Neurochemical Imaging of Dementias

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Neurochemical imaging is one of the most established "molecular" imaging techniques. There have been tremendous efforts expended to develop radioligands specific to each neurochemical system. Investigational applications of neurochemical imaging in dementing disorders are extensive. Cholinergic, dopaminergic, and serotonergic systems, as well as benzodiazepine receptors, opioid receptors, and glutamatergic receptors have been imaged in Alzheimer disease and other dementing disorders. These investigations have provided important insights into disease processes in living human patients. The clinical diagnostic use of neurochemical imaging for dementing disorders is currently limited, but this technique is used to help develop therapeutic drugs at multiple levels.

DEMENTING DISORDERS affect more than 4% of the elderly population older than 65 years.[1] Among dementing illnesses, Alzheimer disease (AD) is reported to be the most common form in the United States as well as worldwide, and its prevalence increases with age.[1,2] With the current trend towards increasing longevity, the prevalence of dementia, particularly AD, will become even higher during the next few decades.[3,4] Dementing illness imposes significant burdens on our society, health care, and economy.[5] The study of dementing illness ranges from molecular mechanisms to socioeconomic analysis.

NEUROCHEMICAL IMAGING

The investigation of dementing disorders using radionuclides dates back to early cerebral blood flow and oxygen metabolic studies,[6,7] but subsequent developments of single-photon emission tomography (SPECT) and positron emission tomography (PET) generated a surge of research directed at brain imaging. In the late 1970s, Sokoloff and colleagues developed the radiolabeled glucose analogue, [C-14]deoxyglucose, to measure regional neuronal activity in the living brain.[8] However, unlike glucose, DG-6-P cannot be converted to fructose-6-phosphate and accumulates in the brain for a duration that is long enough for imaging. This method was quickly translated to a [F-18]labeled tracer, [F-18]-2-fluoro-2-deoxy-D-glucose (FDG),[9] and [C-11]labeled tracer, 2-deoxy-D[1-C-11]glucose[10] for human brain imaging using PET. Initial applications of FDG-PET to dementing disorders were extensive.[11-14] A major finding from these initial studies was a regional heterogeneity in the impairment of energy metabolism (ie, accentuated hypometabolism in the parietotemporal and frontal association cortices) in contrast to relative preservation of primary cortices and subcortical structures. FDG-PET is an example of the oldest "molecular" imaging of the brain, which still serves as an important in vivo imaging technique for the investigation of brain disorders. The diagnostic applications of FDG-PET to dementing disorders also have been debated recently.

In 1983, following FDG development, 2 laboratories reported novel imaging techniques for the dopamine system, C-11 labeled methylspiperone[15] and F-18 labeled L-dopa.[16] One year before these PET approaches, radioiodine I-123 labeled ligand quinuclidinyl benzilate, [I-123]-OH-QNB, was tested for in vivo muscarinic cholinergic receptor imaging using SPECT,[17] and differential uptake by the cerebral cortex and subcortical structures was reported.[18] These early studies ignited efforts of radiochemistry development for neurochemical imaging, with neurodegenerative disorders as one of the major targets. There have been many radiotracers developed to date for the investigations of dementing disorders. These developments include radiotracers to image cholinergic, dopaminergic, serotonergic, and glutamatergic systems, and central and peripheral benzodiazepine receptors.

Neurochemical imaging, one of the most established fields of "molecular" imaging, is still evolving in parallel to advancing knowledge of neurochemistry and molecular genetics of the brain and brain disorders. Figure 1 illustrates many potential targets for in vivo imaging of dementing disor-

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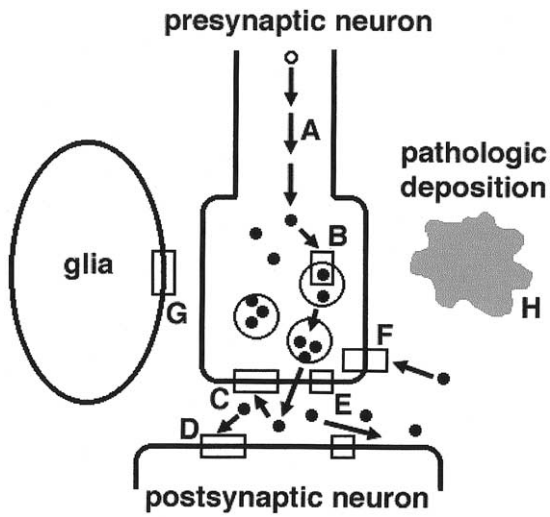

