Current and Future Treatments for Alzheimer Disease

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More than a century ago, Alois Alzheimer described the results of a brain autopsy he performed on a middle-aged woman who had developed rapidly progressive cognitive decline. The amyloid plaques and tau tangles that he noted in the patient's neocortex and other brain regions were thought to explain her condition. Initially, Alzheimer disease was considered a rare presenile dementia; then, in the late 1960s neuropathologists showed that plaques and tangles were present in the brains of older persons who suffered from dementia.Alzheimer disease strikes approximately 10% of people 65 years or older and 45% of those 85 or older.[1] Its incidence and prevalence double every 5 years after age 60 years. Over 5 million people suffer from Alzheimer disease in the U.S., and worldwide prevalence estimates approach 44 million. Due in part to the graying of the world population, the prevalence of the disease is expected to triple by 2050.[1]

In response to the daunting numbers currently afflicted and the looming estimates of future sufferers, scientists have attempted to uncover causes, contributing factors, and treatments. Investigations have identified rare mutations (presenilin and amyloid precursor protein [APP] mutations), common genetic risks such as the apolipoprotein E-4 (APOE-4) allele, and nongenetic factors that contribute to risk. Biomarkers that better define the phenotype have advanced our knowledge and provided potential tools that can focus treatment research.

Initial drug research aimed to boost brain acetylcholine, because of the cholinergic deficits known to contribute to symptoms. The U.S. Food and Drug Administration (FDA) has approved four cholinesterase inhibitors (tacrine [Cognex], donepezil [Aricept], rivastigmine [Exelon], and galantamine [Razadyne]) and one *N*-methyl D-aspartate (NMDA)-receptor antagonist (memantine [Namenda]) for the treatment of Alzheimer disease. These drugs have demonstrated benefits for cognition, behavior, and function, but their modest effect sizes and temporary benefits leave room for improvement. At the 2015 Alzheimer's Association International Conference, many experts expressed optimism about ongoing treatment research, although no disease-modifying drug or symptomatic treatment with a moderate or large effect size has yet been discovered.

WHY SO MANY DRUGS HAVE FAILED

To understand why so many drugs have failed to be effective in treating Alzheimer disease, we need to consider the underlying neuronal mechanisms for their mode of action, and then determine whether those mechanisms could indeed explain the known clinical effects. The cholinergic hypothesis, which provides the rationale for the cholinesterase inhibitors, posits that the primary problem is a deficit in acetylcholine, caused by the death of cholinergic neurons. Cholinergic cell death cannot be the root of the problem in Alzheimer disease, however, because other populations of noncholinergic neurons (e.g., neurons containing monoamines)[2] are additionally prone to neurodegeneration. Moreover, any drug that merely increases the availability of the dwindling transmitter will

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be tackling the symptoms, not the cause of the neurons dying in the first place.

The other major contending hypotheses for drug development are the amyloid and tau theories, originating from the abnormal histopathological markers—extracellular plaques and intracellular hyperphosphorylated tau proteins—that characterize the postmortem Alzheimer brain. Although controversy remains regarding which of the two may be the primary culprit, recent evidence suggests that expression of these two markers may be linked.[3] The problem with targeting either or both as a therapy is that in both cases APP (from which amyloid is abnormally cleaved) and tau protein are virtually ubiquitous features of all neurons; hence, we need to identify a constraining additional feature that would explain why only certain neurons are vulnerable.[4] Drugs that combat either amyloid or hyperphosphorylated tau may have some benefit, but they would not intervene at the basic mechanism. Such drugs could alleviate symptoms and or slow disease progression; nevertheless, only when we have identified the key underlying mechanism will we be able to develop a drug that intercepts that mechanism and halts disease progression.

Another problem contributing to the failure to identify a plausible mechanism is a lack of an exemplary animal model—a prerequisite for developing effective drugs.[5] The goal of such a model is to replicate the salient disease features at the expense of the extraneous ones. For example, modeling flight would entail defying gravity, but without the need for building a machine with beaks or feathers. We need to identify the salient feature of Alzheimer disease in order to identify an animal model that captures the basic mechanism driving disease pathogenesis.

Neither the amyloid nor tau hypothesis could account for the following general observations that are valuable clues to discovering why cells die in neurodegeneration: 1) a frequent co-pathology with Parkinson disease; and 2) a selectivity of cells that are prone to degeneration located in the basal forebrain, midbrain, and brainstem nuclei that form a continuous hub, previously denoted "isodendritic core" and more recently "global neurons."[6] Thus, the co-pathology of degenerative diseases could be explained by damage sufficiently extensive to include not just the basal forebrain, but also the substantia nigra, locus coeruleus, raphe nuclei, and motor neurons. Because these cells have a different embryological provenance (i.e., basal rather than alar plate),[6] it might be unsurprising that these different properties could make them selectively vulnerable. More specifically, developmental mechanisms are atypically retained into maturity, which are subsequently reactivated as part of the degenerative process: This idea is supported by the observation of hypertrophy in these nuclei in Alzheimer disease,[7] accompanied, in the basal forebrain at least, by an increase in dendritic arborization.[8] Hence, it could be the case that neurodegeneration is an aberrant form of development.[9]

BIOMARKERS AND DRUG DEVELOPMENT

Because the clinical features of Alzheimer disease are nonspecific and obtaining brain biopsies is impractical, researchers have pursued various biomarkers to facilitate diagnosis. Examples include amyloid and tau levels in cerebrospinal fluid or blood, as well as noninvasive methods using saliva samples or a sniff test, but such biomarkers may not directly reflect the brain alterations associated with the disease process.

