ACCOUNTS
of chemical research

Dissecting Molecular Mechanisms in the Living Brain of Dementia Patients

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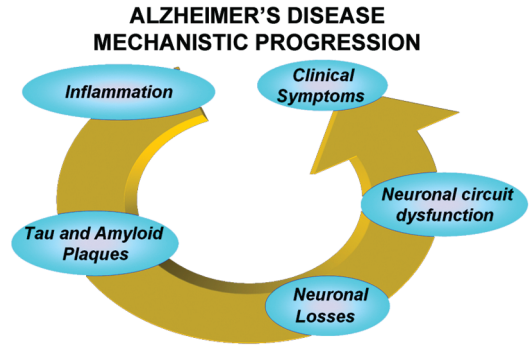
RECEIVED ON SEPTEMBER 1, 2008

CONSPECTUS

Understanding the molecular mechanisms associated with the development of dementia is essential for designing successful interventions. Dementia, like cancer and cardiovascular disease, requires early detection to potentially arrest or prevent further disease progression. By the time a neurologist begins to manage clinical symptoms, the disease has often damaged the brain significantly. Because successful treatment is the logical goal, detecting the disease when brain damage is still limited is of the essence. The role of chemistry in this discovery process is critical.



With the advent of molecular imaging, the understanding of molecular mechanisms in human neurodegenerative diseases has exploded. Traditionally, knowledge of enzyme and neurotransmitter function in humans has been extrapolated from animal studies, but now we can acquire data directly from both healthy and diseased human subjects. In this Account, we describe the use of molecular imaging probes to elucidate the biochemical and cellular bases of dementia (e.g., Alzheimer's disease) and the application of these discoveries to the design of successful therapeutic interventions.

Molecular imaging permits observation and evaluation of the basic molecular mechanisms of disease progression in the living brains of patients. 2-Deoxy-2-[^{18}F]fluoro-D-glucose is used to assess the effect of Alzheimer's disease progression on neuronal circuits projecting from and to the temporal lobe (one of the earliest metabolic signs of the disease). Recently, we have developed imaging probes for detection of amyloid neuropathology (both tau and β-amyloid peptide deposits) and neuronal losses. These probes allow us to visualize the development of pathology in the living brain of dementia patients and its consequences, such as losses of critical neurons associated with memory deficits and other neuropsychiatric impairments.

Because inflammatory processes are tightly connected to the brain degenerative processes, inflammation is now emerging as an important target for new molecular imaging probes. The combination of molecular probes targeting various processes of dementia is a useful tool for detailed monitoring of disease mechanism, progression, and diagnosis, as well as for the development of rational strategies for promising therapeutic interventions.

Introduction

The first indication of the significance of molecular imaging resides in the unequivocal fact that it has permitted direct demonstration, assessment, and validation of basic mechanisms of human biochemistry. Molecular imaging probes (diagnostic) and drugs (therapeutics) share common concepts of design based on biochemical principles targeting enzymes, receptors, neurotransmitter systems, genetic material, and pathological depositions.[1]

Published on the Web 03/12/2009 www.pubs.acs.org/acr
10.1021/ar800189x CCC: $71.50

Whereas in the past human enzyme and neurotransmitter function was extrapolated from animal studies, the development of positron emission tomography (PET) has permitted evaluation of these critical functions directly in humans in both healthy and disease states. This is because most common positron emitters are isotopes of essential elements of organic molecules with which natural substrates or their analogues, as well as drugs, can be labeled without altering the properties of the parent compound. Moreover these positron emitters have very short half-lives (^{15}O, $t_{1/2} = 2.0$ min; ^{13}N, $t_{1/2} = 10.0$ min; ^{11}C, $t_{1/2} = 20$ min; ^{18}F, $t_{1/2} = 110$ min), which permit studies in humans with minimum radiation exposure. It should be noted that fluorine-18 is most frequently used replacing hydrogen or a hydroxyl group on substrates targeting common enzymes or ligands to label receptors to produce analogues that behave in a predictable manner permitting quantification of the process to be measured (e.g., 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) to measure local glucose metabolic rates).