Fig 1. A schematic diagram of neurochemical imaging targets, including enzyme synthesizing a neurotransmitter (A). (B) Vesicular transporter on the presynaptic vesicle. (C) Presynaptic receptor. (D) Postsynaptic receptor. (E) Enzyme degrading a neurotransmitter in the synaptic cleft. (F) Presynaptic transporter and reuptake site. (G) Glial receptor. (H) Pathologic deposit specific to diseases. In addition to these targets, other neuronal elements, such as ion channel, mitochondrion electron transport system, secondary messenger system can be potential targets for in vivo imaging.

ders. These targets include enzymes involved in neurotransmitter synthesis, vesicular transporters located on synaptic vesicles, presynaptic receptors, postsynaptic receptors, enzymes degrading neurotransmitters, presynaptic transporters and reuptake sites, and glial receptors. Pathologic deposits specific to certain dementing disorders, such as β-amyloid in AD, can be imaged as well. There are recent efforts to develop in vivo amyloid imaging probes for the investigation of AD and related disorders.[19-21]

Owing to the quantitative nature of PET measurements and SPECT, if conducted appropriately, quantitative in vivo neurochemical assays are possible by imaging. However, in comparison to in vitro receptor assays that had been used to study postmortem human brain specimens and animal research, in vivo imaging imposes several limitations and requires certain considerations. Unlike in vitro binding studies, radiotracers that can be used for PET and SPECT have to cross the blood-brain barrier (BBB) following intravenous injection. BBB permeability can be influenced by several factors, including the ligand's ionizable groups and lipophilicity.[22,23] The regional specificity of ligand binding to receptor types and subtypes also needs to be considered carefully because it is typically difficult to apply unlabeled displacing ligands as are used for in vitro studies. Ligands can be metabolized within the brain and within other organs. Metabolized ligands within other organs may cross BBB, and may give confounding signals on PET and SPECT. Radiolabeled ligands need to have a high enough specific activity to give signals for imaging without saturating available receptors or inducing physiologic effects.

With the in vivo imaging approach, nonspecific binding and free ligands cannot be minimized by rigorous washing of the specimen as for in vitro assays. Thus, tracer kinetic analysis becomes important to model the behavior of the ligand in the brain. It is important to estimate specific binding separated from nonspecific binding and free components using imaging data obtained from PET and SPECT, and is often combined with blood sampling. However, even the most sophisticated tracer kinetic modeling may not be able to overcome a fundamental limitation of a ligand, such as limited BBB permeability relative to high affinity of the ligand to the receptor system or presence of significant radiolabeled metabolites within the brain. The accuracy of PET and SPECT measurements of neurochemical changes relies on multiple factors, including quantitative accuracy of PET and SPECT instrumentation, nature of radiotracer, imaging protocol, metabolite analysis, tracer kinetic analysis, and image analysis. For these reasons, it is important for investigators to validate new radiotracers rigorously before clinical applications. It is equally important for readers to understand that published data may have limited accuracy regarding in vivo imaging assays and, therefore, may affect interpretation of the results.

CHOLINERGIC IMAGING

AD, first described by Dr. Alzheimer in 1906,[24] is reported to be the most common form of dementia and affects more than half of dementia patients.[1,25,26] Imaging of dementia dates back to the late 1960s before the emergence of cross-sectional imaging techniques.[6,27,28] Because Parkinson disease (PD) was attributed to degeneration of dopamine neurons in the nigrostriatal pathway, investigators attempted to link a particular neurochemical system to cognitive impairment seen in AD. "Cholinergic Hypothesis" of AD, established in late 1970s, was based on observations, including

memory loss induced by cholinergic blockade in normal human subjects and major deficits in cortical cholinergic markers in AD.[29-31] There have been efforts to characterize cholinergic degeneration in AD and drug developments to improve cholinergic transmissions.

