortex and hippocampus [5,6,11].

Nevertheless, these findings can't be considered as a specific only for AD. Decrease in the Aβ42 in CSF was observed for Creutzfeldt-Jakob disease, multiple system atrophy and some others disorders. Despite this fact research into finding biomarkers are constantly on-going [6].

Future Perspectives

Alzheimer disease is still incurable and pathological changes in brain tissue are irreversible. Clinical symptoms are observed after years of degenerative processes. Scientists hold great promises in finding more effective and specific methods of early diagnosis. It is particularly important for modified therapies which can be started only in an initiative stadium of the disease. Thus a great effort is put in obtaining new radiotracers for PET or SPECT, assaying result of fMRI and what is believed as promising perspective – new biomarkers candidates. Recent approach moves towards a combination of available methods, but undeniably there is a great need for methods which could ensure detailed, accurate and early diagnosis. All of us know that it is better to prevent than treat. Maybe preventive therapies will occur to be a turn in a current treatment.

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