In this Account, we will highlight the use of molecular imaging probes in the elucidation of biochemical and cellular bases of dementias, as well as structural considerations for their specificity for the process to be measured. A detailed review on the utilization of imaging approaches as diagnostic tools has been published elsewhere.[2]

Alzheimer's Disease: Molecular Deposits, Neuronal Losses, and Neuropsychiatric Symptoms

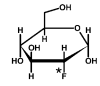
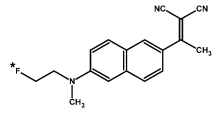
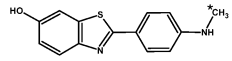
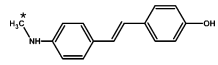
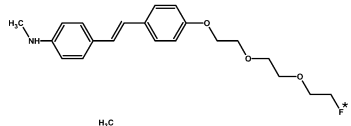
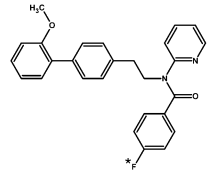
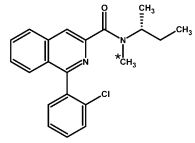
Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder associated with older age with the patient presenting a progressively severe broad spectrum of cognitive impairment.[3] Age is the most important risk factor for AD with an incidence that increases to about 40% in the >85 year age group. No known curative treatment exists for AD, and the only drugs currently approved are acetylcholinesterase inhibitors, but they do not modify the course of the disease. Not unexpectedly, the financial burden to individuals, families, and society can be overwhelming considering the chronic nature of AD and the fact that patients become totally dependent on others when the disease progresses.[4] Since life expectancy has significant increased and will continue to increase for the foreseeable future, neurodegenerative diseases, including AD, have been described as one of the greatest health challenges of this century.[5]

Alzheimer's disease has been extensively studied at the cell biology and morphological level. Alois Alzheimer was first to describe characteristic brain lesions in the brain of a patient affected by dementia,[6] namely, insoluble protein aggregates constituted as neurofibrillary tangles (NFT) and β-amyloid senile plaques (SP). Subsequent work found the accumulation of these aggregates to be progressive with relatively consistent patterns of distribution.[7] Accumulation of these pathologies is always accompanied by loss of neuronal projections and eventually neuronal losses contributing to gray and white matter atrophy. Substantial neuronal loss would compromise the integrity of the neuronal circuits resulting in the observed neuropsychiatric symptoms.[8] Presence of abundant activated astrocytes and microglia near neurons and amyloid deposits also suggests the role of inflammation in AD because glial cells mediate the innate immune response in the central nervous system (CNS).[9]

Neurofibrillary tangles are one of the most prominent pathological lesions encountered in the brains of AD patients. NFTs are intracellular lesions consistently found in the most vulnerable neuronal populations (e.g., glutamatergic pyramidal neurons) of the medial temporal lobe, most specifically entorhinal cortex and hippocampus, where the memory processing centers of the brain reside. In advanced disease, NFTs are also found in other cortical and subcortical regions, and their presence has been closely associated with neuronal death and clinical symptoms.[10,11] NFTs are cytoskeletal structures composed of paired-helical filaments (PHFs) and straight filaments (SF), both of which are fibrillar aggregates of hyperphosphorylated microtubule-associated protein tau[12] as shown by X-ray diffraction.[13]