Imaging investigations of the cholinergic system in AD were performed not only using neuroreceptor and/or transmitter ligands but also by FDG-PET and perfusion SPECT. Cholinergic neurons are located in the basal forebrain, nucleus basalis of Meynert and send cholinergic projections to the entire cerebral cortex. An electrocoagulation lesion in the nucleus basalis of Meynert in primates produced profound metabolic reductions in frontotemporal association cortices that were somewhat similar to those observed in AD.[32,33] However, the blockade of cholinergic transmission by an amnestic dose of scopolamine resulted in increased glucose metabolism in contrast to metabolic reductions commonly seen in AD.[34] Central cholinergic stimulation by physostigmine produced differential responses in regional cerebral blood flow measured by perfusion SPECT in patients with AD in comparison to normal controls.[35] Perfusion changes by cholinergic stimulation were compared with metabolic changes by PET in normal subjects and patients with AD.[36] This study showed the differential effects of physostigmine on cerebral blood flow and metabolic activity, indicating vascular and metabolic responses, complicating interpretation of imaging data with cholinergic drug interventions. A single dose of acetylcholinesterase (AChE) inhibitor, velnacrine maleate, resulted in increased perfusion in the superior frontal association cortex, particularly in patients with more severe AD.[37] These investigations provided functional links between cholinergic modulation, and neuronal activity and cerebral blood flow.

The imaging of muscarinic acetylcholine receptor in AD was first achieved using SPECT and the [I-123]labeled radiotracer, quinuclidinyl benzilate (QNB).[17] A subsequent study involving patients with AD showed impairment of muscarinic receptor binding.[38] SPECT with a high-affinity muscarinic receptor antagonist, 3-quinuclidinyl-4-iodobenzilate, showed focal abnormalities in frontal and posterior temporal cortices in AD, in contrast to patients with Pick disease who showed frontal and anterior temporal deficits.[39] In comparison to FDG-PET, QNB SPECT showed higher deficits than metabolic abnormalities in AD.[40] Chronic cholinergic blockage by low-dose scopolamine administration resulted in increased muscarinic receptor binding on QNB SPECT in AD, in comparison to decreased binding observed in normal controls, indicating differential modulatory mechanisms in AD.[41] However, QNB uptake in the brain showed on SPECT also may be affected by differential distributions of muscarinic receptor subtypes.[42,43] It was also reported that brain QNB uptake was limited by ligand delivery (ie, regional cerebral blood flow and BBB transport).[44]

A subtype, nonselective muscarinic acetylcholine receptor ligand, [C-11]N-methyl-4-piperidyl benzilate , was developed for PET and applied in AD.[45] In part due to the complexity of tracer kinetic modeling to separate ligand delivery versus specific receptor binding, this method resulted in a limited sensitivity and did not show significant alterations of muscarinic acetylcholine receptor density in AD. There are continuing efforts to develop subtype specific muscarinic acetylcholine receptors targeting AD.[46] The development of subtype specific ligands is critical for a better understanding of muscarinic receptor alterations in AD because postmortem studies showed differential preservation and loss of muscarinic receptor subtypes (ie, relative preservation of M1 in contrast with consistent loss of M2 receptors).

There have been attempts to image nicotinic acetylcholine receptors in AD using in vivo imaging techniques, but radioligands suitable for nicotinic receptors are limited to date. A series of PET studies using [C-11]nicotine was reported and showed decreased nicotinic receptor density in AD.[47-51] The [C-11]nicotine PET also showed restoration of nicotinic receptors following treatments with cholinesterase inhibitor and nerve growth factor.[48,50,52,53] However, tracer kinetics of [C-11]nicotine may not be optimally suited for PET due to the influence of regional cerebral blood flow. Correction for blood flow using [C-11]butanol PET was proposed,[51] but this limits the general applications of the technique. There are continuing efforts to develop further nicotinic acetylcholine receptor ligands for better in vivo imaging characteristics and subtype specificity.[54]

A traditional presynaptic marker of cholinergic neurons, choline acetyltransferase (CAT), has not been imaged successfully in vivo. However, vesicular acetylcholine transporters (VAChT) that are

