CME LIVE OPEN ACCESS

Journal of Clinical Immunology Research

Research Article

Novel targets and positron emission tomography radio tracers imaging noradrenaline biomarker in hippocampus, for Alzheimer patients'

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Received: 2023 July 24 **Accepted:** 2023 Aug 13 **Published:** 2023 Aug

Abstract

Advances in neuro-technology keep advancing at an astounding pace, and at times it seems like we are closer to science fiction than reality. Neurotech is evolving faster than ever, and staying on top of trends is a must for researchers [1]. On May 29, 2017, at the 70th session of the World Health Assembly in Geneva, the World Health Organization (WHO) has unanimously adopted a global plan on dementia—the Global Plan of Action on the Public Health Response to Dementia 2017–2025—that includes targets for the advancement of dementia awareness, risk reduction, diagnosis, care and treatment, support for care partners, and research.

Loss of noradrenaline (NA)-rich afferents from the Locus Coeruleus (LC) ascending to the hippocampal formation has been reported to dramatically affect distinct aspects of cognitive function, in addition to reducing the proliferation of neural progenitors in the dentate gyrus. Here, the hypothesis that reinstating hippocampal noradrenergic neurotransmission with transplanted LC-derived neuroblasts would concurrently normalize both cognitive performance and adult hippocampal neurogenesis was investigated [2]. Although β2-AR agonists may provide therapeutic value in combination with novel treatments for AD [3].

Advanced PET scan for recognition and pre diagnosis the conflict area such as hippocampus with neural biomarkers and Aβ are promoted and helpful.

Keywords: positron emission tomography, PET scan, Alzheimer, AD, Noradrenaline, NA, Norepinephrine, NE, imaging, biomarker, β-adrenergic, hippocampus.

1. Introduction

Biomarkers are vital for diagnostics of brain disease and therapeutic monitoring [4]. Multiple imaging modalities, such as MRI, PET, diffusion tensor imaging (DTI), and rs-fMRI, help in capturing diverse pathology patterns that may highlight different disease relevant regions in the brain [5]. A final pillar of evidence for disease or its progression is provided by biomarker monitoring [4].

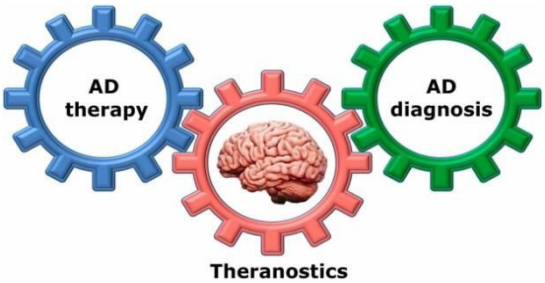

Figure1: The pairing of diagnostic neural biomarkers with therapeutic agents that share a specific target in Alzheimer cells or tissues.

Imaging Biomarkers of Neuronal Injury and Neurodegeneration

Newly developed radioactive isotopes and contrasting agents increase the efficiency of MRI, MRS, and PET scans. As technology advances, new diagnostic approaches will be made to further improve the capabilities of imaging biomarkers [6]. Given the involvement of the noradrenergic system in neurodegenerative diseases, noradrenergic biomarkers could be an important complementary tool to established pathological biomarkers and may provide new insights into the neuromodulatory underpinnings of cognitive and behavioral symptoms [7].

Positron Emission Tomography (PET)

The most used radionuclide is fluoro-deoxy-glucose (FDG), which measures metabolic activity in the brain. PET is especially capable of measuring lesions that are not visible on MRI scans [8]. PET is capable of measuring neuroinflammation and can distinguish components of the neuroimmune response [9]. The PET scan is painless and uses lesser amounts of radioactivity. The noradrenergic system can be assessed using CSF and PET measures will be beneficial for understanding how changes to this neuromodulatory system contribute to the clinical manifestations of Alzheimer's disease and The opportunity to monitor the status of the noradrenergic system using CSF and PET measures may also aid in the early detection of pathological decline and be useful for determining the efficacy of NA drugs in clinical trials [7].

