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Invited Perspective

In vitro evaluation of PET radiotracers reflecting multidimensionality of Alzheimer's disease: building more roadmaps for clinical translation

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Abstract: In the current issue of American Journal of Nuclear Medicine and Molecular Imaging, Vasdev et al. presented a work entitled "In Vitro Evaluation of PET Radiotracers for Imaging Synaptic Density, the Acetylcholine Transporter, AMPA-tarp-γ8 and Muscarinic M4 receptors in Alzheimer's disease". In which, in vitro autoradiography studies using radioligands were employed as a valuable tool to gain more insights for potential clinical translation. In this invited perspective, we would like to briefly introduce the current state of AD diagnosis, especially PET imaging on synapse, and highlight the advances of PET imaging in pre-clinic and clinic that might assist on precise therapy in the future.

Keywords: PET radiotracers, Alzheimer's disease, autoradiography, clinical translation

Alzheimer's disease (AD) is the most common type of dementia affecting elderly people worldwide. The neuropathological hallmarks of AD include amyloid-β (Aβ) plaques, neurofibrillary tangles, and neuronal loss. A conceptual framework of "A/T/N" (amyloid/tau/neurodegeneration) biomarkers recommended by the National Institute on Aging-Alzheimer's Association shifted the definition from a syndrome to a biological classification [1, 2]. Derived from thioflavin-T, carbon-11 labeled Pittsburgh compound B achieved for the first time of visualizing Aβ plaques in the living humans by positron emission tomography (PET) [3], followed by the development of [^{18}F]florbetapir and [^{18}F]flobetaben - fluorine-18 labeled Aβ molecular probes approved by the Food and Drug Administration (FDA) and the European Medicine Agency (EMA). In comparison with Aβ imaging, PET imaging of fibrillary tau is more challenging due to the existence of various proteoforms [4]. Continuous efforts culminated in PET tracers with high specificity for tau and favorable kinetic profiles, such as [^{18}F]AV1451, [^{18}F]MK-6240 and [^{18}F]RO-948. The strong correlation of tau PET imaging with Braak histopathologic classification appears to be an efficient tool for staging AD in clinic [5].

Original biomarkers for AD-related neurodegeneration ("N") include an elevated level of phosphor-tau in cerebrospinal fluid, decreased uptake of fluorodeoxyglucose [^{18}F]FDG and structural magnetic resonance imaging (MRI) with a characteristic pattern. Until 2016, [^{11}C]UCB-J targeting synaptic vesicle glycoprotein 2A (SV2A) was developed providing an invaluable approach to "see" the synaptic loss in patients with temporal lobe epilepsy [6]. Its analogue [^{18}F]SynVesT-1, also known as [^{18}F]SDM-8 or [^{18}F]MNI-1126, displayed excellent kinetics and specific bindings to quantify the alteration of synaptic density in neurological disorders. Synaptic loss measured by [^{18}F]SynVesT-1 demonstrated its close relationship with "A/T/N" biomarkers in the hippocampus and parahippocampal gyrus of patients with Alzheimer's clinical syndrome [7]. Nevertheless, the molecular mechanism underlying the progressive neurodegeneration remains complicated and not yet fully understood.

As a consequence, the failure rate stays high for AD drug development. The cholinergic system may represent the most successful therapeutic target validated as far. Cholinesterase inhibitors approved by FDA, namely donepezil, galantamine and rivastigmine, were found to stabilize or slow decline in cognition, function and behavior in patients with AD dementia [9]. Donepezil and galantamine inhibit acetylcholinesterase (AChE), whereas rivastigmine inhibits both AChE and butyrylcholinesterase. As suggested by the cholinergic hypothesis, the deterioration of cholinergic neurons in the brain and the loss of acetylcholine in synapse clefts are the major causes of cognitive impairment in patients with AD [10]. However, the efficacy of these drugs is accompanied by adverse side effect and cannot completely arrest the disease progression. On the other hand, memantine demonstrated therapeutic effect in moderate and severe AD dementia by regulation of N-methyl-D-aspartate (NMDA) receptor system. Several drug candidates function as NMDA receptor antagonist entered Phase III with the goal of improving neuropsychiatric symptoms of AD [11]. BMS-984923, a silent allosteric modulator of metabotropic glutamate receptor 5 (mGluR5), reversed synapse loss in mouse models of AD

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[12] and is recruiting participants for a multiple ascending dose study in Phase 1b (NCT05804383). The mGluR5 availability measured by [^{18}F]PSS232 showed correlation with neuropathological biomarkers of AD as well as neurodegenerative biomarkers [13]. Of note, owing to PET imaging of Aβ plaques, FDA granted accelerated approval for lecanemab and aducanumab, two antibody-based drugs that bind to and mop up Aβ decomposition. Overall, the multifaceted AD added barriers to the AD drug development. Future investigations in preclinical and clinical stages await multiple tracers to comprehend the molecular bases behind progressive neurodegeneration, to assist drug development with a right target, a right biomarker, and a right timing for interventions.