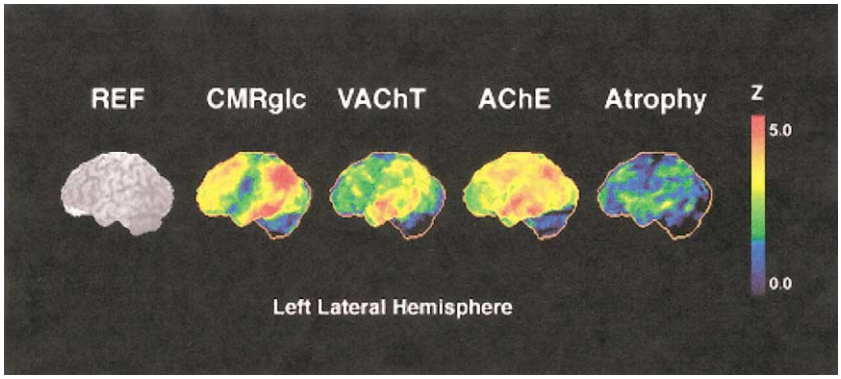

Fig 2. Neurochemical changes seen in Alzheimer disease (AD). The images show Z statistical maps of neurochemical changes observed in a group of patients with AD in comparison with a group of age-similar normal controls. Higher Z values (yellow-to-red color) indicate higher reductions of neurochemical indices. Energy metabolism (CMRglc) measured by [F-18]-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) shows severe reductions in the parietotemporal and frontal association cortices but sparing the primary sensorimotor cortex. In comparison, vesicular acetylcholine transporters (VAChT) measured by (-)-5-[I-123]iodobenzovesamicol (IBVM) single-photon emission tomography (SPECT) and acetylcholinesterase (AChE) activity measured by N-[C-11]methylpiperidyl propionate PET show more diffuse reductions in the cerebral cortex without clear sparing of the primary sensorimotor cortex. In all 3 indices, the cerebellar hemisphere is relatively preserved. Regional cortical atrophy measured quantitatively by magnetic resonance imaging (MRI) (atrophy) shows milder changes in comparison with neurochemical changes in AD, and the pattern of regional atrophy is similar to changes in CMRglc, but not in VAChT and AChE, indicating differential pathologic mechanisms of cortical atrophy and cholinergic neurodegeneration. Kuhl[56,62] and Minoshima[63,64] and coworkers provide more information regarding each imaging study and method.

expressed on presynaptic vesicles of cholinergic neurons were imaged using an iodinated tracer, (-)-5-[I-123]iodobenzovesamicol (IBVM) and SPECT.[55] This tracer was used as a marker for cholinergic presynaptic terminal integrity. Because of good correlation between k3 estimates with blood sampling and static images of IBVM at 22 hours after injection, the protocol of IBVM SPECT could be simplified to static imaging at a few times without dynamic SPECT or blood sampling. The loss of cholinergic presynaptic terminals was estimated to be 3% to 4% per decade with normal aging, but approximately 30% loss in the entire cerebral cortex of patients with AD whose onset age was before 65 years.[56] In contrast, cholinergic presynaptic terminal loss was much milder and restricted to the hippocampus and temporal lobe in patients with an onset age after 65 years. The loss of cholinergic presynaptic terminals detected by in vivo findings was not as marked as had been suggested by CAT measurements of postmortem specimens, but possible discordance between CAT and VAChT has been discussed previously.[57] Nevertheless, imaging of VAChT using SPECT showed quantitatively the loss of presynaptic cholinergic terminals in aging and AD in living human subjects.

Another traditional cholinergic enzyme, AChE, is used not only as a marker for cholinergic neurons, but has been a target for drug treatments as well. The first generation of cholinesterase inhibitors, tacrine or tetrahydroaminoacridine (THA), is approved for the symptomatic treatment of AD. This development was followed by donepezil (Aricept, Eisai, Inc., Teaneck, NJ) and other compounds that became clinically available in the United States. Two research groups developed [C-11]labeled acetylcholine analogues to image an enzymatic activity of cholinesterase using PET, namely N-[C-11]methylpiperidyl acetate[58,59] and N-[C-11]methylpiperidyl propionate.[60] The initial study in patients with AD showed a 30% to 40% loss of AChE activity in the cerebral cortex, most accentuated in the temporoparietal cortices.[61] A pattern of AChE loss measured by PET in AD was similar to that in presynaptic VAChT loss measured by SPECT, but the pattern of these changes was different from glucose hypometabolism measured by FDG-PET (Fig 2).[62]

Discordance between AChE reductions versus changes in glucose metabolism as well as cerebral blood flow also was confirmed.[65] These findings dispute early primate studies indicating a possible role of cholinergic degeneration to account for hypometabolism seen in association cortices.[32,33] Again, the loss of AChE during normal aging was only modest.[62,66] Further investigations revealed significant reductions of AChE in the neocortex,

hippocampus, and amygdala in the patients with early onset AD but only in the temporoparietal cortex and amygdala in the patients with late onset AD.[67] The findings were similar to the patterns of cholinergic terminal loss shown by SPECT.[56] The PET method to quantify AChE activity was simplified without arterial blood sampling,[68,69] permitting more widespread applications.