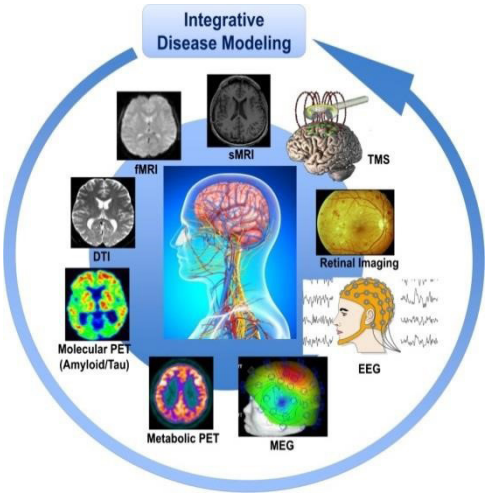

Figure2: Integrative Disease Modeling

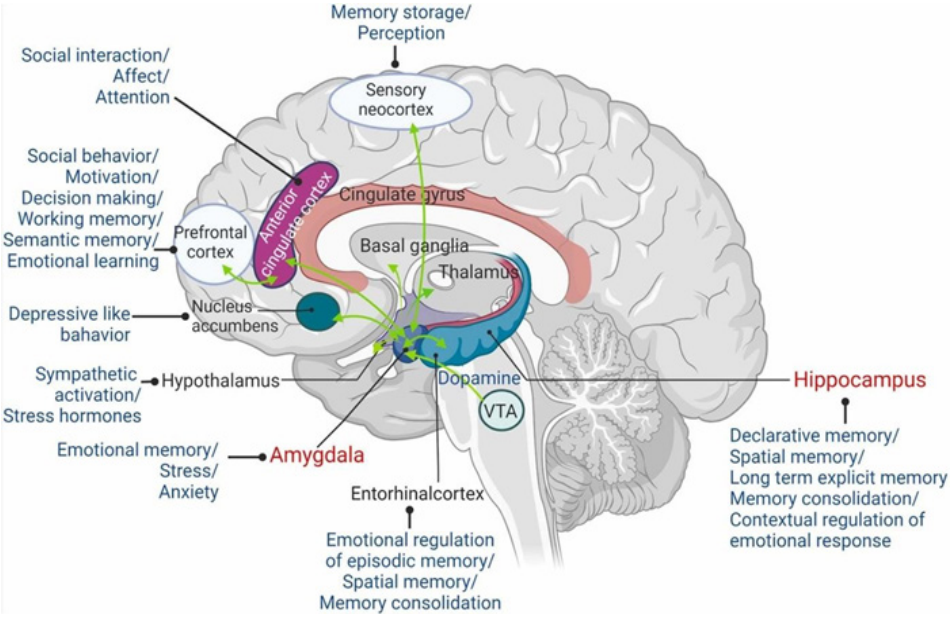

Figure 3: Connectivity of the hippocampus and Amygdala

The hippocampus is related to declarative memory, spatial memory, long-term explicit memory, memory consolidation, and contextual regulation of emotional responses [10]. The impact of PET imaging in psychiatric disorders was largely confined to radiotracers developed to advance to targets that often failed as therapeutics in clinical trials [11].

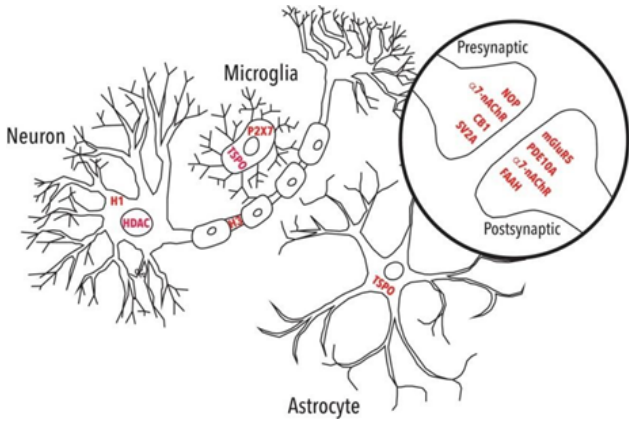

Figure 4: The metabotropic glutamate receptor type 5 (mGluR5), purinergic P2X7 receptor, type 1 cannabinoid receptor (CB1), and phosphodiesterase 10A (PDE10A),

Advanced PET radiotracers are specifically targeted subpopulations of serotonin receptors to study serotonergic neurotransmission in psychoses and mood disorders [12].

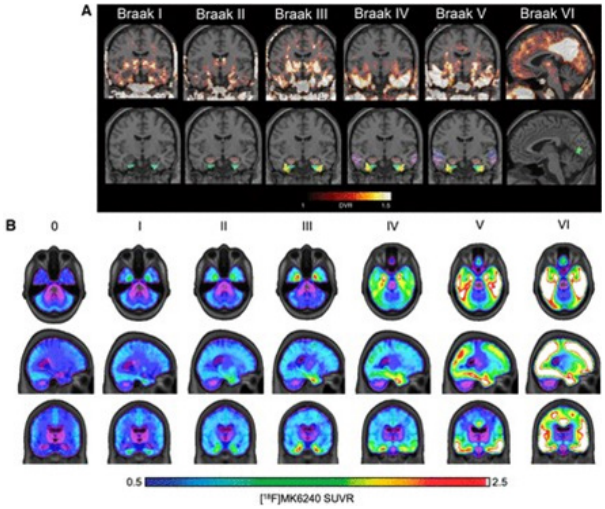

Figure 5: Examples of application of Braak staging in PET imaging studies.