SPs are also commonly found throughout the AD brain, typically in the form of dense core plaques in the neocortex and as diffuse amorphous aggregates, dense focal fibrillar, and dense core plaques in subcortical structures.[14] SPs are brain lesions composed mainly of water-insoluble β-amyloid peptide aggregates, and in contrast to NFTs, they are found in the extracellular space.[15] These aggregates are indeed heterogeneous and, like NFTs, colocalized with a variety of proteinaceous and nonproteinaceous molecules. Key components in these aggregates are 39−43 amino acid long β-amyloid peptides, which are formed from amyloid precursor protein (APP) through the β- and γ-secretase mediated cleavage.[16] The inability of insoluble β-amyloid fibrils to form single crystals[17] has prevented gathering detailed high-resolution X-ray crystallography to obtain structural information and site-specific binding of small molecules to fibrils. However, considerable information about the fibrillar nature of *ex vivo* β-amyloid aggregates is available from X-ray diffraction experiments. From these determinations, cross-β-sheet secondary structure elements are inferred for β-amyloid fibrils because the inter-

TABLE 1. Positron Emission Tomography Molecular Imaging Probes Used for Visualization of Biochemical and Cellular Processes in Alzheimer's Disease and Related Disorders

Molecular probe	Structure	Intended molecular targets / processes probed	Ref.
[F-18]FDG		Glucose metabolism / Neuronal circuit connectivity	1,23
[F-18]FDDNP		β-Pleated sheets in amyloids / Neuropathological aggregation	25,26
[C-11]6-OH-BTA-1		Amyloid plaques	27
[C-11]SB-13		Amyloid plaques	28
[F-18]BAY94,1972		Amyloid plaques	29
[F-18]MPPF		5-HT1A receptors / Pyramidal neuron loss	30
[C-11]PK-11195		Peripheral benzodiazepine receptors in activated microglia / Brain inflammation	63

[a] Asterisk indicates the radioisotope position.

strand and stacking distances in β-sheets produce two characteristic scattering diffraction signals at 0.47 and 1.0 nm.[18,19]

Both β-amyloid and tau aggregates fit under the general definition of amyloids.[20] As interesting as the presence of these amyloid structures in the brain of AD patients is, their association with the disease process is still unclear. It has been argued, for example, that insoluble β-amyloid peptide deposits physically disrupt tissue architecture and, more recently, that small amyloid-like oligomers are indeed neurotoxic and the cause of cell death.[21] Based on this logic, experimental antiamyloid therapies have dominated the profile of AD clinical trials in the past few years, but all attempts to date with vaccines or antiaggregation drugs have been unsuccessful[22] giving support to the notion that removing amyloid aggregates would do little to stop disease progression when significant and irreversible neuronal death has already occurred. Anti-tau therapies, perhaps more predictably considering the direct relationship between the load of tau aggregates and neuronal death,[10] have demonstrated significant promise to modify disease evolution.

The Logic behind the Use of Molecular Imaging

Neuropathological and clinical research support the idea that the pathological processes leading to AD begin many years before a clinical diagnosis of probable AD can be confirmed.[7] Molecular imaging gains significance when used as a tool for detection of early changes during the presymptomatic stages or as a tool to guide prevention well before dementia is clinically detectable. At this time, brain damage is expected to be still limited, which opens the door for successful therapeutic interventions with potential to arrest the progression of pathology and prevent further neuronal losses.

In designing new molecular imaging probes, knowing what to look for and where to look is then essential. Molecular imaging in AD has been directed to the measurement of the basic molecular processes highlighting disease progression (Table 1). For example, *neuronal circuit connectivity* and its relationship with cognitive decline can be established in the living brains of patients by quantification of regional meta-