AChE imaging is an example of how in vivo PET helps not only gain insight into disease mechanisms but also to validate the effects of drug treatments. Donepezil treatment of 5 or 10 mg per day for at least 5 weeks resulted in AChE inhibition of only 27%, in comparison with AChE inhibition of 52% induced by physostigmine in normal controls.[70] Rivastigmine and donepezil achieved a similar degree of AChE inhibition in patients with AD, and the inhibition was most prominent in the frontal lobe 37% to 39% in comparison with 28% in the temporal lobe.

Applications of cholinergic imaging have been focused primarily on AD. However, there are several reports of cholinergic impairment in other dementing disorders. Dementia with Lewy bodies (DLB), the second most common cause of neurodegenerative dementia, was reported to show more severe cholinergic degeneration than pure AD,[71] and there were clinical indications that AChE inhibitor treatments may have a greater effect in patients with DLB. In vivo PET reported low AChE activity in patients with DLB in comparison with those with AD.[65] Many patients with an antemortem diagnosis of PD with dementia show cortical Lewy bodies. Patients with PD with dementia showed extensive cortical cholinergic terminal loss that was similar to AD.[56]

DOPAMINERGIC IMAGING

Dopamine imaging was the first neurochemical PET procedure reported in the literature,[15,16] and extensive investigations have been conducted for dopaminergic targets, including dopaminergic presynaptic enzyme, receptors (D1, D2, and other subtypes), and presynaptic transporters (dopamine and monoamine). Dopamine imaging was applied initially to PD without dementia,[72-75] and confirmed the nigrostriatal degeneration and dopamine deficits described previously by postmortem investigations.

Early studies of dopamine imaging in dementia and AD include D2 receptor PET with [C-11]raclopride[76] and D2 receptor SPECT with [I-123]labeled 3-Iodo-6-methoxybenzamide (IBZM).[77] Patients with dementia with the amyotrophic lateral sclerosis-parkinsonism-dementia complex of Guam were examined using [F-18]fluorodopa PET.[78] A subsequent study using [F-18]fluorodopa found that the Mini-mental State Examination score and age predicted dopamine deficits in AD, indicating impaired dopamine metabolism as dementia became progressively more severe.[79]

Neurochemical correlates of extrapyramidal symptoms frequently observed in AD are not understood fully. A postmortem investigation suggested a correlation between neurofibrillary tangle density in the substantia nigra and extrapyramidal signs in AD.[80] This question became a focus of PET and SPECT investigations. A study using [F-18]fluorodopa PET indicated no significant reduction in [F-18]fluorodopa uptake in the caudate or putamen of rigid or nonrigid patients with AD versus normal controls. In contrast, there were severe reductions in PD, indicating differential underlying mechanisms of extrapyramidal symptoms in AD and PD.[81] The [I-123]IBZM SPECT showed modest striatal D2 receptor reductions of approximately 15% in AD without overt extrapyramidal signs in comparison to controls. This result suggested a decline of postsynaptic striatal dopamine receptors as a part of AD pathophysiology that is different from prevalent presynaptic nigrostriatal degeneration.[82] In contrast, subsequent dopamine transporter imaging using a cocaine analogue, 2-β-carbomethoxy-3-β-(4-[F-18]fluorophenyl)tropane (β-CFT), showed more severe reductions in the putamen or caudate in patients with AD with extrapyramidal symptoms.[83]

A further PET investigation using a dopamine D1 receptor antagonist, [C-11]NNC 756 and a D2 antagonist, [C-11]raclopride showed 14% reductions in D1 receptors in AD but no significant reduction in D2 receptors.[84] However, D1 or D2 receptor changes did not correlate with Mini-mental State Examination scores or motor Unified PD Rating Scale scores. These imaging investigations indicate differential alterations of dopaminergic markers in AD and PD, but the exact neurochemical basis for extrapyramidal signs in AD requires further investigation.

