tude below that necessary to visualize synapses, it is difficult to ascertain synaptic BuChE unless a unique and exclusive synaptic localization of the ligand is demonstrated by independent means.

Based on the above considerations, it is difficult to reach convincing conclusions regarding synaptic BuChE in AD using the positron emission tomography data presented.

[1]Brain-Mind Project and University of Miami School of Medicine, Miami, FL, [2]Departments of Medicine, Anatomy and Neurobiology, Dalhousie University, Halifax, Nova Scotia, Canada, [3]Drug Design & Development Section, Laboratory of Neurosciences, Intramural Research Program, National Institute on Aging, Baltimore, MD, and [4]Laboratory for Neurodegenerative and Aging Research, Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA

References

1. Kuhl DE, Koeppe RA, Snyder SE, et al. In vivo butyrylcholinesterase activity is not increased in Alzheimer's disease synapses. Ann Neurol 2006;59:13–20.
2. Snyder SE, Gunpundi N, Sherman PS, et al. Radiolabeled substrates: in vitro methods for determining structure-activity relationships and identification of a positron emission tomography radiopharmaceutical for in vivo measurement of butyrylcholinesterase activity. J Cereb Blood Flow Metab 2001;21:132–143.
3. Silver A. The biology of cholinesterases. Amsterdam: Elsevier, 1974.
4. Perry EK, Perry RH, Blessed G, Tomlinson BE. Changes in brain cholinesterase in senile dementia of Alzheimer's type. Neuropathol Appl Neurobiol 1978;4:273–277.
5. Geula C, Mesulam M-M. Cholinesterases and the pathology of Alzheimer's disease. Alzheimer Dis Assoc Disord 1995;9:23–28.

DOI: 10.1002/ana.20926

Imaging Butyrylcholinesterase Activity in Alzheimer's Disease

David E. Kuhl, MD,[1] Robert A. Koeppe, PhD,[1] Scott E. Snyder, PhD,[1] Satoshi Minoshima, MD, PhD,[2] Kirk A. Frey, MD, PhD,[1,3] and Michael R. Kilbourn, PhD[1]

It is unverified that the ligand 1-[^{11}C]methyl-4-piperidinyl n-butyrate ([^{11}C]BMP) is not a substrate for acetylcholinesterase (AChE). We identified [^{11}C]BMP based on specificity determined by in vitro assay using nonhuman esterases.[1] We[1] and others[2] have demonstrated in vitro that neither BMP nor any of the other longer chain 1-methyl-4-piperidinyl esters shows cleavage by AChE, even at enzyme concentrations of 100U/ml and incubation times as long as 60 minutes. In no references were butyrate esters found to be substrates for AChE in any species. It is unlikely that cleavage of [^{11}C]BMP by AChE occurs in human brain, particularly within the time frame of a typical positron emission tomography (PET) study.

Can low-resolution PET visualize synapse content? If PET misses plaque-bound cholinesterase, how can it estimate synapse cholinesterase? The PET method using [^{11}C]BMP (see Kuhl and colleagues[3]) provides estimates of butyrylcholinesterase (BuChE) hydrolysis rates in vivo, not BuChE concentration. This method is not merely measuring the distribution of the radiotracer from a static image, but rather is based on the temporal kinetics of the radiotracer in vivo. The limited resolution of PET (10mm in this study) is insufficient to determine the histological location of [^{11}C]BMP cleavage. However, the PET measure is sensitive to BuChE hydrolysis of [^{11}C]BMP wherever it does occur within the field of view, even when each of these multiple sites (synapses, glia) is smaller than the resolution of the imaging system. Other information is needed to inform the histological location of hydrolysis.

For example, hydrolysis of acetylcholine is known to occur predominantly within cholinergic synapses by outwardly facing, membrane-anchored AChE and BuChE.[4] These are the critical sites where acetylcholine is concentrated and to which inhibition therapy is targeted. We have shown that PET methods quantify AChE or BuChE activities within tissue distributions that are accessible to systemically administered cholinesterase inhibitors and that match regional distributions of AChE[5] and BuChE.[3] Consequently, PET-measured AChE activity estimates activity in cholinergic terminals, where AChE is known to be concentrated primarily. The distribution of BuChE activity is known to be much more uniform, but does include the cholinergic synapses.

Unlike tissue homogenate assays of postmortem AD brain, our in vivo PET method could have been insensitive to substantial increases in sparse, but highly concentrated, dead foci of plaque BuChE that were poorly perfused and distant from cholinergic terminals. However, our in vivo method should have detected in living AD brain any substantial increase in BuChE activity that could have been associated with cholinergic synapses, and it did not.

[1]Division of Nuclear Medicine, Department of Radiology, University of Michigan, Ann Arbor, MI, [2]Division of Nuclear Medicine, Department of Radiology, University of Washington, Seattle, WA, and [3]Department of Neurology, University of Michigan, Ann Arbor, MI

References

1. Snyder SE, Gunupudi N, Sherman PS, et al. Radiolabeled cholinesterase substrates: in vitro methods for determining structure-activity relationships and identification of a positron emission tomography radiopharmaceutical for in vivo measurement of butyrylcholinesterase activity. J Cereb Blood Flow Metab 2001; 21:132–143.
2. Kikuchi T, Fukushi K, Ikota N, et al. Synthesis of piperidinyl and pyrrolidinyl butyrates for potential in vivo measurement of cerebral butyrylcholinesterase activity. J Labelled Comp Radiopharm 2001;44:31–41.
3. Kuhl DE, Koeppe RA, Snyder SE, et al. In vivo butyrylcholinesterase activity is not increased in Alzheimer's disease synapses. Ann Neurol 2006;59:13–20.
4. Massoulie J. The origin of the molecular diversity and functional anchoring of cholinesterases. Neurosignals 2002;11: 130–143.
5. Kuhl DE, Koeppe RA, Minoshima S, et al. In vivo mapping of cerebral acetylcholinesterase activity in aging and Alzheimer's disease. Neurology 1999;52:691–699.

DOI: 10.1002/ana.21023