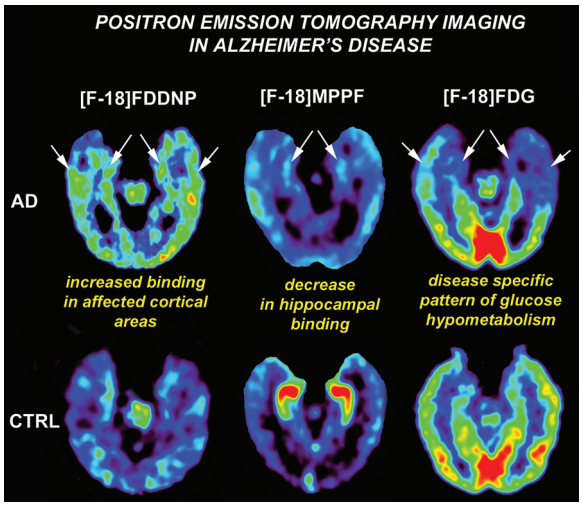


FIGURE 1. Molecular imaging in Alzheimer's disease. Different aspects of the disease can be targeted with appropriate molecular imaging probes: neuropathological deposits with amyloid probes such as [^{18}F]FDDNP, neuronal losses with [^{18}F]MPPF, and neuronal circuit dysfunction with [^{18}F]FDG. Representative parametric images[25,30] of transaxial sections at the level of the medial temporal lobe for these three molecular imaging probes are presented for AD (top row) and control subjects (CTRL, bottom row). Arrows indicate the areas affected in AD, namely, increased pathology deposition ([^{18}F]FDDNP in lateral temporal cortices, decreased [^{18}F]MPPF in hippocampus, and cortical hypometabolism ([^{18}F]FDG)). Warmer colors indicate higher retention of the probe.

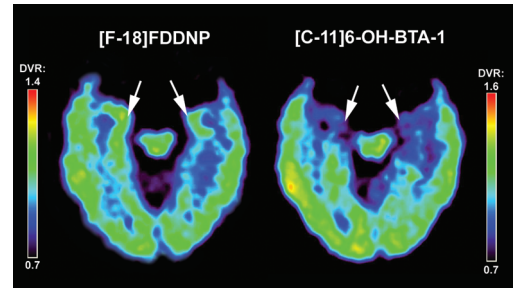


FIGURE 2. In vivo imaging of Alzheimer's disease pathology on the same AD subject at the level of the memory centers in the medial temporal lobe using multiple amyloid molecular imaging probes. The parametric images[25,27] demonstrate that both molecular imaging probes label similar cortical areas with the exception of medial temporal lobe, which shows [^{18}F]FDDNP but not [^{11}C]6-OH-BTA-1 accumulation (arrows) highlighting the ability of [^{18}F]FDDNP to detect tau pathology.

bolic decreases in brain cortical activity with 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) PET[23] (Figure 1). [^{18}F]FDG PET targets neuronal glucose utilization, measures functional viability, and has been used for the diagnosis of AD with 93−95% sensitivity and 89−92% specificity.[23] The success of the procedure has resulted in its introduction in routine medical practice in the U.S., which increased substantially with Medicare and private insurance reimbursement. Deactivation of parietal regions and posterior cingulated gyrus is the earliest metabolic sign of AD, reflecting the disruption of neuronal circuits projecting from and to the memory centers of the brain located in the medial temporal lobe.[24]

More recently imaging probes for detection of *amyloid neuropathology* (both tau and β-amyloid peptide deposits) were developed providing specific access to the visualization of pathology accumulation in the living brain of dementia patients. They included positron-emitter-labeled naphthalene-based molecules (e.g., 2-(1-{6-[(2-[^{18}F]fluoroethyl)(methyl)-amino]-2-naphthyl}ethylidene)malononitrile, [^{18}F]FDDNP),[25,26] benzothiazoles (e.g., [^{11}C]6-OH-BTA-1 (PIB)),[27] and stilbenes (e.g., [^{11}C]SB-13 and [^{18}F]BAY94-9172).[28,29] [^{18}F]FDDNP and [^{11}C]6-OH-BTA-1 PET imaging results from the same AD patient are shown in Figure 2. *Neuronal losses*, significant to the neurodegenerative processes found in AD, have also been accurately measured with specific radiolabeled ligands of serotonin 1A (5-HT$_{1A}$) receptors structurally related to *N*-[(1-piperazinyl)ethyl]-*N*-(2-pyridinyl)benzamides (e.g., [^{18}F]MPPF). These receptors seat on glutamatergic neuron apical dendrites providing a reporting mechanism for losses of these critical neurons.[30] The early presence of *inflammation* in the brain of AD patients provides a molecular imaging target for early detection and would logically provide an additional avenue to detailed monitoring of disease mechanisms, progression, diagnosis, and therapeutic interventions.[31]