Dopamine imaging in dementia received much attention in the investigation of DLB. Lewy bodies are intracytoplasmic eosinophilic neuronal inclu-

sions initially found in pigmented neurons of the brain stem in PD.[85,86] In 1961, association of diffuse cortical Lewy bodies and dementia was observed.[87] Subsequently, an autopsy case of presenile dementia in which Lewy bodies were found not only in the brain stem, but, also, similar inclusion bodies in the cerebral cortex were reported.[88] Cortical and brain stem Lewy bodies were also found to coexist with senile plaques.[89] Despite early nosologic controversy, DLB is recognized as the second most common form of neurodegenerative dementia, and has been found to have substantial pathologic and clinical overlap with AD.[90,91]

In vivo neurochemical imaging depicted dopaminergic abnormalities in living patients with DLB. Decreased striatal dopamine transporters in DLB was detected using iodine-123 2 β-carboxymethoxy-3 β-[4-iodophenyl]tropane ([I-123]β-CIT) SPECT.[92] The caudate/putamen ratio of postsynaptic dopamine D2 neuroreceptor density measured by IBZM SPECT was significantly lower in probable DLB as compared with probable AD and normal controls.[93] Decreased binding of dopaminergic presynaptic marker 2-β-carbomethoxy-3-β-(4-iodophenyl)-N-(3-fluoropropyl)nortropane (FP-CIT) was also shown by SPECT in a case of autopsy proven DLB.[94] PET using [F-18]fluorodopa also showed decreased uptake in the putamen in DLB that distinguished DLB from AD, with a sensitivity of 86% and specificity of 100%.[95] Decreased [F-18]fluorodopa uptake in the putamen measured by PET was also confirmed in an autopsy proven case of pure DLB.[96] When compared with PD, a more symmetric and severe loss of dopamine transporters was found in DLB.[97] FP-CIT SPECT showed significantly lower dopamine transporter density in PD and DLB, as compared with AD and normal controls in the caudate and putamen, indicating a possible differential diagnosis of DLB from AD by CIT SPECT.[98] However, further investigations are necessary to determine if dopamine imaging can distinguish reliably patients with AD with extrapyramidal signs versus DLB, which is often a clinical question.

The dopamine imaging has been applied to other types of dementing disorders. The [F-18]fluorodopa PET showed reduced striatal uptake in patients with progressive supranuclear palsy. However, a patient with short duration of the disease showed only minor changes, indicating that early parkinsonian signs and supranuclear palsy might relate to dysfunction distal to nigrostriatal neurons.[99] IBZM SPECT of D2 dopamine receptors indicated decreased radiotracer uptake in the frontal cortex in frontotemporal lobe dementia (FTD) in comparison with AD.[100] The [C-11]CFT PET showed the same degree of loss of nigrostriatal neurons projecting to the caudate and putamen in patients with FTD, and the degree of the loss correlated with the severity of extrapyramidal signs.[101] The [F-18]fluorodopa and [C-11]raclopride PET showed a loss of nigrostriatal neurons associated with the loss of D2-receptor bearing striatal neurons.[102] PET of D1 and D2 receptors and dopamine transporters, as well as volumes of the caudate and putamen explained much of variance in cognitive levels in Huntington disease, indicating Huntington disease as frontostriatal dementia.[103] Dopaminergic imaging of dementing disorders can increase our understanding of the neuronal correlates of cognitive as well as motor impairments in various dementing disorders.

BENZODIASEPINE RECEPTOR IMAGING

There are 2 classes of benzodiazepine receptors: (1) central and (2) peripheral types. The central benzodiazepine receptor is part of the major inhibitory neurotransmitter system, $GABA_A$ (gamma-amino butyric acid) receptor complex, consisting of the γ–aminobutyric acid receptor, benzodiazepine receptor, barbiturate site, steroid site, picrotoxin site, and chloride channel. This receptor-channel complex is allosterically modulated by benzodiazepines and barbiturates. PET with a radiolabeled benzodiazepine antagonist, [C-11]-flumazenil, showed relatively preserved benzodiazepine binding sites in AD.[104] In contrast, several SPECT with [I-123]labeled iomazenil consistently showed decreased cortical binding in AD.[105-108] One study using [C-11]flumazenil PET and [I-123]iomazenil SPECT indicated relative preservation of both indices in AD in comparison to the degree of cerebral blood flow reduction.[109] It is not certain if the discrepancy between the PET and SPECT of benzodiazepine receptors is due to a difference in kinetics and affinity of the 2 tracers. However, observed reductions in benzodiazepine receptors were relatively mild in comparison to the severe metabolic reductions commonly seen in AD. Modest reductions of the benzodiazepine

and/or $GABA_A$ receptor complex seen by imaging are consistent with results from postmortem investigations.[110,111]

