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Molecular Imaging of the Nicotinic Cholinergic Receptor in Alzheimer Disease

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Molecular brain imaging represents a bridge between basic and clinical neuroscience and provides many opportunities for testing hypotheses *in vivo* in humans that are generated from integrating clinical observations, animal models, and neuropathology studies. In geriatric mental health, molecular imaging methods can provide the fundamental neurobiological data that are needed to address the most challenging issues of the field—namely, the treatment and ultimately, prevention of, cognitive deficits and neuropsychiatric symptoms (NPS). The initial mechanistic focus of single photon emission computer tomography and positron emission tomography (PET) molecular imaging studies in late-life neuropsychiatric and neurodegenerative disease was the monoaminergic targets of antipsychotic and antidepressant medications.¹ More recent advances in radiotracer chemistry have led to an unprecedented opportunity to visualize *in vivo* the neuropathology of Alzheimer disease (AD), as well as neurochemical mechanisms including the cholinergic system (acetylcholinesterase, the vesicular acetylcholine transporter, muscarinic and nicotinic receptors). Converging evidence from neuropathologic and multiradiotracer PET studies support the combined investigation of AD pathology with neurochemical and molecular mechanisms to understand cognitive decline and the emergence of NPS.²

Several lines of evidence highlight the importance of investigating nicotinic receptors *in vivo* and understanding the clinical significance of this system in neuropsychiatric and neurodegenerative disease.³ The nicotinic system has an important role in cognition (attention and memory) as shown by studies in healthy individuals and in neurodegenerative disease. The nicotinic system has several neurobiological functions relevant to cognitive deficits and NPS, including the ability to modulate other neurotransmitters (acetylcholine, glutamate, dopamine) and to promote synaptic plasticity, in addition to the associations with AD pathology. Nicotinic receptor modulators ($\alpha 4\beta 2$ and $\alpha 7$ receptor subtypes), many of which are in preclinical development, have been referred to as “multifunctional agents” that may have clinical benefit for both cognitive deficits and NPS.⁴

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As reviewed by Sultzer and colleagues,³ neuropathology and neuroimaging studies have shown decreased nicotinic receptor binding ($\alpha 4\beta 2$ subtype) in both AD and Parkinson disease. The ability to image nicotinic receptors in vivo has been complicated by such issues as slow brain uptake of radiotracers that require long duration scanning protocols and relatively low specific binding in extrathalamic, cortical, and limbic regions relevant to cognitive deficits and NPS. These issues are being addressed through recent developments in radiotracer chemistry and progress in being made on the development of $\alpha 7$ subtype radiotracers as well.^{5,6} Importantly, major insights into the role of the nicotinic system in aging have been made by combining pharmacological manipulations of the nicotinic system with task-based functional magnetic resonance imaging studies.⁷

Sultzer and colleagues have made major contributions to our understanding of the neural circuitry of cognitive deficits and NPS in AD in a series of methodologically rigorous studies utilizing PET measures of cerebral glucose metabolism. In the current article, the investigators focus on a potential underlying neurochemical mechanism for the glucose metabolic deficits.³ They evaluated the nicotinic $\alpha 4\beta 2$ receptor in a relatively large, well-characterized sample of AD patients and controls and correlated receptor binding with a comprehensive battery of cognitive and NPS measures. Importantly, the investigators used a shorter acquisition protocol performed at steady-state radiotracer concentrations that was feasible to perform in AD patients with NPS. Nicotinic $\alpha 4\beta 2$ receptor binding was decreased in AD patients compared with controls in cortical areas that are affected in AD (medial temporal cortex and posterior cingulate, insula), as well as subcortical regions that are relatively spared (medial thalamus and inferior caudate), based on studies of glucose metabolism and AD pathology. Decreased nicotinic $\alpha 4\beta 2$ receptor binding was more extensive than cerebral atrophy as measured on structural magnetic resonance imaging. This suggested that the $\alpha 4\beta 2$ receptor loss may not be entirely secondary to cerebral atrophy. In the control group, correlations were observed between lower thalamic and hippocampal binding and increased completion time of the Trail Making Test A task, indicative of slowed psychomotor speed and decreased attention. This is consistent with the role of the nicotinic system in cognition. No correlations between the cognitive measures and nicotinic $\alpha 4\beta 2$ receptor binding were observed in the AD patients (possibly because of floor effects). Importantly, in the AD patients, agitation/disinhibition was associated with lower anterior cingulate nicotinic $\alpha 4\beta 2$ receptor binding. As reviewed by the investigators, neuropathology and PET glucose metabolism studies have shown associations between the anterior cingulate and NPS. As suggested by pre-clinical data, the loss of nicotinic $\alpha 4\beta 2$ receptors might have secondary consequences with respect to impaired neurotransmitter modulation and/or synaptic plasticity that might represent a mechanism underlying agitation/disinhibition.