Imaging Neuropathological Deposits

Presence of NFTs and SPs in autopsy brain samples is required for positive diagnosis of AD, and the same logic could be applicable to their detection in the living brain of AD patients using molecular imaging. Unlike receptors, transporters, and enzymes, NFTs and β-amyloid plaques are inert structures lacking specific binding domains. Despite this challenge, molecular imaging probes recognizing the cross-β-sheet structure in the core of the highly ordered arrangement of peptide monomers in amyloid fibrils (anchored by hydrogen bonds formed between the peptide backbones with $\pi-\pi$ stacking of aromatic amino acid residues, as well as glutamic acid−lysine electrostatic interactions) have been developed.[32] Radiolabeled β-amyloid peptides are potentially highly specific imaging agents,[33] but their large peptide backbone severely limits their capacity to penetrate the blood−brain barrier and thus their utility as imaging probes. The blood−brain barrier is also an impenetrable barrier for classical histological dyes used as gold standards for detection of SPs and NFTs in postmortem AD brain tissues, like Congo red and thioflavins, due to their strong anionic or cationic nature.[34] The basis of Congo red assay is an intense green birefringence under

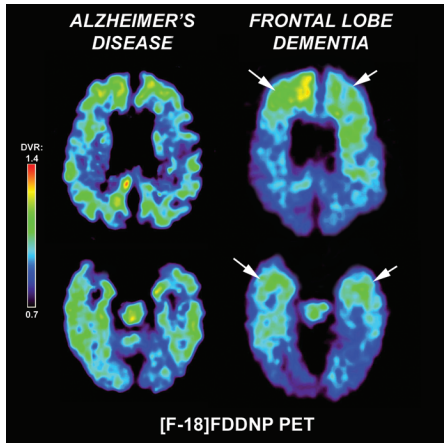


FIGURE 3. [^{18}F]FDDNP PET parametric images[25,26] in patients with frontal lobe dementia and AD. The different [^{18}F]FDDNP distribution is the result of different predominant pathology (e.g., tau aggregates in frontal lobe dementia vs tau and β-amyloid fibrils in AD) and their cortical distribution.

polarized light, which was generally attributed to microenvironmental changes in the dye as a result of intercalation between β-strands of amyloid aggregates. It has been most recently suggested however that interaction between Congo red and amyloid fibrils occurs on the surface of the fibrils because the distance between two lysine groups in the pleated β-sheet model is about 20.8 Å, which is similar to the distance between the two sulfonate groups in Congo red (19.6 Å).[35] In this arrangement, the central biphenyl group of Congo red interacts with hydrophobic side chains of amino acid residues resulting in a binding mode of the long axis of Congo red orthogonal to, rather than parallel to, the fibril axis as earlier proposed.[36]

The ability of Congo red to interact with amyloid fibrils has promoted studies on developing Congo red analogues as potential imaging agents.[37] Analogously, molecular probes with structures related to the other *in vitro* dye, thioflavin T, have also been developed.[27] 2-(1-{6-[(2-[^{18}F]Fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile ([^{18}F]FDDNP) is included among molecular imaging probes with a polyaromatic core element[38−42] and is the first amyloid molecular imaging probe not modeled after existing *in vitro* dyes. Remarkably FDDNP is currently the only molecular imaging probe used *in vivo* that shares with Congo red and thioflavin T complete specificity for β-sheet domains in amyloid fibrils.[34] This ability to recognize specifically β-sheet domains in various pathologies has facilitated extension of [^{18}F]FDDNP *in vivo* use from detecting SPs and NFTs in AD[25,32] to detection of amyloid aggregates (e.g., prion, amyloid, SP, NFT) in prion disease,[43,46] Down's syndrome,[44] familial AD,[45] and frontal lobe dementia (Figure 3).[26]