Neuroimaging technologies[10] often provide more direct information on regional brain changes. Structural imaging can identify space-occupying lesions and help differentiate Alzheimer disease from other dementia causes. In clinical settings, visual interpretations of computed tomography (CT) and magnetic resonance imaging (MRI) scans may assist in diagnosis when regional alterations differentiate the medial temporal atrophy of Alzheimer disease from the frontal and temporal atrophy of frontotemporal lobar degeneration, but visual interpretations may miss subtle changes.

Image analysis programs can quantify CT and MRI volumes: Entorhinal and hippocampal atrophy are associated with a heightened risk for progressive cognitive decline and emergence of Alzheimer dementia. Functional MRI can determine regional blood flow while a volunteer rests or performs mental tasks. This method has demonstrated greater brain activation during memory tasks in nondemented APOE-4 carriers compared with noncarriers, and the degree of activation predicts subsequent cognitive decline.[10] MRI also can quantify neuronal connectivity (diffusion tensor imaging) and tissue substrate or metabolite concentrations (magnetic resonance spectroscopy).[10]

Earlier functional scanning used single photon emission computed tomography and electroencephalography, but recently positron emission tomographic (PET) has been a major focus of biomarker development. PET measures of regional glucose metabolism after injection of fluorodeoxyglucose (FDG) can differentiate Alzheimer disease, other forms of dementia, mild cognitive impairment, and normal aging.[10] In Alzheimer disease, hypometabolism is observed in the posterior cingulate, parietal, temporal, and frontal regions, and these patterns emerge in amnestic mild cognitive impairment. Combining genetic risk assessment with PET scans assists with the early detection of abnormalities: FDG-PET demonstrates regional hypometabolism in nondemented subjects with the APOE-4 allele.[10] In 2004, the U.S. Centers for Medicare and Medicaid Services approved Medicare reimbursement for FDG-PET scans to assist with the differential diagnosis of Alzheimer disease and frontotemporal dementia.

As drug development has focused on anti-amyloid treatment, several small-molecule probes for use with PET imaging have been shown to provide in vivo measures of amyloid plaques, tau tangles, or both. PET scans after 2-(1-{6-[(2-fluorine 18–labeled fluoroethyl)methylamino]-2-napthyl}ethylidene) malononitrile injection provide regional brain measures of both plaques and tangles; differentiate patients with Alzheimer's disease from those with mild cognitive impairment and cognitively intact controls; and predict cognitive decline in nondementia subjects.[11] PET studies using Pittsburgh Compound-B, as well as two newer FDA-approved amyloid ligands (florbetapir [Amyvid] and flutemetamol [Vizamyl]) show significantly greater cortical retention in Alzheimer disease compared with controls and predict clinical course.[12]

Despite FDA approval, insurance companies do not cover the cost of amyloid scans. That may change if use of an imaging biomarker is shown to alter treatment decisions and improve patient outcomes. Other new PET ligands are being developed to image tau tangles as well as other relevant neural events such as inflammation. Because a potentially effective drug may fail to show significant benefits if tested in a heterogeneous patient population, a major goal of biomarker development is to identify methods for defining homogenous subject groups for clinical trials.

CURRENT TREATMENT AND PREVENTION STRATEGIES

Alzheimer disease is a gradually progressive neurodegenerative condition that biomarker and autopsy studies indicate begins decades before symptoms become clinically obvious. The diagnostic criteria for Alzheimer disease are evolving and recent revisions provide criteria for diagnosing the disease prior to the onset of dementia.[13] There is a pressing need for a better understanding of the disease transitions—from normal aging to mild cognitive impairment and dementia—as well as more effective interventions throughout the course of this degenerative process. In addition to oral drugs, transdermal patches, and intravenous infusions, lifestyle behaviors such as physical exercise, mental stimulation, and nutrition are potential intervention strategies.

This issue of the journal includes three controlled studies offering insights into different forms of treatment at different stages of neurodegeneration. In their randomized controlled trial, Bossers and associates[14] showed that a 9-week intervention of aerobic and strength-training was more effective than aerobic-only training in slowing cognitive decline in patients with dementia. This is the first study providing evidence for such effectiveness in older patients with dementia, and the results are consistent with investigations demonstrating the cognitive benefits of physical exercise. Animal and human studies have shown how cardiovascular and strength training not only improve cognitive ability, but also increase brain size and function. Other research indicates the potential benefits of healthy nutrition, stress management, social engagement, mental stimulation, and cognitive training in improving brain health and mental performance as well as reducing risk for Alzheimer dementia.[15] A recent multi-domain, randomized controlled trial of an intervention including diet, exercise, cognitive training, and vascular risk monitoring in older people at risk for dementia demonstrated improvement or maintenance of cognitive functioning after two years.[15]