(A) Cases representative of each PET-based Braak stage included in Rullman et al. (27). Left column includes parametric 18F-PI2620 PET images merged with standard MRI, whereas right column [13].

Alzheimer's disease and β-Amyloid (Aβ)

Among the multiple causes for dementia, Alzheimer's disease (AD) holds the first place in terms of prevalence (60–80%), leading a list that also includes cerebrovascular disease (5–10%), frontotemporal lobar degeneration (5–10%), Lewy body disease (5%), hippocampal sclerosis and Parkinson's disease [14]. One of the most commonly used clinical diagnostic criteria for AD was established by the National Institute on Aging and Alzheimer's Association for presentations that classify as probable AD, possible AD, or probable or possible AD with biomarker evidence [15, 16] . The role of microglia in Aβ deposition is complex. On one hand, physiological mechanisms involving microglia and astrocytes contribute to stop the growth of amyloid-β plaques and remove them. Microglia is able to migrate to the surroundings of Aβ plaques to prevent the recruitment of more Aβ peptide [17]. B-Amyloid (Aβ) and tau proteins are the two main pathological hallmarks related to the development of AD, and both of them imply protein misfolding. Additional mechanisms, including oxidative stress, neuroinflammation, mitochondrial dysfunction and

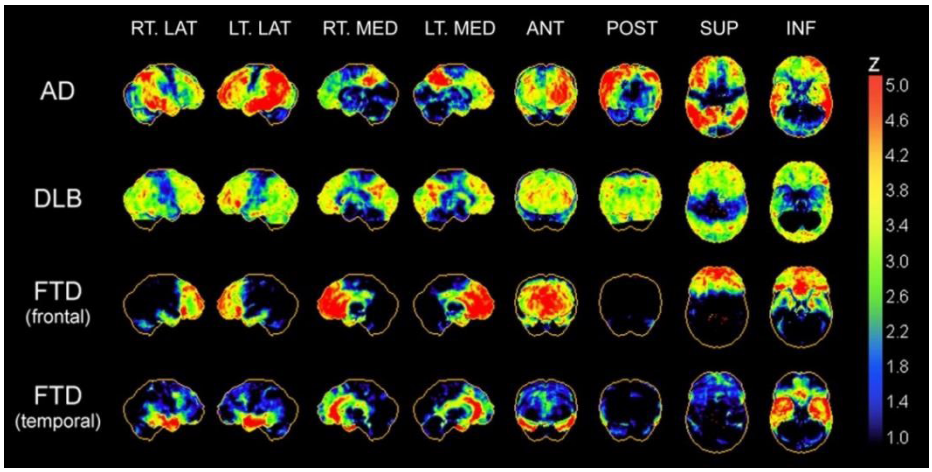

Figure 6: Typical regional cerebral 18F- FDG hypo metabolism patterns in AD, DLB, and frontal and temporal FTD (Nicolaas I. Bohnen, January 2012)

Imbalances in cholinergic and glutamatergic tone, are also present in the progression of the disease [18]. Dementia is accompanied by excessive Aβ plaque accumulation and an impaired neural synaptic network dynamic related to amygdala activity and amygdala-hippocampus connectivity [19]. Some studies have reported that atrophy of the basolateral amygdala, hippocampus, and prefrontal cortex is found in patients with dementia plaque-preceding Aβ oligomer-dependent neuronal hyperactivity is considered to contribute to the system dysfunction present at early stages of AD, supporting the consideration of monomers and oligomers as the primary causing agents of the disease [20, 21, 22, and 23]. The pathogenesis of AD is related to the formation of senile plaques by Aβ.

Amyloid PET can detect cerebral Aβ deposition with precision, has good specificity for AD neuropathology, And is a reliable diagnostic imaging tool, and its use should be encouraged to guide early differential diagnosis in clinical settings and, in the future, to select patients for disease-specific therapies [24].