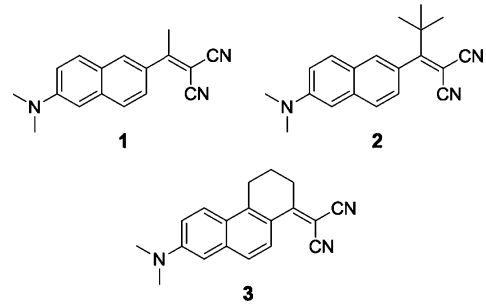


FIGURE 4. Chemical structures of three DDNP derivatives to demonstrate how geometries are related to their binding properties with aggregates. Planarity enables stabilization arising from electron delocalization from the arylnitrogen to the dicyanovinyl group. Planar geometry permits alignment of the dipole, which is a requirement for binding site recognition.

[^{18}F]FDDNP Recognizes the β-Sheet Domain in Tau and β-Amyloid Aggregates

The consistent ability of FDDNP to label all aggregates found in neurodegenerative diseases containing cross-β-sheet structures suggest that this structure is the site target in the fibrils. The displaceable nature of FDDNP binding with other molecules having affinity with β-amyloid Aβ(1−40) fibrils (e.g., the nonsteroidal anti-inflammatory drug (NSAID) naproxen) both *in vitro* in synthetic fibrils and human brain specimens of AD patients[47] and *in vivo* in triple transgenic mice of amyloid deposition[39] demonstrate a specific binding site of FDDNP on the Aβ aggregates. However, FDDNP, Congo red, and thioflavin T do not bind to the same site based on competitive kinetic determinations with *in vitro* Aβ fibrils and autoradiography.[47]

Fluorescence microscopy reveals an intense fluorescence of SPs and NFTs in postmortem AD brain specimens when labeled with FDDNP or analogues with minimal background, which reflects its extended dipole when bound to pockets of hydrophobicity in the aggregates. 6-Dialkylamino-2-naphthylethylidenemalononitriles (DDNP and analogues) are neutral, environmentally sensitive, and fluorescent molecules forming strong inducible dipoles in polar solvents as evidenced by their spectroscopic properties[48] and dipole moment calculations (K. Houk, UCLA Chemistry and Biochemistry Department, personal communication). Crystal X-ray diffraction shows near-planar conformation in DDNP[48] (**1**, Figure 4). which is one prerequisite for tight binding recognition of β-sheet domains in amyloid aggregates in this family of compounds. Analogues with restricted rotation around the exocyclic C−C bond (e.g., *tert*-butyl-DDNP, **2**, Figure 4) present a global minimum well outside the planar conformation, which seems to indicate that in this molecule the acceptor side chain cannot assume coplanar arrangement with the naphthalene ring as reflected in a weak *in vitro* binding affinity to β-amy-