In contrast to central benzodiazepine receptors, peripheral benzodiazepine receptors are expressed on cells of mononuclear phagocyte lineage. Only a small number of peripheral benzodiazepine receptors are expressed in normal brain parenchyma. This receptor can be expressed on activated microglia in the brain. Observations of postmortem specimens indicated the presence of immune responses in AD brains.[112] The involvement of a complement pathway and microglial activation was speculated to be one of the possible mechanisms of neuronal death in AD.[113,114] An initial PET study using [C-11]labeled PK11195 (1-[2-chlorophenyl]-N-methyl-N-[1-methylpropyl]-3-isoquinoline carboxamide), a specific ligand that binds to peripheral benzodiazepine receptors, showed no detectable alteration in patients with mild-to-moderate AD.[115] However, a subsequent study using the enantiomer, (R)-PK11195, showed significantly increased binding in the entorhinal cortex, temporoparietal cortices, and posterior cingulate cortex in patients with mild and early AD.[116] This tracer provides an exciting opportunity for investigators to examine immune responses in neurodegenerative diseases and possible responses to anti-inflammatory drug treatments of dementias.

Other Neurochemical Imaging of Dementia

Serotonergic cells in the brain stem are lost in AD. This postmortem evidence was confirmed by [F-18]setoperone PET of serotonergic 5-HT2 receptors in AD.[117] The study showed a significant loss of 5-HT2 receptors in the cerebral cortex, particularly in the frontal and temporal cortices. PET of 5-HT2 receptors using [F-18]altanserin showed a significant loss of binding in AD in comparison to late-life depression[118] and possible correlation with behavioral aspects of the disease.[119] SPECT, using a selective 5-HT(2A) receptor antagonist [I-123]-5-I-R91150, showed decreased binding in the frontal, cingulate, sensorimotor, parietal inferior, and occipital regions, mostly consistent with previous PET findings.

A limited study of opioid receptor PET using a μ- and κ-opiate receptor antagonist 6-deoxy-6-β-[F-18]fluoronaltrexone (cyclofoxy [CF]) showed global reduction of receptor binding in AD, with a pattern different from regional cerebral blood flow changes.[120] There appeared to be gender differences in the severity of CF binding in AD.[121] However, it is not understood how these changes in opioid receptors correlate with cognitive behavioral changes seen in AD.

Because of the cholinergic hypothesis of AD, neurochemical imaging has focused on the cholinergic system. However, accumulating evidence from postmortem and in vivo imaging indicates that AD affects multiple neurochemical systems at different brain structures. A recent postmortem investigation revealed only mild cholinergic deficits in early AD, challenging the cholinergic hypothesis.[122] Excitotoxic lesioning of the basal forebrain cholinergic structures in baboons resulted in only marginal changes in glucose metabolism in the neocortex, where patients with AD typically showed significant hypometabolism.[123] In contrast, neurotoxic lesions in the entorhinal cortex in baboons produced hypometabolism in the temporoparietal regions similar to AD.[124] However, in human patients with AD, neither the loss of entorhinal efferents nor cholinergic deficit explains all the metabolic features seen in very early AD.[63] These observations indicate that neurochemical systems other than the cholinergic system are likely affected significantly in AD. Major cortical neurons degenerating in AD are large, excitatory pyramidal neurons that use glutamate as a neurotransmitter.

The loss of cortical glutamatergic neurons is a major pathologic process of AD, and dysfunction in glutamatergic neurons in relation to excitotoxic neuronal death has been implicated. Severe cortical hypometabolism in AD seen on FDG-PET probably reflects the loss of cortico-cortical neurons. Imaging of the glutamatergic system and excitatory glutamate N-methyl-D-aspartate (NMDA) receptor was attempted but with no success to date. The use of magnetic resonance spectroscopy to measure glutamate in AD brains failed to show any difference from normal controls,[125] probably in part due to a difficulty in separating metabolic and transmitter pools of glutamate. An NMDA antagonist, MK-801, was labeled with [I-123] for SPECT and applied to patients with AD, but no convincing findings were obtained in AD due to the limited kinetic property of this tracer.[126] The imaging of the glutamatergic system requires a further effort of research and development.