As damaging of noradrenergic neurons in the locus coeruleus (LC) occurs at the prodromal stage of AD, activation of adrenergic receptors could serve as the first line of defense against the onset of the disease [25].

recently used serial amyloid PET and MRI in 1,246 cognitively normal individuals and found that worsening of memory and reduction of hippocampal volume over time preceded amyloid accumulation on amyloid PET in several older individuals, arguing that memory decline in several older individuals was due to the aging process itself, and not to the accumulation of Aβ deposits in the brain. This fits with recent findings of the ADNI investigators, who found many patients who experienced cognitive decline before changes occurred in CSF Aβ [26].

FDG- PET was used by multiple researchers to detect alterations in brain metabolism due to TBI [27]. Flortaucipir and florbetapir are two FDA-approved specific PET tracers that bind tau and amyloid-beta respectively [28].

Amyloid-β (Aβ)

Clinically, it is characterized by a progressive decline in memory, language, and other cognitive functions. These cognitive deficits are consequences of neuronal loss probably related to the accumulation of intracellular inclusions of aberrant forms of phosphorylated tau and extracellular deposits of amyloid-β (Aβ), known as neurofibrillary tangles (NFTs) and amyloid or senile plaques, respectively [29]. Amyloid-β (Aβ) is the predominant pathologic protein in Alzheimer's disease (AD). The production and deposition of Aβ are important factors affecting AD progression and prognosis. The deposition of neurotoxic Aβ contributes to damage of the blood–brain barrier. BBB (blood-brain barrier) dysfunction and Aβ deposition may lead to a vicious cycle that causes AD development [30].

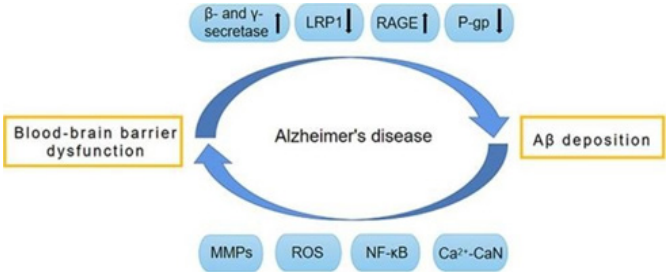

Figure 7: Vicious circle formed by BBB dysfunction and Aβ deposition

Extensive evidence indicates that Aβ removal plays a more pivotal role in the process of Aβ accumulation in the brains of AD patients than does an increase in Aβ production [31].

Norepinephrine and Hippocampus

Locus coeruleus (LC) provides the sole source of noradrenergic (NA) innervation to hippocampus, and it undergoes significant degeneration early in Alzheimer's disease (AD). Norepinephrine (NE) modulates synaptic transmission and plasticity at hippocampal synapses which likely contributes to hippocampus-dependent learning and memory [32].

B-AR agonists, such as isoproterenol (ISO), have been shown to facilitate or strengthen hippocampal-dependent memory [33]. Amyloid pathology has been recently linked to psychosis in prodromal dementia [34]. B2-AR agonists may provide therapeutic value in combination with novel treatments for AD [3].

What is particularly compelling about β-AR is that these receptors play a central role in this process, by driving the direction of change of synaptic strength and in grading the persistency of synaptic plasticity in the different hippocampal subfields [35, 36, 37, and 38]. Loss of noradrenaline (NA)-rich afferents from the Locus Coeruleus (LC) ascending to the hippocampal formation has been reported to dramatically affect distinct aspects of cognitive function, in addition to reducing the proliferation of neural progenitors in the

dentate gyrus. Here, the hypothesis that reinstating hippocampal noradrenergic neurotransmission with transplanted LC-derived neuroblasts would concurrently normalize both cognitive performance and adult hippocampal neurogenesis was investigated [2].

Relevant original research and review articles on radiotracers that confirmed NA or NE following recurrent AD were retrieved. The results gathered from the above data were summarized based on the biomarkers assessed through imaging or measurements in hippocampal body fluid and blood.

2. Methodology

EMBASE (Scopus), PsycINFO, PROQUEST and MEDLINE (PubMed) databases were searched for studies eligible for inclusion. Studies with both neuropsychological and biomarker evidence by Novel PET Radiotracers with Potential Clinical Applications were included in the final narrative synthesis.

The PUBMED database was searched using the following keywords: positron emission tomography, PET scan, Alzheimer, AD, Noradrenaline, NA, Norepinephrine, NE, imaging, biomarker, β-adrenergic, and hippocampus.

This review used the Preferred Reporting Items for Systematic reviews checklist as a guideline for the dissemination of materials collected and was registered in PROSPERO (registration number CRD42020172733: 2020) [39, 40].

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