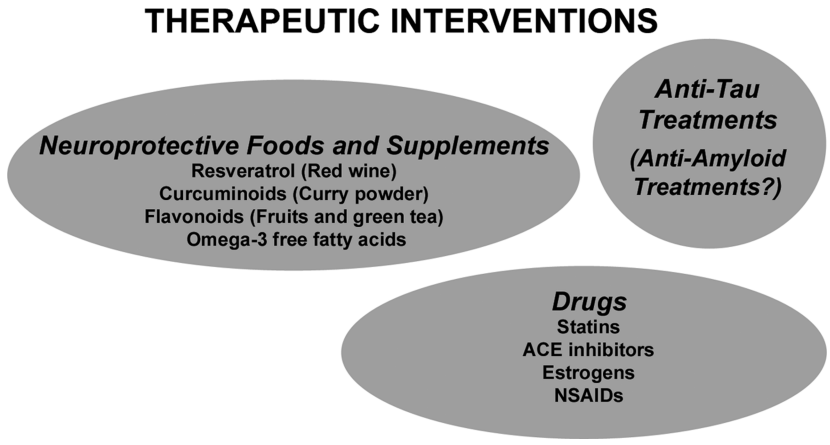


FIGURE 5. Experimental therapeutic interventions aimed at Alzheimer's disease prevention and early treatment based on known drugs and food components with efficacy in modifying the course of the disease.

loid fibrils (10^{-6} M). On the other hand, DDNP derivatives restricted to near-planar conformation by a six-membered ring (**3**, Figure 4) in the crystal and in solution present subnanomolar binding affinity to the same *in vitro* β-amyloid fibrils.[49] Planarity enables efficient delocalization of electron density from donor toward the acceptor group, enhanced by planar arrangement of groups around the donor nitrogen atom, which facilitates binding to β-amyloid fibrils.

Imaging Neuronal Losses

As stated earlier, clinical symptoms found in AD stem from the disruption of major neuronal circuits caused by the extensive loss of neurons forming these circuits. In severe AD, neuronal losses could be as high as 30% of available brain neurons, but the disease does not affect all neuronal circuits at the same time. The large pyramidal neurons in the memory centers of the medial temporal lobe are particularly vulnerable, and the extent of neuronal loss is the best parameter to correlate with degree of cognitive decline.[7,50] Since 5-HT_{1A} receptors are highly expressed on these neurons, their *in vivo* quantification with [^{18}F]MPPF PET offers a technique for assessment of neuronal losses in the living brains of these patients at the earliest possible stages of the disease.[30] Remarkable in its sensitivity, [^{18}F]MPPF PET already shows significantly decreased hippocampal neuronal densities in the earliest states when only mild cognitive decline exists, for example, in clinically defined mild cognitive impairment (MCI). Thus [^{18}F]MPPF PET is a powerful tool to detect early evidence of AD.[7] As AD progresses, severe loss (>50%) of neurons in the memory centers, for example, hippocampal CA1 field, occurs,[7,50] which is confirmed in the living brains of AD patients with [^{18}F]MPPF PET.[30] Concomitantly, neuropathological changes are also observable with [^{18}F]FDDNP in these subjects, most prominently in the medial temporal lobe, the brain area with earliest pathology deposition.[25,30]

Integrating Molecular Imaging Observations of Neuropathological Deposits, Neuronal Losses and Neuronal Circuit Connectivity

In summary, the following early chain of events leading to AD is clearly observable with molecular imaging probes in the living brain of human subjects:

1. The presence of *neuropathological deposits*, predominantly NFTs, in the memory centers of the medial temporal lobe is already detectable in asymptomatic subjects with [^{18}F]FDDNP PET.[25,30] MCI patients also show the presence of cortical pathology in the medial temporal lobe, often at levels quantitatively similar to those found in AD.[25]
2. Consistent with these observations, significant *neuronal losses* are measurable with [^{18}F]MPPF at very early stages of the disease when compensatory plasticity mechanisms either hide or still limit the overall cognitive decline.[30] It can be inferred from these results that early pathology deposition is the trigger, although not necessarily the determinant factor, for the relatively slow and progressive neuronal degeneration that follows.[51]
3. Concomitant cortical reduction in glucose metabolic rates, as measured with [^{18}F]FDG, reflects the *disruption of neuronal circuits* (e.g., posterior cingulated gyrus in MCI subjects), demonstrating its interconnection with pathology deposition and neuronal death.[52]
4. Ultimately, extensive spreading of pathology deposition occurs throughout the brain in a rather consistent cortical pattern as shown with [^{18}F]FDDNP PET.[7,53] As the disease advances, further neuronal losses will progressively dis-

rupt projecting cortical neuronal circuits leading to increasing cognitive decline.[30]