The neurobiological mechanisms of NPS in neurodegenerative disease are incompletely understood. NPS, including agitation/disinhibition, occur in the majority of individuals with neurodegenerative diseases and are associated with accelerated cognitive and functional decline, poorer quality of life, earlier institutionalization, and accelerated mortality (as reviewed¹). Preventing the emergence of NPS in neurodegenerative disease may slow cognitive and functional decline. The clinical management of NPS is one of the major challenges in geriatric psychiatry. The medications that are effective in treating these symptoms in younger individuals tend not to be effective in treating NPS in

neurodegenerative disease. Molecular brain imaging studies are logistically challenging, but are especially critical to identify the neurobiological mechanisms of NPS and to inform the development of more effective and safe treatments. The findings of Sultzer and colleagues suggest that nicotinic receptor modulators may be a potentially effective treatment strategy for agitation/disinhibition that could show a benefit to cognition, as well.

The observations by Sultzer and colleagues highlight the importance of radiotracer development for cortical and limbic $\alpha 4\beta 2$ receptors and, potentially, other nicotinic receptor subtypes ($\alpha 7$) and the application to aging and pre-clinical disease processes (MCI, mild behavioral impairment). In vivo molecular imaging studies can have an important and unique impact on identifying targets for early detection and for prevention of cognitive deficits and NPS.

Post-mortem studies have identified molecular mechanisms implicated in neurodegenerative disease. In vivo molecular imaging studies can provide more direct information about how these mechanisms relate to cognitive deficits and NPS, as well as their prognostic value. Further, longitudinal, multiradiotracer imaging can identify new targets for prevention and treatment by evaluating the relationships between AD pathology (beta-amyloid and tau), neurochemical and molecular mechanisms (including inflammation, epigenetic mechanisms, synaptic vesicle proteins) that may be detected prior to visualization of substantial AD pathology.

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References

1. Hirao K, Pontone GM, Smith GS. Molecular imaging of neuropsychiatric symptoms in Alzheimer's and Parkinson's disease. *Neurosci Biobehav Rev*. 2015; 49:157–170. [PubMed: 25446948]
2. Mufson EJ, Ikonovic MD, Counts SE, et al. Molecular and cellular pathophysiology of preclinical Alzheimer's disease. *Behav Brain Res*. 2016; 311:54–69. [PubMed: 27185734]
3. Sultzer DL, Melrose RJ, Riskin-Jones H, et al. Cholinergic receptor binding in Alzheimer disease and healthy aging: assessment in vivo with PET imaging. *Am J Geriatr Psychiatry*. 2017; doi: 10.1016/j.jagp.2016.11.011
4. Terry AV Jr, Callahan PM, Hernandez CM. Nicotinic ligands as multifunctional agents for the treatment of neuropsychiatric disorders. *Biochem Pharmacol*. 2015; 97:388–398. [PubMed: 26231940]
5. Horti AG, Kuwabara H, Holt DP, et al. Recent PET radioligands with optimal brain kinetics for imaging nicotinic acetylcholine receptors. *J Labelled Comp Radiopharm*. 2013; 56:159–166. [PubMed: 24285321]
6. Horti AG. Development of [(18)F]ASEM, a specific radiotracer for quantification of the $\alpha 7$ -nAChR with positron-emission tomography. *Biochem Pharmacol*. 2015; 97:566–575. [PubMed: 26232729]
7. Dumas JA, Newhouse PA. The cholinergic hypothesis of cognitive aging revisited again: cholinergic functional compensation. *Pharmacol Biochem Behav*. 2011; 99:254–261. [PubMed: 21382398]