Vasdev et al. used in vitro autoradiography and various molecular probes to assess the altered target expression on post-mortem human brain tissues. [^{3}H]UCB-J and [^{3}H]SynVesT-1 were applied as a starting point to detect the variability of synaptic density in the cerebellum (CRB), prefrontal cortex (PFC) and hippocampus (HIP) of AD, mild cognitive impairment (MCI) and normal healthy volunteer (NHV). Both radioligands showed reduced synaptic density in MCI and AD tissues compared to NHV sections, with [^{3}H]SynVesT-1 being more sensitive. These results were consistent with the crucial role of [^{18}F]SynVesT-1 played in clinical investigations for synaptic loss in AD progression [14]. Most recently, our group carried out clinical studies to investigate the influence of apolipoprotein E (APOE) ε4 on synaptic density in the individuals with cognitive impairment [15]. It is in line with apolipoprotein E (APOE) ε4 stands for the major genetic risk factor for sporadic AD [8]. Using [^{18}F]SynVesT-1, even though after the control of Aβ burden, we can still observe significant synaptic loss in the brain regions of APOE ε4 carriers, and provided the first time a direct evidence that APOE ε4 potentiates synaptic loss via tau pathology in humans.

Acetylcholine synthesized in the presynaptic cholinergic neuron is transported via the vesicular acetylcholine transporter (VAChT) into presynaptic vesicles. Upon triggering, the released acetylcholine binds to and activates nicotinic and muscarinic acetylcholine receptors (nAChRs and mAChRs). Afterward, AChE in synapse clefts cleaved it into acetate and choline. [^{18}F]FEOBV and [^{18}F]VAT are two VAChT PET tracers transferred to clinical studies with favorable characteristics. Previously, [^{18}F]FEOBV displayed superior ability over [^{18}F]FDG on discriminating AD from NHV [16]. In contrast, the development of selective PET tracer towards mAChRs subtypes was lagging behind. [^{11}C]MK-6884 disclosed by Li et al. made a breakthrough in the regards of high selectivity and showing capability of measuring target engagement in the living human brain [17]. A declined non-displaceable binding potential of [^{11}C]MK-6884 in a small cohort of AD patients was reported, reflecting the loss of the M4 subtype of mAChRs. In the work performed by Vasdev et al., substantial reduction of VAChT was detected neither by [^{18}F]FEOBV nor [^{3}H]VAT on brain tissues with confirmed neuropathology. Meanwhile, [^{3}H]MK-6884 revealed 27% and 41% reductions in the hippocampal regions of MCI and AD, respectively. Clinical PET studies might be of interests to unveil the variability of various cholinergic components during the diseased progression. Together with minimal mental state examination and Montreal cognitive assessment, this hopefully may gain more insights into pathophysiology, guide clinical trials, and ultimately personalized treatment.

Besides NMDA receptors mentioned-above, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionic acid (AMPA) receptors represent another subtype of ionotropic glutamate receptor, which is crucial to synaptic plasticity and memory [18]. [^{11}C]K-2 with higher affinity to GluA2 and GluA4 subunits of AMPA receptors provided a valuable tool for visualizing the aberration of target expression in neuropsychiatric disorders [19]. JNJ-55511118, a small molecule targeting the transmembrane AMPA receptor regulatory protein γ8 (TRAP-γ8), emerged as a novel tool for reversible AMPA receptor inhibition and potentially as a new agent for neuroprotectant [20]. Interestingly, as shown by Vasdev et al., the specific binding of [^{3}H]JNJ-55511118 showed the substantial reduction in the hippocampal region of MCI (-41%) and AD (-56%) compared to those of NHV, which was more profound than synaptic loss detected by [^{3}H]SynVesT-1 and decreased M4 subtype of mAChRs detected by [^{3}H]MK-6884. The details for its mechanism warrant further investigations.

In summary, Vasdev et al. presented in vitro autoradiography using radioligands as powerful tools to interpretate the target alterations in AD pathology. This provides valuable insights for potential PET imaging studies in patients with AD and related dementia. In the meantime, novel PET tracers with promising results in preclinic are emerging to image targets in cholesterol degradation [21], endocannabinoid system [22-24] and purinergic signaling [25]. We hope these advances could assist on the elucidation of the molecular bases underlying AD pathology and culminate in novel diagnostic and therapeutic options with clinical relevance.

Disclosure of conflict of interest

Fang Xie serves as a consultant for Zentera Therapeutics (Shanghai) Co., Ltd.

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