Inflammation: The Missing Link

The integrated application of molecular imaging probes monitoring NFT and SP deposition ([^{18}F]FDDNP), neuronal losses ([^{18}F]MPPF), and integrity of neuronal circuits ([^{18}F]FDG) adds new evidence in living subjects to the interconnected biological mechanisms of AD progression. How are NFTs and SPs related to neuronal circuitry alterations and neuronal loss? CNS inflammation, accompanied by extensive microgliosis and astrocytosis, has been implicated as a key component of the neurodegenerative cascade. One line of evidence is the presence of cortical NFTs and SPs in some cognitively normal elderly subjects in numbers sufficient for diagnosis of AD[54] but still not leading to synaptic loss and neuronal damage in the absence of inflammation.[55−58]

Activated microglia, the resident macrophages of the CNS, not only produce a variety of pro-inflammatory molecules detrimental to neuronal cell and survival[57] but may also contribute to SP and NFT formation via production of APP in an activated state[59] or via production of interleukin IL-1, which activates p38-MAPK kinase driven phosphorylation of tau protein[60] to induce tau aggregation.

Inhibition of microglial activation and production of inflammatory molecules has been demonstrated with a variety of exogenous and endogenous compounds, such as hormones (e.g., 17-β-estradiol (E2) and progesterone),[61] dietary polyphenols (curcuminoids (in curry powder), resveratrol (in grapes), and flavonoids (in fruits and green tea)),[62] or NSAIDs and statins among others. E2 can inhibit microglia activation either directly via scavenging of NO and reactive oxygen species or via inhibitory interaction of activated estrogen receptor α (ERα) with neuronal factor κB (NF-κB) translocation to the nucleus via phosphoinositide-3 kinase (PI3K).[61] Therapeutically, prevention or control of inflammation in AD via NF-κB inhibition by endogenous estrogen (e.g., by activating enzymes involved in brain *de novo* E2 synthesis) or by polyphenols, such as resveratrol or curcuminoids (e.g., by deactivating directly or indirectly E2 metabolizing enzymes) may prove to be efficient mechanisms to prevent or delay disease progression (Figure 5). On the diagnostic side, PET imaging of inflammation in AD targeting factors contributing to microglial activation, such as estrogen α receptors or estrogen producing and metabolizing enzymes, would provide a new way of *in vivo* detection of neuroinflammation, which is currently achieved by targeting peripheral benzodiazepine receptor with specific PET ligands ([^{11}C]PK11195).[63]

As observed with other neurodegenerative diseases (e.g., Parkinson's disease),[64] neuroplasticity mechanisms play a very important role in delaying the appearance of clinical symptoms in AD. Clinical manifestations remain hidden for years, and molecular imaging is a powerful tool to visualize in living subjects the existing interdependent molecular and cellular mechanisms at play even before neuropsychiatric symptoms are observable. This is important because early molecular diagnosis of abnormalities would permit disease-modifying interventions at the earliest stage of the disease, the only stage when these interventions are meaningful.

Financial support from the Department of Energy (Grant DE-FC03-02ER63420) and from the National Institutes of Health (Grant P01AG025831) is acknowledged. J.R.B. gratefully acknowledges the support of the Elizabeth and Thomas Chair Endowment in Gerontology.

BIOGRAPHICAL INFORMATION

Jorge R. Barrio was born in Buenos Aires, Argentina. He received a B.S. degree and a Ph.D. in Biochemistry from the University of Buenos Aires followed by a Ph.D. in Chemistry from the University of Illinois at Urbana−Champaign. He later joined the faculty at the David Geffen School of Medicine at UCLA, where he is currently a Professor of Molecular and Medical Pharmacology and holds the Elizabeth and Thomas Plott Chair in Gerontology.

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