The work of Wroolie and associates[16] targeted a nondementia population: Women at risk for Alzheimer disease who were taking estrogen-based hormone therapy for at least 1 year. Women randomized to continue hormone therapy performed better on cognitive testing after 2 years compared to those who

discontinued therapy. The continuation of estrogen-based hormone therapy appeared to protect cognition in women with heightened risk for Alzheimer disease when initiated close to menopause onset. The women in this study all started hormone replacement therapy during perimenopause or early post menopause when cognitive benefits have been observed in previous studies. The findings from this study support the importance of intervention timing: Hormone replacement therapy and other potential treatments such as anti-inflammatory drugs may exert their beneficial effects only at certain stages of neurodegeneration and may worsen cognitive function at late disease stages.[17]

Weintraub and colleagues[18] addressed an important issue regarding the treatment of agitation in Alzheimer dementia: the time course and prediction of response to citalopram. The results indicate that treatment of agitation with citalopram needs to last at least 9 weeks for a full response to emerge. As Alzheimer disease progresses, agitation and other disruptive behaviors develop, impairing social function and triggering institutionalization. Antipsychotics, antidepressants, anticonvulsants, and other medication classes have been used, but the FDA has not yet cleared any medication for treating the agitation associated with dementia. Recent research has demonstrated a potential benefit of citalopram for reducing patient agitation and caregiver distress, and the Weintraub et al. study offers further guidance of timing and duration of treatment.

NEW MECHANISMS AND DRUGS IN THE PIPELINE

Despite the fact that a large variety of compounds has been developed as candidates for therapeutic intervention over the past decade, their mechanisms of action are limited to relatively few targets: general neuronal health, conventional receptor agents, tau hyperphosphorylation, and, the most popular still, amyloid expression.

Within the approach of promoting general neuronal health, a popular strategy has been to combat the accumulation of free radicals, molecules with an unpaired electron that will destabilize the cell membrane. Antioxidants such as vitamins C and E can offset to some extent the normal age-related decline in free-radical scavenging mechanisms. A more direct therapeutic approach, however, has been to intervene with the process of generation of electrons, whereby chelation of transition metal ions such as iron, copper, or zinc will reduce the likelihood of cell damage—although this mechanism will be generic to all neurons, not selectively targeting those prone to degeneration.

An alternative strategy is to block at the level of the receptor—specifically, the NMDA receptor with drugs such as memantine—where excessive calcium entry triggered by glutamate could lead to "excitotoxicity": excessive calcium influx such that surplus intracellular calcium is then taken up into the mitochondria; oxidative phosphorylation is compromised; electrons leak from the electron transport chain; free radicals are formed; and hence the cell membrane is once again destabilized. Although the mechanism of excitotoxicity on its own might play a part in the bigger picture of Alzheimer disease, it is not the exclusive mechanism. Other receptor agents would include galantamine, an anti-acetylcholinesterase (anti-AChE) that also works at the nicotinic receptor, but as noted, the central problem of Alzheimer is not one of cholinergic transmission.

Another cholinergic agent, however, working at the alternative muscarinic receptor, has been of interest not for its role in cholinergic transmission, but because it stimulates secretion of alpha secretase, which might deter APP from being abnormally cleaved by beta and gamma secretases to yield the toxic amyloid. This is just one of the many stratagems for tackling the accumulation of amyloid that include: β-secretase inhibitors, γ-secretase inhibitors/modulators, Aβ-aggregation inhibitors, apolipoprotein E promoting Aβ clearance, and drugs influencing Aβ blood–brain barrier transport.

Similarly, many approaches have been attempted for combating tau phosphorylation, including prevention of the process itself, aggregation, and misfolding. Finally, an "immunotherapy" approach has been used for both tau and amyloid, of which the most recently publicized has been the administration of antibodies against amyloid: Aducanumab, developed by Biogen. A dose has yet to be found that is neither too low to be effective nor too high to incur side effects, however.[19]

The problem with all these possible drugs is that they are not specific to the as-yet unidentified primary mechanism that underlies Alzheimer neurodegeneration. We still need to elucidate the process that accounts for the cell selectivity characterizing the disease. After all, cell damage (say, with a stroke) does not inevitably lead to

a neurodegenerative condition. Limited attention has been paid to the cells that are primarily vulnerable and to determining what special properties they possess that would expose them to the otherwise generic malfunctions of excitotoxicity, tau hyperphosphorylation, and abnormal cleavage of amyloid.

One intriguing clue that could inspire an innovative therapeutic approach comes from a close association between the pathology of Alzheimer disease and AChE, acting independent of cholinergic transmission.[9] In Alzheimer disease, the biochemical forms revert from a tetramer to a monomer, as in development;[20] a soluble form of AChE is selectively modified in the adrenal medulla; AChE forms in plasma are also changed; and AChE appears to have an interaction with amyloid. Because a common feature of all the "global neurons" is that they contain AChE irrespective of the particular transmitter used, perhaps this protein, acting as an independent signaling molecule, could be a novel therapeutic target.[9]

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