Extended Abstract Journal of Alzheimer's & Dementia
2021
Vol.4 No.2

Dementia-2014: Altered copper metabolism as a theranostic biomarker in neurodegeneration

Fangyu Peng

Copper is an essential nutrient element, but excess of copper is harmful. Copper homeostasis is tightly regulated by a delicate network of copper transporters and chaperons. Wilson?s disease, or hepatolenticular degeneration, caused by mutation of ATP7B gene is characterized by accumulation of excess copper ions in liver and brain tissues. Positron emission tomography (PET) is a versatile tool for real-time assessment of copper fluxes in vivo noninvasively and quantitatively. Increased accumulation of 64Cu in liver of Atp7b-/- knockout mice, a well-established mouse model of Wilson?s disease, was demonstrated by measuring copper fluxes in vivo with PET/CT using copper-64 chloride (64CuCl2) as a radioactive tracer (64CuCl2-PET/CT). Age-dependent increase of 64Cu radioactivity was detected in the brain of Atp7b-/- knockout mice at 20 weeks of age compared with 64Cu radioactivity in the brains of Atp7b-/- knockout mice at 6 to 12 weeks of age. In addition to hepatolenticular degeneration, emerging body of evidence suggests the role of altered copper metabolism in pathophysiology of Alzheimer?s disease (AD) and other neurodegenerative diseases. Altered copper metabolism may be a useful theranostic biomarker for early diagnosis of AD at preclinical stage with PET/CT using 64CuCl2 as a radioactive tracer. Based on favorable outcome of copper-modulating therapy in clinical management of the patients diagnosed with Wilson?s disease, altered copper metabolism holds potential as a therapeutic target for copper modulating therapy of AD and other neurodegenerative disease associated with disturbance of cerebral copper metabolism.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder described in 1907 by Alois Alzheimer. He observed amyloid plaques and neurofibrillary tangles (NFTs) in the brain of patients showing signs of dementia. Today, AD is the most prevalent neurodegenerative disease affecting 10% of people aged 65+ and 50% of people aged 80+.

In 2016, it was estimated that there were about 47 million AD patients in the world and this number is expected to increase to more than 130 million by 2050. The World Alzheimer Report evaluated the annual social and economic cost of dementia to be US$ 818 billion worldwide in 2015 and this amount is expected to increase to one trillion by 2018.

Alzheimer's disease is ultimately lethal, characterized by the developing damage of neuronal tissues in the brain. Signs include memory loss, paranoia, loss of reasoning powers and confusion. Unfortunately, AD is recognized only after the manifestation of cognitive signs, which may be too late for effective treatment.

Moreover, approved drugs have inconsiderable effects on patients' well-being, which may be because many factors are responsible for AD. Indeed, there are several theories to demonstrate the cause of AD In brain regions affected in AD, such as the cortex and hippocampus, extracellular senile plaques, and intracellular NFTs accumulate. Senile plaques or amyloid plaques, as the name implies, are mainly composed of small peptides called β-amyloid. Senile plaques or amyloid plaques, as the name implies, are mainly composed of small peptides called β-amyloid.

The latter is produced from β-amyloid precursor protein (APP) through successive cleavages first by β-secretase at residue 671 and then by γ-secretase at residues 711 or 713 (residue numbering according to the APP770 isoform) in amyloidogenic pathway. Alternatively, APP molecules can be cleaved by α-secretase within the β-amyloid domain at residue 687 and prevent β-amyloid production in non-amyloidogenic pathway. There are three main isoforms of APP including APP695, APP751, and APP770 with APP695 being expressed at high levels in brain compared to other isoforms. Furthermore, NFTs, mainly composed of tau proteins, is the other important factor that accumulates in AD brain. Tau proteins mostly expressed in neurons have the ability to induce microtubule assembly in vitro. In fact, microtubules, one of the main components of the cytoskeletal system, are involved in the maintenance of neuronal morphology and the formation of axonal and dendritic processes.

One of the first and most severely injured brain areas in AD is the hippocampus, which is associated with neurogenesis and long-term memory storage. It is also thought to be more susceptible to metal disturbance than other brain areas. Another brain region that suffers from damage in AD due to plaque pathology is the cortex, associated with functions such as argumentation, feeling, and language. β-amyloid aggregations into senile plaques are one of the main characteristics of AD. A considerable co-localization of adenosine receptors and β-amyloid has been reported in senile plaques (Angulo et al., 2003). Adenosine, a purine ribonucleoside that has neuromodulatory and neuroprotective properties, affects various important brain functions such as sleep, cognition, memory, and neurodegeneration.

Foot Note: This work is partly presented at 2nd International Conference on Alzheimer's Disease and Dementia, September 23-25, 2014 | Valencia Convention Centre, Spain