Diagnostic Use

The neurochemical imaging of dementing disorders not only confirms previous postmortem analyses that are often performed on tissues obtained from end-stage disease, but also permits investigation of very early changes in living subjects and longitudinal serial examinations owing to the noninvasive nature of imaging technology. Despite certain technical limitations, findings from in vivo imaging data contribute significantly to our understanding of regional neurodegenerative processes and neurochemical correlates of clinical symptoms. There also has been an expectation that neurochemical imaging could be used as a diagnostic aid for certain brain disorders. It is interesting to note that an article in *Seminars in Nuclear Medicine* published a decade ago predicted the use of PET and SPECT in the day-to-day practice.[127] SPECT dopamine imaging may be the closest molecular imaging for the diagnostic use of PD, but other neurochemical imaging techniques for dementing disorders are currently far from use in the average day-to-day clinical practice. One of major reasons for this delay is due to a limited radiotracer supply for neurochemical imaging in the clinical setting. However, the development of commercial suppliers of neurochemical tracers has been hampered by the realization through past investigations that there is no single neurochemical agent that can diagnose accurately and differentially dementing disorders in an early stage when symptomatic drug treatments are often most effective. In fact, the oldest and most prevalent "molecular imaging" of the brain, FDG-PET, can detect a very early stage of AD before a point when a clinical diagnosis can be made and does allow certain differential diagnoses among dementing disorders.[128-132]

The lack of fundamental treatments of AD is also a factor that currently attenuates enthusiasm to develop expensive imaging diagnostic techniques. Although the efficacy and safety of neurochemical ligands could be established, approval for reimbursement as a valid routine diagnostic test is a different hurdle. At the time of this writing, the most extensively published PET method in dementia, FDG-PET, has not been approved as an effective and reimbursable test for dementia work-up. One of the major factors to determine the efficacy of the clinical test is the body of published evidence. According to the guideline established by the Medicare Advisory Committee, 2 criteria need to be met in the diagnostic test evaluation: (1) adequacy of evidence–enough scientific evidence to draw conclusions about the effectiveness of the intervention in the routine clinical use in the population of Medicare beneficiaries; and (2) size of health effect–evidence from well designed studies must establish how the effectiveness of the new intervention compares with the effectiveness of established services and medical items. Despite the careful establishment of neurochemical imaging techniques and extensive scientific use in the investigation of dementing disorders, it is clear that the evidence to justify the use of neurochemical imaging as a diagnostic aid for dementia is severely limited. Unless investigators or industries make a substantial effort to establish such evidence, the day-to-day use of neurochemical imaging may not become a reality. However, the situation may change if effective but expensive or high-risk treatments that exert therapeutic effects through specific neurochemistry are developed in the future. An example of this possibility is amyloid imaging for anti-amyloid treatments, such as an amyloid vaccination and secretase inhibitors.[133,134]

NEUROCHEMICAL IMAGING AND DRUG DEVELOPMENTS

In vivo PET and SPECT can help drug development for dementia at multiple levels. First, imaging can assess pharmacokinetics and dynamics of the drug in the human as well as animal brains. Imaging also can establish a relationship between the behavioral and biological effects of drugs. As indicated in cholinergic imaging, neurochemical imaging can evaluate therapeutic changes in brain functions and help optimize a therapeutic dose. There are many studies using neurochemical imaging as one of the outcome markers of drug effects in dementia treatments.[53,70,135,136] Also, imaging can help identify patients with very early stage of the disease for clinical trials.[137] Finally, it is often overlooked that in vivo imaging is one of the few methods that can elucidate the pathophysiology of dementing disorders in living subjects. Findings from living patients give us many important clues as to the mechanisms of disease processes, which ultimately lead to potential targets for drug developments.

SUMMARY

As summarized previously, neurochemical imaging has been used extensively for the investigation of dementing disorders during the last 2 decades. In vivo imaging research unveils biochemical alterations of the brain in living subjects. The techniques not only permit the investigations of pathophysiology and disease mechanisms of dementing disorders but also help evaluate the effects of treatment drugs and promote future drug developments. Dementing disorders are human diseases, and in vivo imaging is one of the few methods that allows us to observe disease in vivo and to permit translation of advancements between clinical and basic research findings. Although the diagnostic use of neurochemical imaging is currently limited, continuing efforts to develop more fundamental treatments of neurodegeneration based on a better understanding of molecular genetic mechanisms of diseases will lead to a more specific target identification for imaging. Neurochemical imaging will probably play a major role for such advanced treatments by permitting patient selection, prediction for treatment response, and evaluation for treatment responses. Radiotracer developments and widespread distribution will continue to be key factors in such future developments of neurochemical imaging.

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